Assurance de Qualité pour le cancer du rectum – Phase 1 - Recommandation de bonne pratique pour la prise encharge du cancer rectal

KCE reports 69B

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
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PREFACE

Les médias et les pouvoirs publics accordent à juste titre beaucoup d'attention à certains cancers. Il suffit de penser au cancer du sein ou au cancer du colon, lequel a récemment fait l'objet d'initiatives en matière de dépistage. Par contre, il est moins souvent question d'autres cancers tout aussi fréquents. Le cancer du rectum en est un exemple.

On pourrait penser que le cancer du rectum requiert le même traitement que son voisin le cancer du colon. Rien n'est moins vrai. Il existe certes des ressemblances, mais la prise en charge – notamment chirurgicale - exige une expertise spécifique. Quelques spécialistes éminents du cancer le pressentaient depuis des années. Ils ont réussi à réunir un grand groupe d'experts issus d'horizons divers et à mettre en route un projet commun d'amélioration de la qualité de la prise en charge. Cette initiative a été baptisée PROCARE (PROjet relatif au Cancer du REctum). Son objectif est d'améliorer la qualité des soins grâce à des recommandations de bonne pratique clinique et à un projet éducatif basé sur des indicateurs de qualité scientifiquement fondés.

En Belgique on relève, comme d'ailleurs dans beaucoup d'autres pays, des différences interhospitalières dans la prise en charge du cancer du rectum. La question est alors souvent de savoir comment traiter ces différences, pour en arriver parfois à des solutions simplistes. Le projet PROCARE procède autrement. Il est porté par le groupe professionnel élargi. Les experts cliniques les plus éminents y collaborent avec enthousiasme malgré leur charge de travail journalière exigeante. Le Centre d'Expertise offre dès lors volontiers l'appui nécessaire à une telle initiative.

Ce rapport qui, à l'instar d'autres rapports du KCE contient des recommandations de bonne pratique evidence-based, constitue une première étape. La deuxième qui est en cours d'élaboration par les mêmes experts, consistera à traduire les recommandations PROCARE en indicateurs de qualité mesurables. Ceux-ci devraient permettre de suivre bientôt la qualité des soins du cancer du rectum et de disposer d'un instrument positif d'amélioration de celle-ci. L'initiative PROCARE est innovante et unique en son genre en Belgique. Le Centre d'Expertise, en collaboration avec le Registre du Cancer et l'Inami, est fier de pouvoir la soutenir. In fine, ce sont les patients eux-mêmes qui en bénéficieront, ce qui est bien sûr l'objectif essentiel des soins.

Closon Jean-Pierre
Directeur général adjoint

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Résumé

INTRODUCTION

Des études antérieures menées en Belgique et à l'étranger mettent en lumière une variabilité importante entre les hôpitaux sur le plan du type de traitement du cancer du rectum et de ses résultats. Dans plusieurs pays d'Europe, une standardisation du traitement par la mise en œuvre de recommandations diagnostiques et thérapeutiques est recherchée. Le contrôle de qualité a lieu au moyen d'indicateurs validés dont l'application a débouché sur une amélioration significative du pronostic du cancer du rectum dans les autres pays. L'évaluation de la qualité des soin sur la base des données d'enregistrement du cancer doit rattraper un retard certain en Belgique. Dans la littérature internationale, la Belgique demeure provisoirement une zone d'ombre sur la carte européenne en matière d'enregistrement des données.

En 2004, le projet 'PROject on CAncer of the Rectum' (PROCARE) a été lancé en Belgique dans le but d'améliorer la qualité des soins liés au cancer du rectum en Belgique grâce à la standardisation des traitements consécutive au développement et à la mise en œuvre de recommandations spécifiques et au contrôle de la qualité par l'enregistrement et le feed-back des données enregistrées. Toutes les spécialités médicales impliquées dans le traitement du cancer du rectum ont été réunies au sein d'un groupe de travail pluridisciplinaire regroupant des représentants des associations scientifiques concernées. Une première version provisoire des recommandations PROCARE a été rédigée en 2005 et fut suivie par des workshops (chirurgie, pathologie, radiothérapie, chimiothérapie et radiologie). Une database rassemblant les données individuelles des patients a été développée et l'enregistrement volontaire a débuté en 2006 par le biais de la Fondation « Registre du Cancer ». Toutes les données pertinentes relatives aux patients atteints d'un cancer du rectum fournies par les centres participants (du staging au follow-up) ont été introduites dans cette base de données prospective. Ces données constitueront la base d'un benchmarking national et international.

Le présent rapport publie la version actualisée des recommandations PROCARE. Dans le prochain rapport (2008), un ensemble d'indicateurs de qualité sera testé pour la première fois à l'aune des données prospectives PROCARE et de données couplées issues respectivement du Registre du Cancer, de l'Agence Intermutualiste et du Service Public Fédéral de la Santé Publique, de la Sécurité de la Chaîne Alimentaire et de l'Environnement.

MÉTHODOLOGIE

Pour le développement de cette recommandation, la méthodologie ADAPTE a été utilisée. Dans un premier temps, les principales questions cliniques ont été formulées. Les recommandations (inter)nationales existantes ont été recherchées dans Medline, la National Guideline Clearinghouse et les sites web des organisations oncologiques. Les 33 recommandations trouvées ont été évaluées sur le plan qualitatif au moyen de l'instrument AGREE par quatre évaluateurs indépendants. Ces recommandations ont été sélectionnées ou rejetées sur base d'une évaluation générale de la qualité. Ensuite, les 17 recommandations sélectionnées ont été actualisées pour chaque question clinique, en recherchant des évidences additionnelles dans Medline et la Cochrane Database of Systematic Reviews. Un niveau d'évidence a été attribué à chaque recommandation originelle ainsi qu'à chaque étude additionnelle par l'utilisation du système GRADE.

Sur base des données probantes, des recommandations ont été formulées par le groupe de développement pluridisciplinaire . Ces recommandations ont ensuite été formalisées par le groupe de pilotage PROCARE. Les conflits d'intérêt ont été relevés.

RECOMMANDATIONS FINALES

Les détails de la recommandation sont décrits dans le rapport scientifique faisant immédiatement suite au présent résumé.

DIAGNOSTIC ET STAGING

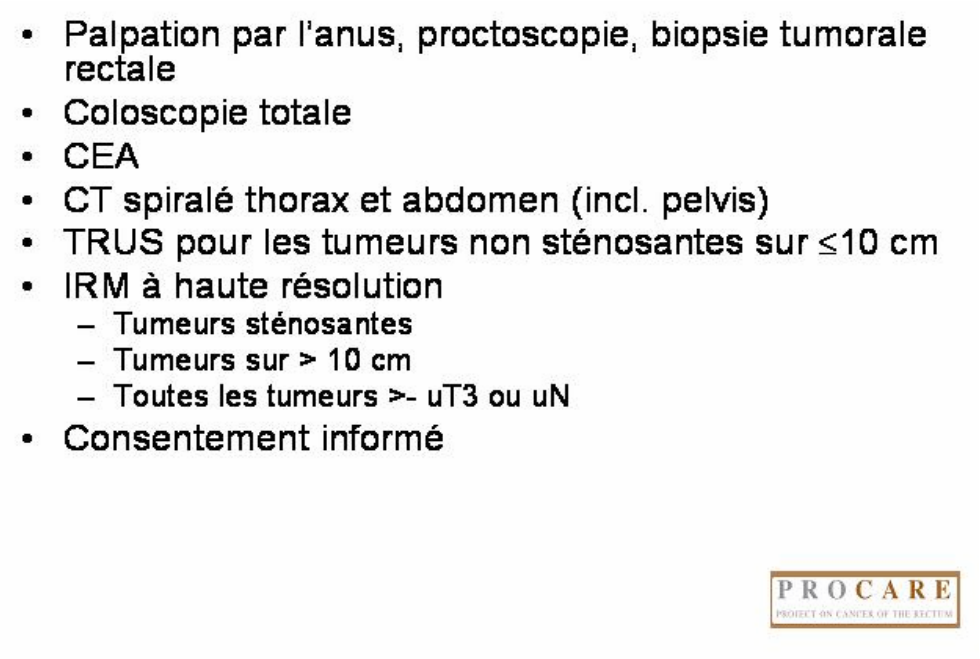
Une tumeur est considérée comme rectale lorsque l'extrémité distale (mesurée de préférence par proctoscopie rigide) se situe à 15 cm ou moins de la marge anale. Une biopsie de chaque tumeur rectale doit être prélevée avant le début du traitement (en ce compris le traitement endoscopique ou local) (figure 1). Une palpation par l'anus est recommandée, certainement dans le cas de tumeurs situées à 10 cm ou moins de l'anus.

Une coloscopie totale avec résection des polypes résiduels éventuels est conseillée. Au cas où une coloscopie totale s'avérerait trop risquée ou serait refusée par le patient, une radiographie à double contraste de qualité du colon doit être réalisée. Si une coloscopie totale n'est pas possible avant l'opération (ex. en cas de chirurgie urgente), celle-ci doit avoir lieu avant le début de la thérapie adjuvante ou dans les 3 à 6 mois après l'opération.

Chez tous les patients atteints d'un cancer du rectum, l'antigène carcinoembryonnaire (CEA) doit être déterminé avant le début du traitement. Les évidences scientifiques sont insuffisantes pour recommander la détermination d' autres marqueurs tumoraux.

L'imagerie du thorax et de l'abdomen (un scanner hélicoidal combiné avec injection de contraste [CT] du thorax et de l'abdomen/pelvis) est conseillée pour la localisation des métastases chez les patients atteints d'un cancer du rectum, et ce, avant le début du traitement. Une échographie transrectale du rectum (TRUS) est conseillée en cas de tumeurs non sténosantes et résécables dans le tiers moyen et inférieur du rectum. Une tomographie à spin nucléaire haute résolution (IRM) est conseillée pour la confirmation des stades uT3/4 et uN+, pour les tumeurs localisées dans le tiers supérieur du rectum et pour la définition de la marge latérale exempte de tumeurs (cCRM).

Figure 1. Diagnostic préopératoire et staging du cancer du rectum.



TRAITEMENT

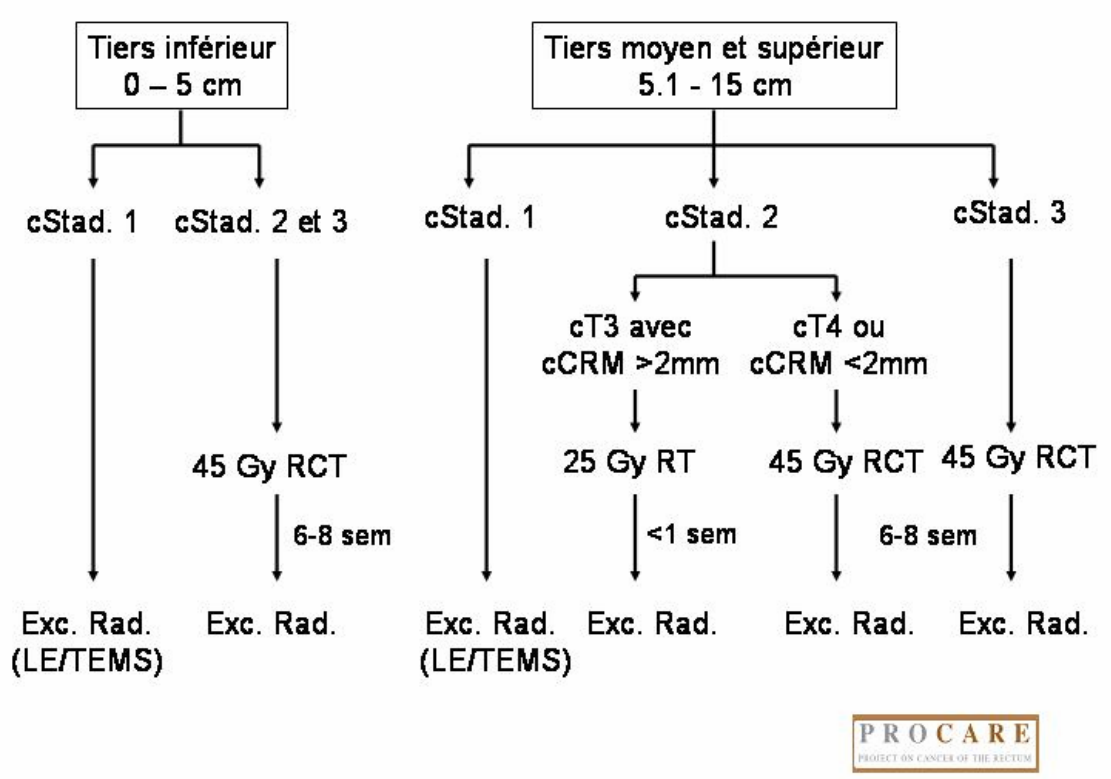
Radio- et chimiothérapie préalables : traitement néoadjuvant

Pour tous les patients atteints d'un cancer du rectum au stade clinique II ou III, la radiothérapie est conseillée pour améliorer le contrôle local de la tumeur (figure 2). Un schéma de longue durée de radiothérapie préopératoire combinée à une chimiothérapie basée sur le 5-fluorouracil [FU] (de préférence via perfusion continue) est préférable. Pour améliorer l'opérabilité, un intervalle de 6 à 8 semaines est conseillé entre la radiothérapie et l'intervention chirurgicale. Pour les patients présentant un risque faible à modéré de récidive locale (tiers moyen et supérieur et/ou cCRM > 0,2 cm), un schéma de courte durée de radiothérapie préopératoire constitue une solution alternative au schéma long. Les patients doivent alors être opérés dans la semaine qui suit la fin de la radiothérapie.

Quelle que soit la réponse clinique à la thérapie préopératoire, tous les patients atteints d'un cancer primaire du rectum présentant un risque opératoire acceptable doivent subir une résection radicale.

Pour les patients présentant une tumeur irrésécable du rectum, un schéma long de chimio-radiothérapie est conseillé pour faire régresser le stade tumoral.

Figure 2. Traitement néoadjuvant du cancer du rectum.



Chirurgie

La préparation pré- et périopératoire englobe les points suivants : préparation de l'intestin, prophylaxie de la thrombose (bas de compression graduelle et héparine à faible poids moléculaire administrée par voie sous-cutanée), prophylaxie antibiotique (dose préopératoire unique), préparation de la transfusion sanguine, discussion du risque de dysfonctionnement urogénital postopératoire (tumeurs dans le tiers moyen et inférieur), et informations préopératoires concernant les stomies au cas où une telle éventualité serait envisageable.

Le sphincter anal doit être préservé chaque fois que cela s'avère possible. Une excision mésorectale totale (TME) est conseillée pour les tumeurs dans le tiers moyen et inférieur du rectum, soit dans le cadre d'une proctectomie restauratrice, une procédure de Hartmann ou une résection abdominopérinéale (APR). Pour les tumeurs dans le tiers supérieur, une excision mésorectale partielle (PME) est conseillée. Avant l'opération (surtout pendant l'APR), la perforation du rectum ou la rupture de la tumeur doivent être évitées.

Au terme d'une proctectomie restauratrice et d'une TME, une poche, une coloplastie ou une anastomose coloanale latéroterminale doivent être envisagées pour améliorer le résultat fonctionnel et la qualité de vie. Une ouverture artificielle temporaire est à envisager en cas de fuite résultant de l'anastomose (certainement en cas d'anastomose infra-péritonéale après une TME).

Une excision locale ou une résection microchirurgicale endoscopique par voie transanale (TEMS) n'est pas un traitement standard pour les stades précoces du cancer du rectum. Ces techniques peuvent être conseillées pour les petites lésions uT1 (< 3 cm) avec la perspective d'un adénome villeux et de biopsies négatives. En raison du risque de métastases glandulaires et d'un contrôle réduit de la tumeur, toutes les lésions uT1 doivent subir une résection TME radicale chez les patients présentant un risque opératoire acceptable.

Dans le cas de tumeurs sténosantes, une exploration laparoscopique et la pose d'une ouverture artificielle de dérivation doivent être considérées avant le début d'un traitement néoadjuvant. Le stenting dans l'attente d'une chirurgie curative n'est pas conseillé.

Pathologie

La pièce de résection doit être livrée non ouverte au pathologiste dans les 2 à 3 heures suivant la résection. La topographie exacte de la tumeur doit être décrite. La qualité (complète, presque complète, incomplète) d'une excision mésorectale doit être évaluée sur l'échantillon non ouvert. Les paramètres suivants doivent être mesurés après fixation et section : le point le plus profond de l'invasion tumorale, la distance jusqu'à la surface circonférentielle la plus proche. Un minimum de 12 ganglions lymphatiques doit se trouver et être analysé dans la pièce de résection.

Le rapport pathologique sera standardisé et inclura toutes les données importantes du point de vue macroscopique et microscopique. Les résultats feront l'objet de discussions lors d'une concertation pluridisciplinaire avec le pathologiste, le chirurgien, le radiothérapeute, l'oncologue et le gastro-entérologue.

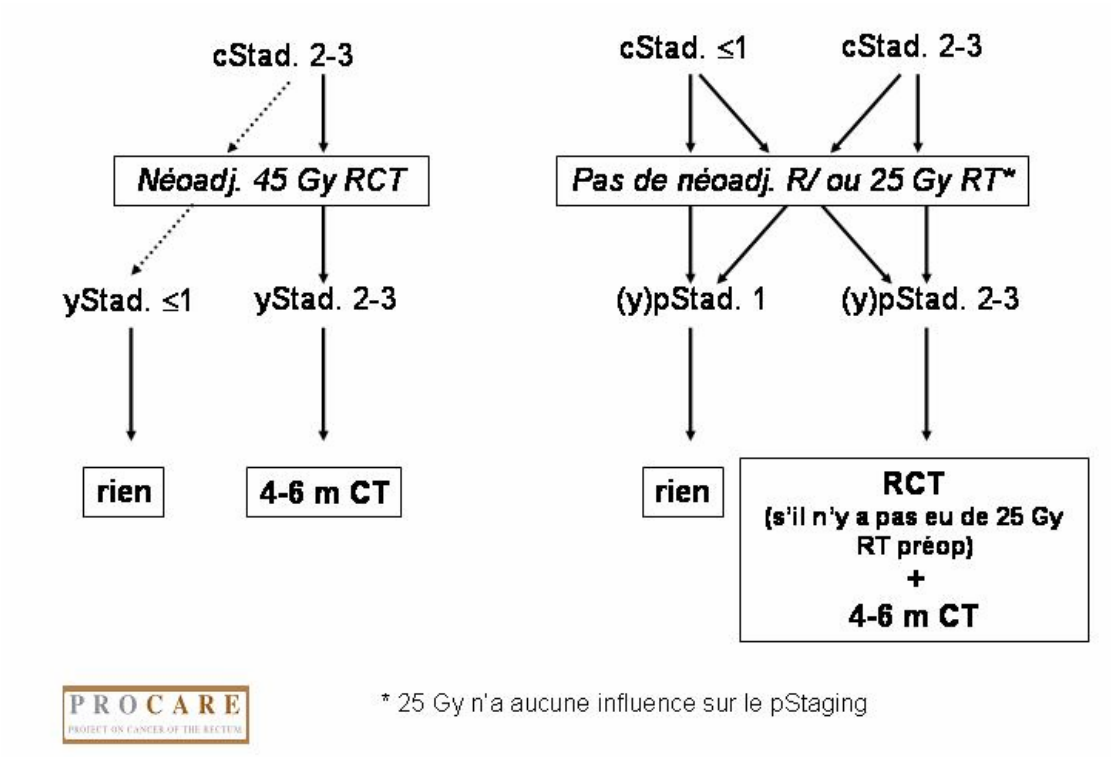
Chimio- et radiothérapie complémentaires : traitement adjuvant

Chez tous les patients atteints d'un cancer du rectum de stade pathologique II ou III, qui ont reçu une radiothérapie préopératoire sans chimiothérapie, une chimiothérapie adjuvante avec 5FU doit être envisagée (figure 3).

Chez les patients atteints d'un cancer du rectum de stade II ou III qui n'ont pas reçu de traitement néoadjuvant, la combinaison de radiothérapie adjuvante et de chimiothérapie est recommandée. C'est également le cas des patients qui ont subi d'une résection R1. Si la chimiothérapie contient du 5FU, une perfusion continue est plus efficace qu'une perfusion bolus (figure 3).

Le traitement adjuvant doit être lancé dans les 3 mois qui suivent la chirurgie.

Figure 3.Traitement adjuvant du cancer du rectum.



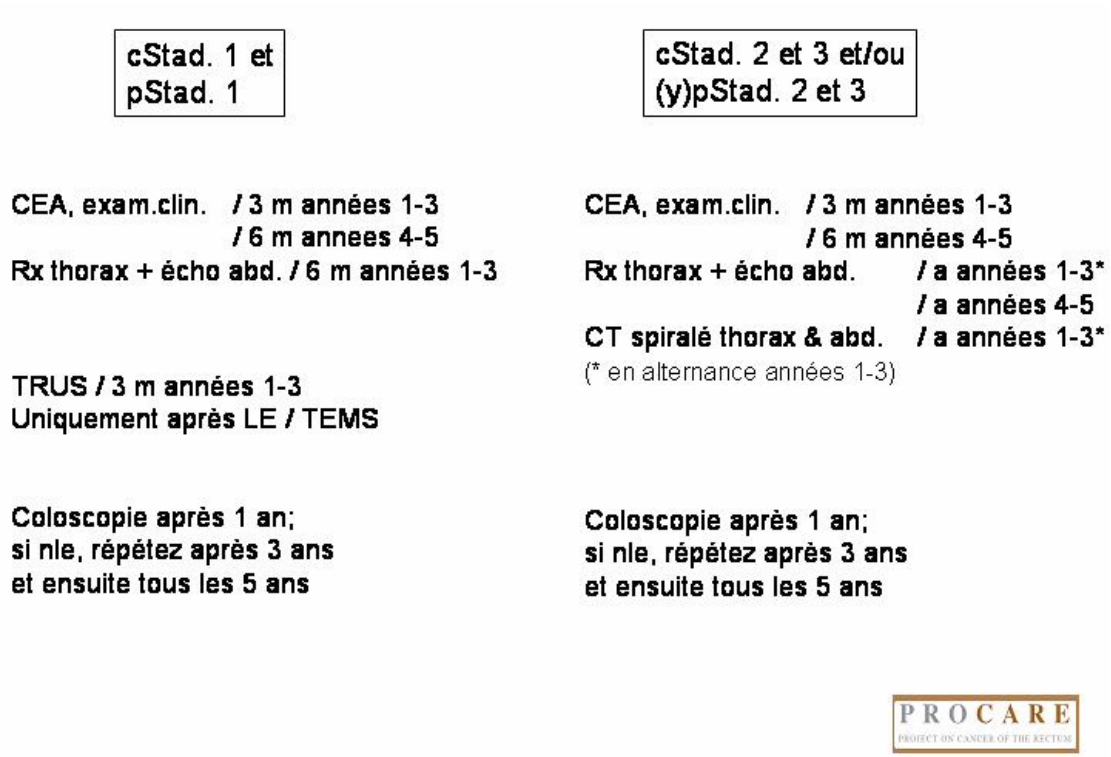
Follow-up à l'issue du traitement curatif

Chaque patient traité de manière curative pour un cancer du rectum fera l'objet d'un follow-up intensif (y compris examen clinique, anamnèse, détermination CEA, imagerie des poumons et du foie), pour autant qu'aucune autre comorbidité ne limite le pronostic. Un CT ou IRM du bassin est recommandé chez les patients présentant un risque élevé de récidive locale (stades II et III). Un TRUS est uniquement recommandé si l'on suppute une récidive locale ou lors du follow-up après une excision locale ou TEMS.

Chaque patient doit subir régulièrement une coloscopie totale. Une coloscopie est conseillée pendant la période péri-opératoire et un an après l'opération.

Les fréquences des examens principaux de follow-up sont indiquées à la figure 4.

Figure 4. Follow-up après un traitement curatif du cancer du rectum.



Traitement de la maladie métastasique

L'approche des patients présentant des métastases au foie et aux poumons doit être discutée lors de la concertation pluridisciplinaire. Dans les cas où la résection des métastases hépatiques synchrones ou métachrones est envisagée, la chimiothérapie péri-opératoire est conseillée.

En cas de métastases irrésécables et pour autant que le patient soit en bonne condition physique, la chimiothérapie est conseillée. Si le patient n'a pas encore reçu de radiothérapie, la combinaison de chimiothérapie et de radiothérapie peut être envisagée en cas de douleur pelvienne lors d'une récidive locale ou de cancer du rectum avancé.

CONCLUSION

- **La recommandation PROCARE offre un cadre aux associations professionnelles et au Collège d'Oncologie pour l'amélioration de la qualité des soins du cancer du rectum en Belgique.**
- **La dissémination et la mise en œuvre de cette recommandation sont prévues par le groupe de pilotage PROCARE, et auront lieu, entre autres, au travers d'une publication à grande échelle de la recommandation par le biais des associations professionnelles et scientifiques de médecins et autres spécialistes concernés dans le milieu hospitalier.**
- **Une actualisation de cette recommandation – après une pré-évaluation de la littérature – sera probablement requise en fonction de l'évolution des données probantes dans 3 à 5 ans.**
- **Un ensemble d'indicateurs de qualité sera développé et testé sur base de cette recommandation. Ces indicateurs seront utilisés pour le suivi de la mise en œuvre de la recommandation PROCARE et pour le suivi de la qualité des soins du cancer du rectum en Belgique.**

Scientific summary

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ABBREVIATIONS

5-FU	5-fluorouracil
95% CI	95 percent confidence interval
AGREE	Appraisal of Guidelines Research and Evaluation
AJCC	American Joint Committee on Cancer
APR	Abdomino-perineal resection of the rectum
ASA	American Association of Anaesthetists score
ASCO	American Society of Clinical Oncology
BED	Biological effective doses
CBC	Complete blood count
CBO	Dutch Institute for Healthcare Improvement
CCO	Cancer Care Ontario
CDSR	Cochrane database of systematic reviews
CEA	Carcinoembryonic antigen
CE-CT	Contrast-enhanced computed tomography
CPG	Clinical practice guideline
CRC	Colorectal cancer
CRM	Circumferential resection margin
CRT	Chemoradiation therapy
CT	Computed tomography
CTV	Clinical target volume
DCBE	Double contrast barium enema
DFS	Disease-free survival
DVT	Deep venous thrombosis
EBRT	External beam radiotherapy
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EUS	Endoscopic ultrasonography
FAP	Familial adenomatous polyposis
FBCR	Foundation Belgian Cancer Registry
FNCLCC	Fédération Nationale des Centres de Lutte Contre le Cancer
FUFA	Fluorouracil/folinic acid
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTV	Gross tumour volume
Gy	Gray
HCFU	1-hexylcarbamoyl-5-fluorouracil
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
HNPCC	Hereditary nonpolyposis colorectal cancer

HR	Hazard ratio
HR-MRI	High-resolution magnetic resonance imaging
IBD	Inflammatory bowel disease
ICD	International classification of diseases
ICRU	International Commission of Radiation Units
IMA	Intermutualistisch Agentschap
IMRT	Intensity-modulated radiotherapy
IOM	Institute of Medicine
LE	Local excision
LRR	Local recurrence rate
LV	Leucovorin
LVI	Lymphovascular invasion
MDT	Multidisciplinary team
MeSH	Medical Subject Headings
MKG/RCM	Minimale klinische gegevens/Résumé clinique minimum
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health
NQF	National Quality Forum
PET	Positron-emission tomography
PME	Partial mesorectal excision
PROCARE	PROject on CAncer of the Rectum
PTV	Planning target volumes
PVI	Protracted venous infusion
RC	Rectal cancer
RCRG	Rectal cancer regression grade
RCT	Randomised controlled trial
RR	Risk ratio
RT	Radiotherapy
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic review
TEMS	Transanal endoscopic microsurgical resection
TME	Total mesorectal excision
TRUS	Transrectal ultrasonography
UICC	International Union Against Cancer
US	Ultrasonography

1 GENERAL INTRODUCTION

In 2003, 1873 rectal cancers were registered in Belgium, based on code C-20 of the International Classification of Diseases (ICD-10) for rectum cancer below 16 cm from the anal verge [1]. The cumulative incidence of rectal cancer at 75 years of age can be estimated at 1,06% and 0,78% for males and females respectively. The risk of cancer strongly increases after 75 years of age. In view of the overall ageing of the population, an increasing incidence has to be expected [2].

The importance of quality care for cancer patients, including those with colorectal cancer, was highlighted by the Institute of Medicine (IOM) report on Ensuring Quality Cancer Care, which recommended that the quality of cancer care be monitored and measured using a core set of quality measures [3]. However, the IOM report also noted that specific quality measures for cancer care require further development and testing.

Although most regulatory agencies have not yet adopted quality measures for colorectal cancer surgery, quality measures for colorectal cancer care have been identified by the National Quality Forum (NQF) (http://www.qualityforum.org) and the American Society of Clinical Oncologists/National Comprehensive Cancer Network (http://www.asco.org/portal/site/ASCO). Although these groups used different methodologies, they developed similar groups of three to four measures each. The identification of these measures raises a number of issues. Can these measures be used for detailed programmatic quality improvement? Is this number of quality measures sufficient or representative for the topic of colorectal cancer surgery? If not, there are potential sources for additional quality indicators including clinical practice guidelines for colorectal cancer surgery. Guidelines for colon and rectal surgery generally address important issues such as anatomic definitions (e.g. colon versus rectum), staging, surgical techniques, and surgical documentation. However, it is important to note that the intended conceptual and clinical purposes of guidelines differ from those of quality measures [4]. Whereas clinical practice guidelines are useful for internal improvement and are open to clinical judgment, quality measures represent the most basic level of quality and thus are useful for both internal improvement and external reporting. They also provide specific indicators of the quality of care [5, 6].

The issue of variability in the outcome of treatment of rectal cancer is well known. This has also been confirmed in Belgium through several studies [7-9]. Although *surgery* remains the mainstay of treatment, many more disciplines play a major role in the outcome. Adequate *preoperative staging* is essential for the planning of treatment [10-12]. Several factors in *surgical technique* are important for long-term outcomes, including use of TME and avoidance of residual tumour as well as attention to lateral margins [13-15]. TNM guidelines also suggest that pN classification should usually be based on the *histological examination* of 12 or more regional lymph nodes [16]. Lymph node status is important to determine adjuvant therapy [17]. Examining a higher number of nodes increases the likelihood of proper staging and thus appropriate treatment. However, the number of lymph nodes examined not only varies by surgeon [18, 19]. Compliance with adjuvant therapy guidelines is also vital as they are based on research that shows survival benefits.

In other words, the multidisciplinary approach of rectal cancer care, including quality measurement and improvement, is essential. The concept of quality should include the entire structure and process of care from the preliminary assessment to the time of discharge and beyond. Although this is widely recognized, the vast majority of reports on the relation between quality and outcome of care focuses on surgical outcomes [20] mainly related to surgeon or hospital volume [21-27], level of surgical training [28-35], ethnicity or socio-economic status of the patients [36-40]. Those are in fact basically structural indicators that fail to take the whole process of rectal cancer care into account. Little performance measurement has been conducted in the area of oncology, and the number of initiatives developing indicators to measure the quality of cancer care taking the whole process into account are scarce [41, 42].

In view of published therapeutic variability and the reported benefit of national projects and trials, all Belgian scientific societies involved in the treatment of patients with rectal cancer at any stage, decided in December 2004 to set up a nationwide and multidisciplinary project PROCARE (PROject on CAncer of the REctum). The project aims to improve outcomes in patients with rectal cancer based on standardization through guidelines, implementation of these guidelines and quality assurance through registration and feedback.

A preliminary version of a guideline (CPG) was drafted in 2005, followed by workshops (surgery, pathology, radiotherapy, chemotherapy, radiology). A set for data entry of individual patients was constructed and voluntary registration in the PROCARE database at the Foundation Belgian Cancer Registry (FBCR) was started in 2006. Of the participating centres, all consecutive patients with rectal cancer (at any stage) are prospectively entered in this database. The PROCARE registration form entails all data relevant for any discipline on the staging and treatment of rectal cancer. Through feedback all centres will be able to position themselves in comparison to national (and possibly international) indicators and comparators. Above this, the opportunity will be given to call upon the expertise of accredited peers to analyze the results and support them in taking corrective actions if deemed useful or necessary.

In the present report, an updated version of the PROCARE CPG is presented. In a subsequent report, scheduled for 2008, a set of quality indicators will be pilot tested using the prospective PROCARE database and coupled data of the FBCR, the Minimal Clinical Data (MKG/RCM) and the Common Sickness Funds Agency (Intermutualistisch Agentschap, IMA). Also, an overview will be provided of international experiences with the measurement of quality indicators for rectal cancer.

2 UPDATED PROCARE GUIDELINES FOR THE TREATMENT OF RECTAL CANCER

2.1 INTRODUCTION

Although several CPGs related to rectal or colorectal cancer already exist, most deal with specific aspect(s) of the disease. In July 2006, the PROCARE steering group (see below) established a working group to update and improve the quality of its multidisciplinary guideline in collaboration with the KCE. The following aspects of the management of patients with rectal cancer are covered: diagnosis and pre-treatment staging, indications and type of neoadjuvant therapy, surgical aspects related to elective and emergency surgery as well as to radical and local excision, pathological examination of the resected specimen, indications and type of adjuvant therapy, follow-up after curative treatment, and therapeutic aspects of patients with metastatic rectal cancer. This CPG does not cover screening and prevention (including symptom criteria to guide referral to a specialist and surveillance of patient groups at high risk), anal cancer, rectal cancer in the context of hereditary syndromes, and genetic counselling.

This CPG is intended to be used by all professionals involved in the care of patients with rectal cancer. The recommendations are based on the best available evidence and are adopted by the multidisciplinary steering group of PROCARE. This CPG is endorsed by the Belgian Section for Colorectal Surgery (BSCRS), a section of the Royal Belgian Society for Surgery (RBSS) represented in the PROCARE steering group by Bertrand C, De Coninck D, Duinslaeger M, Kartheuser A, Penninckx F, Van de Stadt J and Vaneerdeweg W, the Belgian Society of Surgical Oncology (BSSO) represented by Claeys D, the Belgian Group for Endoscopic Surgery (BGES) represented by Burnon D, the Belgian Society of Pathology and Digestive Pathology Club represented by Ectors N, Jouret A and Sempoux C, the Belgian Society of Radiotherapy – Oncology (BSRO) represented by Haustermans K, Scalliet P and Spaas P, the Belgian Group Digestive Oncology (BGDO) represented by Laurent S, Polus M, Van Cutsem E and Van Laethem JL, the Belgian Society Medical Oncology (BSMO) represented by Bleiberg H, Humblet Y and Van Cutsem E , the Royal Belgian Society Radiology (RBSR) represented by Danse E, Op De Beeck B and Smeets P, the Vlaamse Vereniging Gastro-Enterologie (VVGE) represented by Cabooter M, Pattyn P and Peeters M, the Société Royale Belge Gastro-Entérologie (SRBGE) represented by Melange M, Rahier J and Van Laethem JL, the Belgian Society Endoscopy represented by Buset M, the Belgian Professional Surgical Association (BPSA) represented by Haeck L and Mansvelt B, and the FBCR represented by Van Eycken E. The CPG is also endorsed by the College of Oncology, represented by Scalliet P. Nationwide implementation of highly recommended CPGs is warranted in order to reduce diagnostic and therapeutic variability. However, the ultimate decision about the appropriateness of any specific procedure must be made by the physician in the context of an individual patient.

2.2 METHODOLOGY

2.2.1 General approach

The present CPG was developed by adapting (inter)national CPGs to the Belgian context [43]. This approach is currently being structured in a formal methodology by the ADAPTE group, an international group of guideline developers and researchers [43]. The ADAPTE methodology generally consists of three major phases:

Set-up Phase: Outlines the necessary tasks to be completed prior to beginning the adaptation process (e.g., identifying necessary skills and resources).

Adaptation Phase: Assists guideline developers in moving from selection of a topic to identification of specific clinical questions; searching for and retrieving guidelines; assessing the consistency of the evidence therein, their quality, currency, content and applicability; decision making around adaptation; and preparing the draft adapted guideline.

Finalization Phase: Guides guideline developers through getting feedback on the document from stakeholders who will be impacted by the guideline, consulting with the source developers of guidelines used in the adaptation process, establishing a process for review and updating of the adapted guideline and the process of creating a final document.

This stepwise approach is currently being validated in an evaluation study using the (qualitative and quantitative) information from multiple case studies.

2.2.2 Guideline development group composition

The working group delegated by PROCARE consisted of 1 radiologist (Etienne Danse), 2 radiation oncologists (Karin Haustermans, Sarah Roels), 3 surgeons (Daniël De Coninck, Daniël Leonard, Freddy Penninckx), 1 pathologist (Nadine Ectors), and 5 gastrointestinal oncologists (Jochen Decaestecker, Caroline De Vleeschouwer, Stéphanie Laurent, Marc Peeters, Eric Van Cutsem). Methodological and organizational support was provided by experts from the KCE (Gert Peeters, Joan Vlayen). All persons involved were editorially independent.

2.2.3 Clinical questions

Clinical search questions were formulated for all aspects of rectal cancer management based on the PICO principle (patient, intervention, comparison, outcome). The clinical practice guideline addresses the following clinical questions:

1. Diagnosis and staging:
    a. What method should be used for the detection of synchronous colonic lesions (polyps, cancer) in patients with rectal cancer?
    b. Are tumour markers useful staging tools in patients with rectal cancer?
    c. What imaging technique(s) can be recommended for the detection of metastatic disease in patients with rectal cancer?
    d. What imaging technique(s) can be recommended for the locoregional cTN staging of patients with rectal cancer?
        1. Can transrectal ultrasonography (TRUS) distinguish between a pT1 and a pT0 in patients with a benign looking, biopsy negative villous adenoma of the rectum?
        2. What imaging technique should be used to identify transmural invasion in a patient with rectal cancer?
        3. What imaging technique should be used to identify nodal involvement in patients with rectal cancer?
        4. When there is no agreement between the results of different staging tools, what result is to be considered in the decision for neoadjuvant treatment in patients with resectable rectal cancer?
        5. What imaging technique should be used to evaluate the cCRM (lateral margin) in patients with rectal cancer?
2. Neoadjuvant treatment:
    a. Can preoperative radiotherapy improve the outcome in patients with resectable rectal cancer compared to surgery alone?

b. Is preoperative chemoradiotherapy better than preoperative radiotherapy alone in the outcome of patients with resectable rectal cancer?

c. Is preoperative (chemo)radiotherapy better than postoperative chemoradiotherapy in the outcome of patients with resectable rectal cancer?

d. Is 5-FU continuous infusion superior to bolus 5-FU in combination with preoperative radiotherapy in the outcome of patients with resectable rectal cancer?

e. Is intravenous 5-FU better than oral 5-FU in the outcome of patients with resectable rectal cancer?

f. Is a long course of preoperative (chemo)radiation better than a short course of preoperative radiation in the outcome of patients with resectable rectal cancer?

g. Is a long treatment interval between preoperative (chemo)radiation and surgery better than a short interval in the outcome of patients with resectable rectal cancer?

h. Is there any benefit from alternative regimens of preoperative (chemo)radiotherapy compared to the standard regimen of (chemo)radiotherapy (short course or long course) in the outcome of patients with resectable rectal cancer? What is the role of brachytherapy/contact X-ray therapy in the preoperative treatment of resectable rectal cancer?

i. Is restaging after preoperative treatment useful in patients with resectable rectal cancer?

j. What is the role of (chemo)radiotherapy in patients with unresectable rectal cancer?

3. Surgery:

a. Can urinary or sexual dysfunction be avoided by good quality total mesorectal excision (TME) sphincter saving or abdominoperineal resection in rectal cancer patients for whom curative surgery is scheduled?

b. Can postoperative morbidity be reduced by preoperative bowel preparation in rectal cancer patients for whom curative surgery is scheduled?

c. Can postoperative deep venous thrombosis (DVT) be reduced by perioperative thromboprophylaxis in rectal cancer patients for whom curative surgery is scheduled?

d. Can postoperative septic complications be reduced by antibiotic prophylaxis in rectal cancer patients for whom curative surgery is scheduled?

e. Can preoperative stoma counselling, including stoma sitting, improve postoperative quality of life in rectal cancer patients for whom curative surgery is scheduled?

f. What is the impact of high versus low ligation of the inferior mesenteric artery on outcome in rectal cancer patients for whom curative surgery is scheduled?

g. What is the impact of lateral lymphatic dissection (iliac nodes) on outcome in rectal cancer patients for whom curative surgery is scheduled?

h. Can sphincter saving operation be performed for rectal cancer of the lower third of the rectum without compromising the (oncological and functional) outcome in patients for whom curative surgery is scheduled?

i. Can laparoscopic resection be performed without compromising the outcome in rectal cancer patients for whom curative surgery is scheduled?

j. Does inadvertent perforation of the rectum during surgery influence oncological outcome in rectal cancer patients for whom curative surgery is scheduled?

k. Does rectal stump wash-out prior to anastomosis decrease local recurrence in rectal cancer patients for whom curative surgery is scheduled?

l. Should a colonic pouch, a coloplasty or a straight coloanal anastomosis be performed for optimal functional outcome in rectal cancer patients for whom curative surgery is scheduled?

m. Should a temporary defunctioning stoma routinely or selectively be constructed at restorative proctectomy in order to reduce clinical leak rate in rectal cancer patients for whom curative surgery is scheduled?

n. Can a local resection or transanal endoscopic microsurgical resection be performed instead of a radical resection without compromising the outcome in rectal cancer patients for whom curative surgery is scheduled?

o. Is stenting an appropriate alternative for stoma construction as a bridge to radical surgery in case of stenosing rectal cancer?

p. Is stenting a valid alternative for stoma construction in a palliative setting?

4. Pathology

   a. How should a rectal cancer resection specimen be assessed macroscopically (with specific criteria for the evaluation of TME quality)?

   b. How should a rectal cancer resection specimen be assessed microscopically?

   c. What are the data to be reported by the pathologist?

5. Adjuvant treatment

   a. In patients who received neoadjuvant radio(chemo)therapy, when should adjuvant chemotherapy be considered?

   b. In patients who received neoadjuvant radio(chemo)therapy, what chemotherapy is to be recommended?

   c. In patients who did not receive neoadjuvant radio(chemo)therapy, when should adjuvant treatment be considered?

   d. In patients who did not receive neoadjuvant radio(chemo)therapy, what type of adjuvant treatment and regimen is to be recommended: radiotherapy, chemotherapy or combined radiochemotherapy?

6. Follow-up:

   a. Has follow-up an impact on survival and quality of life in patients curatively treated for rectal cancer?

b. What clinical, biochemical or technical investigations have to be done in terms of local recurrence, distant recurrence and resectability of recurrence in patients curatively treated for rectal cancer?

c. How frequently and for how long clinical, biochemical or technical investigations have to be done in terms of local recurrence, distant recurrence in patients curatively treated for rectal cancer?

7. Metastatic disease:

a. What diagnostic tools can be used to determine the resectability of a metastatic disease? What are the resectability criteria?

b. What is the best management in patients with resectable primary tumour and resectable metastases?

1. Should induction treatment be applied in resectable metastatic rectal cancer?

2. What course of radiotherapy should be considered (long versus short)?

3. What is the best management in patients with resectable primary tumour and resectable metastases: sequential or synchronous surgery?

4. What is the best management in patients with metachronous resectable metastases, neoadjuvant or adjuvant chemotherapy?

c. Is radical treatment of a resectable primary tumour useful in patients with non resectable metastases?

d. Does first-line chemotherapy alone as compared to observation have an impact on prognosis in patients with synchronous or metachronous non resectable metastases?

e. Does second-line chemotherapy alone as compared to observation have an impact on prognosis in patients with synchronous or metachronous non resectable metastases?

f. What combination(s) should be considered for first- and second line chemotherapy?

g. How to manage non-resectable metastatic rectal cancer?

h. What is the management of isolated peritoneal carcinomatosis?

2.2.4 Search for evidence

2.2.4.1 Clinical practice guidelines

The search for guidelines on all or any aspect of the management of rectal cancer was performed in August 2006 by 2 members of the PROCARE panel (Daniel Leonard, Freddy Penninckx).

The following sources were consulted:

- National Guideline Clearinghouse: www.guideline.gov (search terms “rectal neoplasms”, “rectal cancer”);
- Medline (via PubMed; free text words “rectal neoplasms”, “rectal cancer”, “colorectal neoplasms”, “colorectal cancer” and “guideline”; MeSH-terms "Rectal Neoplasms" and "Practice Guideline");
- Sites of specific oncology organisations:

- ASCO: http://www.asco.org/portal/site/ASCO/menuitem.56bbfed7341ace64e7cba5b4320041a0/?vgnextoid=1c09201eb61a7010VgnVCM100000ed730ad1RCRD;
- NCCN: http://www.nccn.org/;
- FNCLCC: http://www.fnclcc.fr/sor/structure/index-sorspecialistes.html;
- Cancer Care Ontario: http://www.cancercare.on.ca/;

All retrieved hits were screened by title and abstract (and full-text if required), taking into account the following inclusion and exclusion criteria:

- Inclusion criteria:
  - CPGs related to rectal or colorectal cancer;
  - Publication and/or update in 2001 or thereafter;
  - Publication in English, German, French or Dutch.
- Exclusion criteria: patient versions of CPGs on (colo)rectal cancer care; CPGs exclusively addressing population screening, primary prevention (including surveillance in patient groups at high risk), and/or genetic counselling; CPGs relating to anal cancer, familial adenomatous polyposis, hereditary non-polyposis colon cancer, and the Peutz-Jeghers syndrome.

2.2.4.2 Additional evidence

For each clinical question, the evidence – identified through the included CPGs – was updated by searching Medline (MeSH-term 'Rectal Neoplasms', not exploded; in combination with domain-specific MeSH-terms) and the Cochrane Database of Systematic Reviews (domain-specific free text words) from the search date of the CPG on.

The following inclusion criteria were applied:

- Design: systematic reviews, meta-analyses, randomized controlled trials (in the absence of these designs, also non-randomized controlled trials, cohort studies and/or case-control studies were included);
- Date of publication: 2001 – search date (August 2006)
- Language: English, French, German, Dutch.

Searches related to metastatic rectal cancer and palliative treatment were limited to meta-analyses and randomized controlled trails published in the last three years (11/2003 – 11/2006) in order to represent as much as possible the actual state of the art in this fastly evolving domain.

2.2.5 Quality appraisal

2.2.5.1 Clinical practice guidelines

The English version of the AGREE instrument (www.agreecollaboration.org) was used for the critical appraisal of the identified CPGs. All thirty-three guidelines were scored by 4 independent experts (see appendix for the scores per guideline). The score of the domain methodology was used as an important criterion in the final selection of guidelines.

At the end, 17 guidelines were included (see appendix).

2.2.5.2 Additional evidence

The quality of the retrieved systematic reviews and primary studies was assessed using the checklists of the Dutch Cochrane Centre (www.cochrane.nl).

2.2.6 Data extraction and summary

For each included CPG the following data were extracted: organisation, scope, search date, publication year, relevant recommendations with supporting evidence.

For each systematic review, the search date, publication year, included studies and main results were extracted. For RCTs and observational studies, the following data were extracted: publication year, study population, study intervention, and outcomes.

For each clinical question, the recommendations from the identified CPGs and the additional evidence were summarized in evidence tables. A level of evidence was assigned to each recommendation and additional study using the GRADE system (see appendix) [44].

2.2.7 Formulation of recommendations

Based on the retrieved evidence, a first draft of recommendations was prepared by each expert responsible for its subdiscipline. This first draft together with the evidence tables was circulated to the guideline development group, and discussed during several face-to-face meetings and by email. Based on these discussion meetings a second draft of recommendations was prepared. A grade of recommendation was assigned to each recommendation using the GRADE system (see appendix), including 'expert opinion' where applicable. The second draft was once more circulated to the guideline development group for final approval.

2.2.8 External review

On February 9th 2007, the second draft of recommendations was circulated by e-mail to the PROCARE steering group: Bertrand C, Burnon D, Claeys D, De Coninck D, Duinslaeger M, Kartheuser A, Pattyn P, Penninckx F, Van de Stadt J, Vaneerdeweg W (surgeons), Ectors N, Jouret An , Rahier J, Sempoux C (pathologists), Danse E, Op De Beeck B, Smeets P (radiologists); Haustermans K, Scalliet P, Spaas P (radiation oncologists); Haeck L, Mansvelt B(surgeons representing the Belgian Professional Association), Bleiberg H, Humblet Y, Laurent S, Peeters M, Polus M, Van Cutsem E, (oncologists), Buset M, Cabooter M, Melange M, Van Laethem JL (gastroenterologists); Van Eycken E (Foundation Belgian Cancer Registry) . All steering group members were invited to discuss these recommendations and their grades (including expert opinion) during a consensus meeting on February 22nd 2007. As a preparation of the meeting, all steering group members were asked to score each recommendation on a 5-point Likert-scale to indicate their agreement with the recommendation, with a score '1' indicating 'completely disagree', '2' indicating 'somewhat disagree', '3' indicating 'unsure', '4' indicating 'somewhat agree', and '5' indicating 'completely agree'. The scorers were also able to answer 'not applicable' in case they were not familiar with the underlying evidence. In case of disagreement with the recommendation (scores '1' or '2'), scientific evidence for the disagreement had to be provided. All received scores were anonymized and summarized into a mean score, standard deviation and % of 'agree'-scores (score '4' and '5'). Consensus agreement was defined as 60% 'agree'-scores.

Fifteen individual colleagues returned there scores, as well as one group of 4 specialists working at the same institution (considered as one score). The latter score was reported but not used to calculate the global score (see appendix). All disciplines were represented. A copy of the individual and global scores per recommendation as well as the comments was provided at the face-to-face meeting.

All recommendations reached >60% agreement. However, items that were commented and/or items that had one or more individual scores of '1' or '2' were discussed. Items with scores '4' and '5' were not discussed. During the meeting a consensus was reached on all recommendations. The summary of the discussion and the final version of the recommendations were attached to the minutes of the meeting, and sent to all members of the PROCARE steering committee. No requests for further adaptation(s) were made.

2.3 DEFINITIONS

2.3.1 The rectum

Tumours with their distal edge at 15 cm or less from the anal verge, as measured with a rigid rectosigmoidoscope, are classified as rectal. Distances from the anal verge measured with a flexible sigmoido- or colonoscopy are not always reliable.

The anal verge should be the usual landmark. Nonetheless, the distance between the lower edge of the tumour and the upper limit of the anal canal can be useful. The distance between the lower edge of the tumour and the anal verge is very important for stratification and because it influences the type of neoadjuvant treatment, the type of surgery and outcome.

For international benchmarking, rectal tumours can be categorized according to their distal edge as "low" (up to 5.0 cm above the anal verge), "mid" (from 5.1 till 10.0 cm above the anal verge) and "high" (from 10.1 – 15.0 cm above the anal verge) [45-47].

2.3.2 Staging

The TNM classification of tumours described by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) is used for tumour staging [16, 48]:

- cTNM: pre-treatment clinical classification, based on clinical examination, imaging, endoscopy, biopsy, surgical exploration or other;
- pTNM: post-surgical histopathological classification;
- ypTNM: post-surgical histopathological classification following preoperative therapy (radio- and/or chemotherapy).

2.3.2.1 Classification adapted from UICC and AJCC [16, 48]

T - Primary tumour

Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis*	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1°	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through muscularis propria into subserosa or into non-peritonealized perirectal tissues
T4	Tumour perforates visceral peritoneum or directly invades other organs or structures

- * The extent of mucosal cancer can be expressed in depth of invasion relative to the thickness of the mucosa: i.e. superficial third m1, middle third m2 and deepest third m3.
- ° The extent of submucosal cancer can be assessed absolutely (sm1 = less than 0.5 mm; sm2 = 0.5–1 mm; sm3 = more than 1 mm) or relatively (sm1 = superficial third; sm2 = middle third; sm3 = invasion reaching the deepest third) [49].

Tis – Primary tumour: invasion of lamina propria

m1	Superficial third of the mucosa
m2	Middle third of the mucosa
m3	Deepest third of the mucosa

T1 – Primary tumour: invasion of submucosa

sm1	Superficial third of the submucosa or invasion depth of less than 0.5 mm
sm2	Middle third of the submucosa or invasion depth of between 0.5 and 1 mm
sm3	Deepest third of the submucosa or invasion depth of more than 1 mm

N – Regional lymph nodes

Nx	Regional lymph nodes cannot be assessed. It should be mentioned if no nodes are found.
N0	No regional lymph node metastasis. The number of nodes examined should be mentioned
N1	Metastasis in 1 to 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes

For this project, extramural deposits of tumour that are not obviously within lymph nodes are regarded as discontinuous extensions of the main tumour if they measure <3 mm in diameter, but as lymph node involvement if they measure >3 mm in diameter [16].

M – Distant metastasis

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Pathological M staging can only be based on distant metastases that are submitted for histology. Pathologists will therefore only be able to use M1 (distant metastasis present) or Mx (distant metastases unknown).

2.3.2.2 TNM Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1 or T2	N0	M0
Stage II A	T3	N0	M0
Stage II B	T4	N0	M0
Stage III A	T1 or T2	N1	M0
Stage III B	T3 or T4	N1	M0
Stage III C	Any T	N2	M0
Stage IV	Any T	Any N	M1

Throughout this CPG TNM stage groupings will be referred to as cStage or (y)pStage. In contrast, c or (y)p T, N or M classifications will be referred to as c or (y)p T, N or M categories.

2.3.2.3 Histopathological grading

Gx	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

2.3.3 Extent of resection (R) and radial margin

Rx	Presence of residual tumour cannot be assessed
R0	No residual tumour
R1	Microscopic residual tumour
R2	Macroscopic residual tumour (including distant metastasis)

In case of rectal cancer the specimen should be labelled (inked) in the area of concern so that the specimen can be properly oriented and examined by the pathologist (cfr. infra). Resections should be categorised as follows, based on surgical and pathological data:

- R0: all gross disease is resected by en bloc resection with margins histologically free of disease. Non-en-bloc resection, positive radial margin i.e. <1 mm, positive proximal or distal bowel margins, residual lymph node disease, Nx, or even intraoperative inadvertent perforation of the tumour bearing bowel segment should not be considered R0. These patients are candidates for adjuvant radiochemotherapy or adjuvant chemotherapy in case preoperative radiotherapy has been given in order to reduce recurrence rates. Non-en-bloc resection and inadvertent perforation of the tumour-bearing segment during dissection must be documented in the surgical report.
- R1: all gross disease is resected by en bloc resection with margins histologically positive for disease or with cancer at less than 1 mm from a margin (or intraoperative perforation, cf. supra).
- R2: residual macroscopic disease, either locoregional or distant, remains unresected (thus including distant disease).

2.3.4 Other definitions related to surgery

- Emergency: immediate operation within 2 hours of admission or in conjunction with resuscitation
- Urgent: operation carried out within 24-hrs of admission.
- Scheduled: an early operation, but not immediately life-saving.
- Elective: operation at the time to suit both patient and surgeon.
- Hartmann's procedure: anterior resection of the rectum with closure of the distal resection margin and end colostomy.
- Partial mesorectal excision (PME): anterior resection with excision of part of the rectum and colorectal anastomosis. It is indicated for cancer of the rectosigmoid junction or the upper rectal third of the rectum. A partial mesorectal excision should be performed down to 5 cm below the lower edge of the tumour.
- Total mesorectal excision (TME): resection of the entire mesorectal fat, down to the levator plane, with respect of the circumferential mesorectal integrity (as proven by pathology) and preservation of the nerve plexuses and nerves surrounding the mesorectum. A TME is indicated for cancer in the mid and lower third of the rectum.
- Restorative proctectomy: sphincter-saving complete resection of the rectum with total mesorectal excision and colo-anal anastomosis (with or without pouch or coloplasty). It is indicated for tumours of the middle and lower third of the rectum.
- Abdomino-perineal excision of rectum (APR): excision of the whole rectum and anus with total mesorectal excision and terminal colostomy.

2.3.5 Definitions related to radiotherapy volume and International Commission of Radiation Units (ICRU) reference point

2.3.5.1 Clinical target volume (CTV)

The CTV is defined as the gross tumour volume (GTV) plus the areas at risk for microscopic tumour extension. The locoregional lymph nodes at risk for subclinical disease include the internal iliac lymph nodes, the presacral nodes and the mesorectal nodes for all patients. According to the level of the primary tumour and the involvement of other organs, additional lymph node regions become at risk. If there is involvement of adjacent organs or structures, nodal drainage can arise via the lymphatics of the involved organ. This involves the external iliac nodes when there is tumour extension to anterior organs (bladder/prostate/seminal vesicles/uterus) and the inguinal nodes if the anal canal and/or lower third of the vagina are involved.

If the patient is planned to undergo an abdominoperineal resection or the lesion is within 6 cm from the anal margin and the surgeon aims at a sphincter saving procedure, the perineal region, defined as the anal sphincter complex and the surrounding ischiorectal fossa, should be included in the CTV. Further information and the rationale behind these delineation guidelines have been published [50].

The CTV will be delineated using a CT scan in the treatment position.

2.3.5.2 Planning target volumes (PTV)

The PTV includes the CTV plus a margin for set-up error and/or patient/organ motion. Additional margins may be required based upon clinical judgment.

Radiation beams are designed to adequately cover the PTV. This applies for the conventional treatment technique as well as for the 3D conformal treatment technique or intensity modulated radiation. With the latter technique, planning CT can help to adjust the field borders to ensure adequate coverage of the PTV.

2.3.5.3 International Committee on Radiation Units (ICRU) reference point

The ICRU reference point is to be located in the central part of PTV (ICRU 50.62). The specification of the target dose is in terms of a dose to a point at or near the centre of target volume:

- For arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.
- Other or complex treatment arrangements: at the centre of the target area(s).

2.4 FINAL RECOMMENDATIONS

2.4.1 Access to treatment

No formal search was performed on this topic, but the following statements, derived from other guidelines seem to be appropriate and are to be recommended:

1. The interval between making a diagnosis of cancer and the start of treatment should be less than 4 weeks [51].
2. All patients should have the benefit of objective information [51].
3. The patient should be informed that rectal cancer treatment deserves a multidisciplinary approach. Rectal cancer should be treated by specialists (gastroenterologists, radiologists, surgeons, pathologists, radiation oncologists, oncologists) with appropriate training and experience [51]. The use of a single multidisciplinary document for informed consent is recommended when available.
4. The patient who develops colorectal cancer before the age of 45 years or who belongs to a family in which colorectal or associated cancers (endometrium,…) have occurred, must be informed about the risk for his/her relatives to develop the disease. The physician or specialist will insist on appropriate investigations and surveillance in the patient's family members [51, 52].

2.4.2 Diagnosis and staging

2.4.2.1 Diagnosis of rectal cancer

Digital rectal examination should be carried out in all patients. Since the treatment of rectal cancer is invasive, the diagnosis should be based on the results of pathologic examination of biopsies, which should be obtained from all rectal tumours before the start of any type of treatment, including endoscopic or local excision. Pre-treatment staging is important for prognosis and for decision-making on the type of neoadjuvant

treatment and surgical resection/reconstruction. Also, it provides accurate case-mix data for stratification. Therefore, it should be of the best possible accuracy.

The distance between the lower edge of the tumour and the anal verge is very important, since it co-determines the indication for neoadjuvant treatment, the type of surgery and outcome. It is recommended to determine this distance at rigid proctoscopy (rectoscopy). Colonoscopy (at withdrawal) could be an alternative, but cannot be recommended because it is not always reliable [52]. A tumour with its distal edge at 15 cm or less from the anal verge is classified as rectal (cfr. definitions). Although the anal verge should be the usual landmark, the distance between the lower edge of the tumour and the upper limit of the anal canal (anal sphincters) can also be useful. However, for international benchmarking the tumour location as referred to the anal verge is used.

For tumours within 10cm of the anal verge, the operating surgeon should record fixation, location of the tumour in relation to the anal sphincters and quadrant(s) occupied by the tumour[52].

1	**A tumour with its distal edge at 15 cm or less from the anal verge should be classified as rectal. A biopsy should be obtained from all rectal tumours before the start of any type of treatment (including endoscopic or local excision) (1C recommendation).**
2	**It is recommended that the distance from the lower edge of the tumour to the anal verge should always be determined by rigid proctoscopy (rectoscopy) before the start of neoadjuvant treatment. Colonoscopy (at withdrawal) is not always reliable for measurement of this distance (1C recommendation) [52].**
3	**A digital rectal examination should be performed in all patients with rectal cancer. The operating surgeon should record information on the fixity, location (longitudinal and circumferential) and proximity to the sphincters in patients with low or mid rectal tumours (1C recommendation) [52].**

2.4.2.2 Detection of simultaneous colonic lesions in patients with rectal cancer

Extensive use of preoperative colonoscopy is recommended in the evaluation of colorectal cancer, in order to promote detection of synchronous tumours, reduce the incidence of 'early metachronous' cancer and avoid malignant degeneration of adenomatous polyp. The incidence of a synchronous polyp has been reported to be 14 % and the incidence of a synchronous carcinoma 4 % [53]. The highest incidence is to be expected in patients with a genetic predisposition (e.g. FAP, HNPCC, …) or in patients at increased risk for colorectal cancer (e.g. IBD).

Studies on the detection of simultaneous colonic lesions in patients with rectal cancer are limited and most have been poorly reported [52, 54, 55]. There are no good data directly comparing the performance of double contrast barium enema (DCBE) with colonoscopy for the detection of synchronous colon polyps or cancer in patients with rectal cancer. Thus, the accuracy of both examination in the screening and evaluation of patients presenting with symptoms suggestive of colorectal cancer were used (extrapolation). It has to be taken into account that these data are mainly based on studies that used a different referral pattern for the two techniques. Moreover, no good reference standard is available to verify the results of the techniques. Indeed, it is important to realize that colonoscopy is not a perfect ('gold') reference test. Nevertheless, it is recommended that patients with rectal cancer should have a total colonoscopy with resection of concomitant polyps if possible [52, 54, 55]. However, if total colonoscopy is judged to be too risky or if colonoscopy is refused after informed consent, a high quality DCBE should be performed [52, 54, 55]. In emergency circumstances, when a total colonoscopy is not possible preoperatively, it should be performed before the start of adjuvant therapy or at least within 3-6 months postoperatively [52, 55]. According to the NICE guideline, the quality of colonoscopy should be recorded with the aim to achieve a high total colonoscopy rate with a low perforation risk [54].

Virtual CT or MRI based colonography are sensitive methods for the detection of colorectal cancer and/or large polyps, but not for polyps less than 10 mm in diameter [55]. Systematic reviews indicate that studies are poorly reported and that heterogeneity of sensitivity must raise concerns about consistency of performance and about technical variability [56, 57]. These issues must be resolved before virtual colonography can be advocated for routine use in the screening for synchronous colon cancer.

4 Patients with rectal cancer should have a total colonoscopy with resection of concomitant polyps if possible. If total colonoscopy is judged to be too risky or if colonoscopy is refused after informed consent, a high quality double contrast barium enema should be performed (1C recommendation) [52, 54, 55].

5 CT-colonography cannot (yet) be recommended for routine use. However, it may be useful in case of stenosing rectal cancer if the radiological equipment and expertise with audit is available (1C recommendation) [55-57].

6 In emergency circumstances, when a total colonoscopy is not possible preoperatively, it should be performed before the start of adjuvant therapy or at least within 3-6 months after surgery (1C recommendation) [52, 55].

7 The quality of colonoscopy should be recorded with the aim to achieve a high total colonoscopy rate with a low perforation risk (2C recommendation) [54].

2.4.2.3 Tumour markers in patients with rectal cancer

Lack of sensitivity and specificity preclude the use of any available serum marker for the early detection of colorectal cancer [52, 58]. However, pre-treatment carcinoembryonic antigen (CEA) levels have been related to cancer stage and survival (independent of pTN stage in nonmetastatic colorectal cancer). Significantly increased CEA levels may indicate the presence of metastatic disease, warranting further pre-treatment evaluation (e.g. using FDG PET or PET/CT scan).

8 The serum carcinoembryonic antigen (CEA) level should be determined in all patients before the start of any treatment (1B recommendation) [52, 58].

9 There is not enough evidence to recommend the routine use of other tumour markers (1B recommendation) [58].

2.4.2.4 Staging of rectal cancer

The TNM stage of a (colo)rectal cancer is a very important predictor of prognosis.

The aim of imaging techniques such as CT, MRI and PET is to detect hepatic and extra-hepatic metastatic disease. The recommendations presented below are mainly based on the French guidelines [59]. A recent meta-analysis of Bipat et al. included studies on CT, MRI and PET [60]. Per patient, PET was found to be the best technique. Per lesion MRI with intravenous injection of gadolinium had the best sensitivity. Nonetheless, spiral CE-CT (MSCT) is recommended for routine use. When contrast-CT can not be performed, MRI can be considered as a valid, even more accurate alternative. CT is to be combined with FDG-PET for the better staging of patients with potentially resectable metastatic disease.

All guidelines agree that patients with rectal cancer should have locoregional cTN staging [52, 54, 55]. Investigation with TRUS and MRI is recommended by most guidelines.

Polyps with/without dysplasia (T0 or Tis) do not infiltrate the submucosa, have virtually no risk of lymph node metastasis, and do not require full thickness excision of the rectal wall. However, the deep resection margin should be evaluable at pathology (one specimen) and microscopically negative (i.e. more than 1 mm margin). These lesions are usually small, although (very) large adenomas with focal invasion do occur.

Some endoscopic features (umbilication, non-elevation of the lesion after submucosal lifting) may be indicative of invasion. This setting requires accurate pre-treatment distinction between T1 versus T0 lesions. Until recently, a small cT1 rectal cancer with prognostically good pathological characteristics ('low risk') was generally considered an appropriate indication for full thickness local excision (LE, TEMS) (cfr. chapter 2.4.4 on surgery). Thus, pT0-T1 tumours have frequently been reported together in the past.

The aim was to distinguish T0-1 and T2 or more lesions. However, LE for pT1 has become controversial in view of significantly decreased local disease control after LE as compared with radical excision, except maybe for pT1sm1 [61-64]. TRUS is the best method to visualize the different layers of the rectal wall. In contrast with previous reports and opinions, T0 can be identified by TRUS with a high accuracy, but, higher frequency, higher resolution probes have to be used [65] Not only high-quality equipment but also highly-experienced examiners are essential in order to obtain valid US data. TRUS should preferentially be performed before or together with biopsy(ies) in order to avoid secondary effects potentially distording TRUS findings and interpretation.

Accurate identification of cStage II tumours (i.e. cT3-4N0M0), and cStage III tumours (i.e. cTanyN+M0) is relevant for the decision about neo-adjuvant radio(chemo)therapy (cfr. chapter 2.4.3 on neoadjuvant treatment). Overstaging of T2 lesions can occur because of peritumoral inflammatory reaction. Thus, it may be indicated to confirm the diagnosis of a cT3 lesion by a second morphologically oriented imaging modality. However, the relevance of differentiating a small T3 from a full T2 may be limited, as both are well away from the resection margin, except in the lower rectum. In the latter case, both tumour types receive neoadjuvant (chemo)radiation in most centres (cfr. infra).

Existing guidelines are mainly based on a systematic review performed by Kwok [66]. It was concluded that the performance of all imaging modalities (TRUS, CT and MRI) to distinguish between T3-4 and T1-2 are comparable. This was confirmed in the meta-analysis of Bipat [60]. However, TRUS is operator dependent, more difficult to perform for high rectal tumours and impossible in stenosing cancer. Also, it can not provide information on the depth of perirectal fat invasion and on the lateral tumour-free margin (cCRM). Therefore, MRI can be advocated as the single diagnostic tool able to provide these clinically important data in one session. CT induced much more understaging (hence potential undertreatment) than MRI. However, contrast enhanced multislice CT may be(come) a valid alternative. Also, UPSIO-MRI is still under investigation [67].

For clinical decision making, particularly related to neoadjuvant treatment, it is recommended to take into account the highest tumour and/or nodal category found by means of any imaging modality. However, no existing recommendations were found in guidelines, nor data in the recent literature. This recommendation has therefore to be regarded as expert opinion. In clinical practice, the 'fail safe' principle is usually applied. However, over-staging may result in over-treatment with its inherent complications. Thus, imaging should be of high quality. In order to avoid the harm of neoadjuvant treatment in small pT3 lesions with good CRM (i.e. located > 6 cm above the anal verge) it seems appropriate for decision making to take into account the result of the imaging modality with the lower T category for RC in the mid and upper third of the rectum if cN = 0 and cCRM not threatened. However, preoperative chemoradiation with an interval of 6-8 weeks to surgery results in about 20% of complete response (no viable tumour found in the resection specimen); this type of response as well as major tumour regression is reported to be related to improved outcome, including disease-free survival (DFS). These observations indicate that neoadjuvant treatment with the aim to downsize the tumour could be applied (at this time) in all except Stage I rectal cancer.

Transmural invasion (T3 or Stage II) and N+ (Stage III) are both related to increased local recurrence rate (LRR). N+ was found to have the most important effect on LRR despite TME surgery of good quality [45].

Therefore, it is appropriate to take into account the result of the imaging modality with the highest N category, although it must be admitted that cN-staging is less accurate than cT staging.

There is no evidence to support the routine performance of preoperative re-staging. However, in some selected patients, it may be considered (cfr. chapter 2.4.3 on neoadjuvant treatment).

10 All patients with rectal cancer should have imaging of abdomen and chest for the detection of metastatic disease before elective treatment (1B recommendation) [52, 55, 59, 68].

11 A combined thorax and abdomen/pelvis spiral contrast-enhanced CT is recommended for the detection of metastatic disease. If a contrast-enhanced CT is contra-indicated, a thorax spiral CT without contrast and a contrast-enhanced magnetic resonance imaging (MRI) of the liver can be performed (1B recommendation) [59, 60, 68].

12 FDG-PET/CT can be recommended as an additional investigation, especially for the further staging of patients with apparently resectable metastasis, because of its high overall accuracy (1B recommendation) [54, 59, 60].

13 In case of emergency surgery, staging for metastatic disease should be performed intra-operatively and postoperatively, if not done pre-operatively (1C recommendation) [54, 55].

14 If cTN staging will drive therapeutic decisions, transrectal ultrasonography, if performed by an experienced examiner, is recommended for all non-stenosing, resectable tumours in the middle and lower third of the rectum (1B recommendation) [52, 54, 55, 60, 68, 69].

15 If cTN staging will drive therapeutic decisions, any uT3/4 and any uN+ category should be confirmed by phased array high resolution magnetic resonance imaging (HR-MRI). The clinical circumferential resection margin should also be determined by HR-MRI (1B recommendation) [52, 54, 55, 67, 69, 70].

16 If cTN staging will drive therapeutic decisions, a phased array high resolution magnetic resonance imaging (HR-MRI) is recommended for all tumours in the upper third of the rectum (1C recommendation) [52, 54, 68, 71].

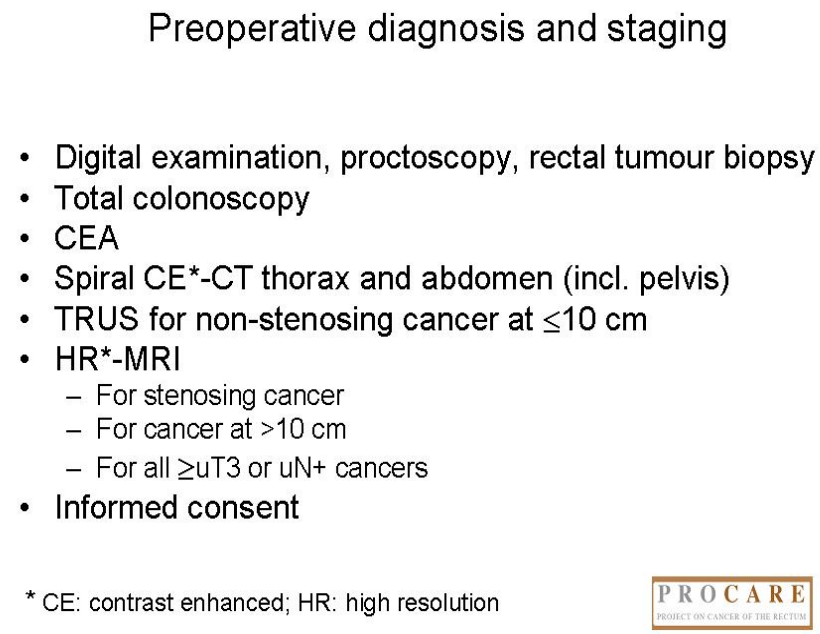
17 Diagnostic imaging and its accuracy should be discussed and audited by all (colo)rectal cancer multidisciplinary teams (1C recommendation) [68, 70, 72].

18 Early rectal cancer as well as benign looking, biopsy negative villous adenomata of the rectum should be assessed with transrectal ultrasonography by an experienced examiner before any type of treatment (including excisional biopsy). Audits of diagnostic performance should be performed (1C recommendation) [54, 65, 73].

19 For identification of transmural penetration (T3 or more) and node positivity it could be recommended to use 2 staging modalities (transrectal ultrasonography [TRUS] and high resolution magnetic resonance imaging [HR-MRI], or TRUS and multislice CT are recommended) (expert opinion).

20 For clinical decision making, particularly related to neoadjuvant treatment, it is recommended to take into account the highest tumour and/or nodal category found by means of any imaging modality (expert opinion).

Figure 1. Summary of staging recommendations.



2.4.3 Neoadjuvant treatment

2.4.3.1 Indications for neoadjuvant treatment in patients with resectable rectal cancer

Most of the evidence reported in CPGs comes from older studies, using suboptimal doses of RT, outmoded RT techniques to deliver RT to larger volumes of healthy tissue [54, 55, 74]. Moreover, TME was not the standard surgical technique for radical resection and pathology reports were not up to present standards (no reporting of circumferential resection margin (CRM), insufficient number of examined lymph nodes). Therefore, the generalization of these findings to current practice was considered questionable and less supportive for recommendations. In contrast, recent RCTs use adequate biological effective doses (BED) and 3 or 4 field techniques to deliver RT to smaller volumes of healthy tissue (cfr. infra). Moreover, standardization and quality control with respect to TME surgery and pathological examination were introduced in the past decade. Thus, these recommendations are mainly based on the evidence from more recent publications. However, it should be taken into account that surgical technique and use of adjuvant chemotherapy were not standardized in some recently published large RCTs [75, 76].

The PROCARE recommendations are mainly based on the results of the Dutch colorectal cancer study group trial [45, 77-80] and on the early results of the MRC-CR07 trial [47, 81], both well conducted high quality RCTs. When comparing preoperative radiotherapy with TME surgery alone, a short-course of preoperative radiotherapy improves local control [45, 77-80], but is associated with higher acute and late toxicity. Similarly, a long course of preoperative radiotherapy combined with 5-FU chemotherapy improves local control compared to surgery followed by postoperative chemoradiation [82].

No effect has been demonstrated on survival, and a long-course of preoperative radiotherapy slightly increases acute toxicity, but long-term toxicity is not affected.

Thus, both schedules result in an acceptable and comparable patient outcome, but a longer treatment scheme offers the advantage of tumour downstaging and of a reduced risk of late RT induced morbidity.

Data from univariate subgroup analyses in the Dutch Colorectal Cancer Group trial suggest an improved local control for middle and low seated tumours and for stage II and III RC, but not for high seated tumours and stage I and IV rectal cancer. However, a multivariate test for interaction between tumour stage and treatment group and between tumour level and treatment group was not significant, indicating that the local effect of preoperative RT is similar for all TNM stages and tumour levels [45, 77-80]. Results from the MRC CR07 trial confirm a benefit of short course RT on local control for all tumour levels and stages; results of local tumour control according to tumour level after a long course of chemoradiation followed by TME surgery have not been found [47, 81]. Although there is no strong evidence that patients with clinical stage I rectal cancer and patients with high seated (>10 cm) rectal cancer would not benefit from RT or chemoradiation before TME surgery, the absolute benefit in these cases is obviously more limited than in more advanced rectal cancer stages. If RT or chemoradiation is applied, it should be considered to outweigh (late) toxicity. In view of the absence of mesorectal fat in front of the distal third of the rectum, an exception has been made for full cT2 cancer in this location.

Acute or chronic toxicity may be associated with radio(chemo)therapy, such as enteritis, diarrhoea, bowel obstruction/stricture or perforation and fibrosis within the pelvis. Haematological and non-haematological adverse effects may occur when radiotherapy is combined with chemotherapy. Thus, patients to whom neoadjuvant radiotherapy or radiochemotherapy is proposed, should be informed of the potential harmful effects [55].

21 In order to improve local control, preoperative radiotherapy should be considered for resectable rectal cancer. It is recommended for all cStage II and cStage III lesions at any level. Radiotherapy is not recommended for cStage I lesions. However, it should be discussed in the multidisciplinary team for full cT2 lesions located ventrally in the lower third of the rectum because of the eccentric location of the rectum in the mesorectal fat (1A recommendation) [45, 47, 77-81].

22 Patients to whom neoadjuvant radiotherapy or radiochemotherapy is proposed, should be informed of the potential harmful effects (expert opinion).

2.4.3.2 Type of neoadjuvant treatment in patients with resectable rectal cancer

Two recent RCTs specifically addressing the value of additional chemotherapy to preoperative RT were found [75, 76]. Although both studies can be classified as high quality and provide the best evidence available at this time, TME was not the standard surgical procedure and pathology reports were not up to present standards; moreover, compliance to postoperative chemotherapy was poor in the EORTC trial [75]. These limitations can be of great consequence to the measured outcomes and should be taken into account in the interpretation of the results. The addition of 5-FU chemotherapy to a long course of preoperative radiotherapy was found to improve local control and to increase downsizing and downstaging compared to a long course of radiotherapy alone, resulting in more pathological complete responses. However, the rate of sphincter saving procedures was not influenced by the addition of chemotherapy. Preoperative chemoradiation resulted in higher acute grade 3/4 toxicity compared to RT alone, but postoperative complications were not significantly different. The incidence of late complications in the EORTC trial was not different in the 4 arms [75].

Whether preoperative (chemo)radiotherapy is better than postoperative chemoradiotherapy in patients with resectable rectal cancer can be answered with the findings of a German trial [82] comparing preoperative long course chemoradiation with a similar regimen given postoperatively. TME was performed but pathology quality assurance was not implemented. Both treatment modalities resulted in a similar overall and disease-free survival rate, but preoperative chemoradiation was associated with significantly less local recurrences and toxicity compared to postoperative chemoradiation. Also, compliance with preoperative CRT was remarkably better than with postoperative treatment.

Overall, no difference in sphincter saving procedures were observed; however, more patients who were intended to undergo an APR, received a sphincter sparing procedure after preoperative CRT, indicating that preoperative CRT can induce tumour shrinkage resulting in more sphincter saving operations in low-lying tumours.

Recommendations in existing guidelines [55] on the choice between continuous or bolus 5-FU in combination with preoperative radiotherapy are based on prospective cohort studies that have proven the safety and feasibility of the 3 following regimens: intermittently infused FUFA [83], continuous FU [84], or bolus FUFA [83, 85]. Bosset et al. reported the findings of 3 phase II studies, using the same preoperative CRT schedule, but different 5-FU doses [83]. The overall response rate was 87% for local disease, with 14,6% complete remissions among 41 macroscopically completely resected tumours. 29,3% of these tumours were downstaged. The authors concluded that a dose of 350 mg/m²/day was associated with an optimal toxicity and compliance profile. Another CT schedule, consisting of infusional 5-FU (300mg/m²/day) concomitant with each fraction of RT, was proven to be effective in the preoperative setting of locally advanced rectal cancer [85]. Rich et al. obtained an excellent local control of 96%. No RCTs were found that focussed on this subject in the preoperative setting. There is evidence from combined CRT in the postoperative setting in patients with high risk RC [86]. The authors found an increased time to relapse and improved survival with FU given by protracted venous infusion (PVI). The overall local control was good and slightly better in the PVI arm. Since these results only relate to postoperative CRT, the evidence is of a low quality level to support the use of a PVI in the preoperative setting.

There is low quality evidence from two small RCTs that continuous oral 5-FU is equivalent to bolus intravenous 5-FU in patients with T3N1 rectal cancer treated with preoperative chemoradiation [87, 88]. Overall, oral doxifluridine-based CRT showed comparable tumour response rates, local recurrences and systemic disease compared to IV FU-based CRT. Toxicity was not significantly increased, but more patients in the oral arm had a grade 1 or 2 diarrhoea [88]. Capecitabine was better tolerated than bolus intravenous 5-FU and was more effective in the promotion of down-staging [87]. Whether oral 5-FU is equivalent to a protracted infusion of 5-FU combined with preoperative radiotherapy remains unanswered.

Only one RCT directly compared a short course of preoperative RT with a long course of CRT in patients with low T3-4 rectal cancer [89]. Its results should be interpreted with caution because of several weaknesses. Although both regimens demonstrated comparable results in terms of patient outcome, the advantage of tumour regression and downstaging after a longer RT schedule combined with CT was confirmed. Despite these pronounced tumour responses after CRT, no more sphincter sparing procedures were performed in comparison with short-course RT. Acute RT toxicity was higher after CRT, postoperative complications were slightly lower in this group and late toxicity rates were comparable.

Similar downsizing and downstaging effects after a long course of CRT have been observed in other RCTs [75, 76]. On the contrary, short courses of preoperative RT followed by immediate surgery have failed to demonstrate any downstaging effect [45, 47].

If one considers the reported number of positive CRM in all these trials, it can be concluded that long-course preoperative RT with or without chemotherapy results in a positive CRM in about 4% to 7% of the patients [76, 89], compared to 10% to 18% [47, 78, 89] after a short-course of RT and 11% to 20% without any preoperative treatment [47, 78]. These findings indicate that a long course of CRT may induce a reduction in CRM positivity, which is an important prognostic factor for local control. An important finding in the Dutch trial is that the benefit for preoperative RT in terms of local control was only significant for patients with a wide (CRM > 2mm) and narrow margin (CRM 1-2 mm), but not for patients with a positive CRM (CRM ≤ 1mm) [78]. Thus, short course RT followed by TME surgery within one week should be reserved for cases where the CRM is certainly not at risk.

The results of trials comparing preoperative short course RT with CRT, both followed by surgery after an interval of 6-8 weeks, have to be awaited.

The role of a long interval (6 to 8 weeks) between preoperative RT and surgery versus a short interval (2 weeks) was investigated in patients with low lying T2-3 RC [90]. Waiting for 6 to 8 weeks after RT resulted in an increased tumour response rate and downstaging effect, with no detrimental effect on survival, local control, morbidity and functional outcome. The increased downstaging was associated with more complete pathologic responses and a higher rate of sphincter saving resections, but these differences were not significant. Similar downstaging effects were observed in other RCT after a long course of CRT followed by a 3-10 weeks interval [75, 76, 82, 89].

In all RCTs using a short course of RT (5x5Gy), patients are operated within a week after completion of RT [45, 47, 81]. Until now no evidence is available that a longer treatment interval is safe and effective after a short course of RT. Therefore, tumour resection within a week after short course RT is recommended.

The results of one RCT are in favour of the use of high-dose preoperative RT and delayed surgery to increase tumour response and sphincter preservation in patients with low rectal cancer [91]. Higher doses of preoperative RT, given through endo-cavitary contact X-ray as additional boost to external beam RT (EBRT), could safely be administered, without increasing acute side effects. However, this study included a small number of patients and some patients received additional brachytherapy. Other studies that have investigated the role of brachytherapy with higher doses of preoperative RT in RC patients have only been conducted in phase II setting [92]. Higher doses of preoperative EBRT did not yield similar results in several RCTs [93-98]. In the future, intensity-modulated RT (IMRT) and tomotherapy could be used for dose escalation without jeopardizing the surrounding normal tissues [99, 100].

No evidence was found in existing guidelines on the value of restaging after preoperative RT or CRT. Review of the recent literature indicates a poor agreement between locoregional clinical and pathologic staging after preoperative chemoradiation. The main problem is overstaging, but some patients, considered as complete responders on preoperative re-evaluation still harbour viable tumour cells in the resected specimen. However, the interval between completion of CRT and re-staging could have been too short to allow maximum tumour necrosis. Furthermore, the precise role of microscopic residual tumour cells after irradiation is not determined [101-103].

Evaluation of tumour response after neoadjuvant therapy could be useful to select patients for more limited surgical interventions, such as local excision or sphincter saving surgery in low lying RC. Patients with a complete clinical tumour response could even be selected for a policy of close observation, avoiding surgical morbidity and mortality. In the study by Habr-Gama et al. [104] overall and disease-free 5-year survival were comparable in patients with incomplete clinical response but ypT0 after preoperative CRT (5-FU, Leucovorin and 5040 cGy), treated with radical surgery, and in a highly selected group of patients with complete clinical response after neoadjuvant CRT followed by close observation and salvage surgery as indicated. At this time, evidence in favour of observation after complete clinical response to neoadjuvant chemoradiation is too weak and radical surgery remains the standard treatment for rectal cancer.

23 **A long-course of preoperative radiotherapy combined with some form of 5-FU based chemotherapy (pre- or postoperative) is recommended (1A recommendation) [75, 76, 105, 106].**

24 **A long course of preoperative radiotherapy (RT) (25 times 1.8 Gy combined with 5-FU based chemotherapy at a dose of 225 mg/m²/d during the RT) is recommended for patients with resectable Stage II or III rectal cancer, because it offers the advantage of tumour downsizing and downstaging (1A recommendation) [75, 76, 82, 89, 105-109].**

25 **Based on evidence from combined chemoradiation in the postoperative setting in patients with high risk rectal cancer, the use of a continuous infusion of FU during preoperative pelvic radiation is recommended (1C recommendation) [86].**

26 **The use of a protracted infusion of 5-FU during preoperative pelvic radiation is recommended for patients with Stage II-III rectal cancer. Oral 5-FU is an acceptable alternative to intravenous 5-FU during preoperative pelvic radiation (1B recommendation) [88].**

27 **A short-course of preoperative radiotherapy (RT) can be an alternative for a long course RT regimen in patients with a moderate or low risk for local recurrence (middle and high seated rectal cancer and/or circumferential resection margin [CRM] > 0,2 cm) (2A recommendation) [45, 47, 77-81].**

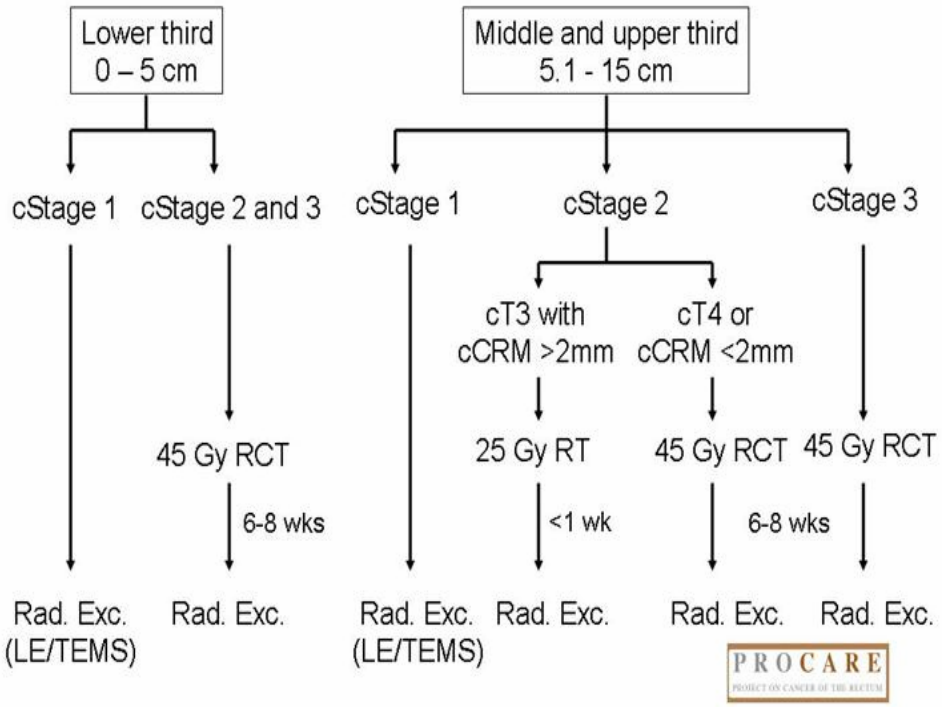
28 **A long course of radiotherapy (RT) (minimum 25 x 1,8Gy) should be followed by a long interval (6 to 8 weeks) to improve tumour resectability as a result of tumour downstaging. If a short course of RT (5 x 5Gy) is used, patients should be operated within a week after the end of RT (1A recommendation) [45, 47, 75-81, 89, 90, 105-109].**

29 **Higher doses of radiotherapy (> 28 x 1,8Gy) can be used in order to increase tumour response and tumour resectability, provided it is associated with an acceptable toxicity rate (2B recommendation) [91].**

30 **Brachytherapy/contact X-ray therapy is not a standard approach in resectable rectal cancer and the use should be limited to clinical trials and specialized centres with experience in these techniques (2B recommendation) [91].**

31 **Actually, clinical and imaging diagnostic tools, incl. digital rectal examination, proctoscopy with biopsies, transrectal ultrasonography (TRUS), CT, pelvic magnetic resonance imaging (MRI) and FDG-PET scan, do not allow a confident prediction of a histological complete response after chemoradiation. All acceptable-risk patients with a diagnosis of primary rectal cancer should undergo radical resection, regardless of their clinical response to preoperative therapy (1C recommendation) [110-128].**

Figure 2. Algorithm of neoadjuvant treatment for resectable rectal cancer.



2.4.3.3 Type of neoadjuvant treatment in patients with non-resectable rectal cancer

There is moderate quality of evidence that patients with unresectable RC could benefit from a long course of chemoradiation therapy to enhance tumour shrinkage and improve the chance of curative resection [129]. The total dose of radiation that can be administered depends on the volume and type of normal tissues within the irradiated volume and the drugs used in combination with the radiotherapy [130-134]. In case of insufficient shrinkage, chemoradiation can be followed by chemotherapy (cfr. chapter on palliative treatment).

32 For initially non-resectable rectal cancer, a long-course (at least 25 fractions of 1.8 Gy) of chemoradiation is recommended in order to obtain tumour downstaging and downsizing. The total dose of radiation that can be administered depends on the volume and type of normal tissues within the irradiated volume and the drugs used in combination with the radiotherapy. The target volume can be limited to the macroscopic tumour after the first 25 fractions of 1.8 Gy in order to allow a higher total dose of irradiation with optimal sparing of the normal surrounding tissues (2B recommendation) [129].

2.4.4 Surgical treatment

2.4.4.1 Preoperative preparation

All patients undergoing surgery for rectal cancer should give informed consent. The use of a single multidisciplinary document is recommended.

Functional impairment after surgical resection of rectal cancer is regularly reported, but the rate of urinary and/or sexual dysfunction is rarely documented. There is a trend of worse functional outcome for low tumours requiring very low anterior resection [80, 135, 136]. Even good quality surgery puts the patient at risk of poor functional outcome. Thus, patients should receive clear information prior to surgery [54]. Regarding general quality of life, a very small or no difference is found between low anterior resection and abdomino-perineal resection in several studies, one of them being a systematic review [55, 80, 137-141]. Further investigation is needed to better characterize the patient group at risk.

RCTs evaluating mechanical bowel preparation in elective colorectal surgery either show no benefit or a negative effect of mechanical bowel cleaning [54, 55, 142-145]. Studies have compared ethylene glycol mechanical bowel preparation with no preparation. Less is published about fleet enemas or low fibber diet prior to surgery. No definitive conclusions can be made for rectal cancer surgery, because patients with mid or low rectal cancer were either excluded or their number was very limited in all studies reported until now.

Patients undergoing oncological pelvic surgery are at risk for thromboembolic adverse events. Three Cochrane reviews suggest that the optimal prophylaxis in colorectal surgery is the combination of low-dose unfractionated heparin and compression stockings [54, 55, 146]. The unfractionated heparin can be replaced by low molecular weight heparin. These studies were not specifically related to rectal cancer patients.

Although the evidence is poor, preoperative stoma site marking and patient stoma education positively influence the outcome in terms of postoperative hospital stay, psychological adjustment [54, 55, 147]. They also reduce stoma related interventions.

Relevant blood loss during surgery, in particular cancer surgery, should be avoided as much as possible. Blood transfusion per se may not be a risk factor for poor prognosis after colorectal cancer surgery. However, the combination of perioperative blood transfusion and subsequent development of postoperative infectious complications may be associated with a poor prognosis [148]. Nonetheless, preparations for blood transfusion should be made in all patients undergoing surgery for rectal cancer, except when an individual patient refuses.

33 Before total mesorectal excision (TME) surgery, patients should be informed about the risk of urogenital dysfunction after resection for mid and low rectal cancer (1C recommendation) [54, 55, 80, 135-141].

34 In the absence of specific data, mechanical bowel preparation is recommended in the context of rectal cancer surgery, although no benefit was observed in the context of colon surgery (including anterior resection) (1C recommendation) [54, 55, 142-145].

35 Thromboembolism prophylaxis should be administered in the perioperative period of patients with rectal cancer using graduated compression stockings and appropriate doses of subcutaneous low molecular weight heparin, unless there is a specific contraindication (1B recommendation) [54, 55, 146].

36 All patients undergoing surgery for rectal cancer should have a single immediately preoperative dose of antibiotic prophylaxis. Several intravenous antibiotics appear to be effective, but only those covering aerobic and anaerobic germs should be used (1A recommendation) [54, 55].

37 Whenever (definitive or temporary) stoma construction is planned, preoperative counselling by a specialized nurse, and stoma site marking by the surgeon or by a specialized nurse under his/her supervision, are recommended (1B recommendation) [54, 55, 147].

38 Preparations for blood transfusion should be made in all patients undergoing surgery for rectal cancer except when an individual patient refuses (1C recommendation) [148].

2.4.4.2 Elective surgery for cure

Radical resection

The main emphasis of surgery is to obtain clear surgical margins yielding a curative R0 resection (no residual tumour). The term curative resection should be based on histological confirmation of complete excision of tumour with negative margins (proximal, distal and radial). The distal margin is the transsected full thickness edge and does not include the tissue donut from the endoluminal stapler if the tumour is at > 3 cm from the cut end of the main specimen.

The ideal distal tumour-free margin for rectal cancer is 2 cm or greater in the ex vivo unstretched specimen. For tumours of the distal rectum the minimally acceptable length of distal margin is 1 cm in the fresh anatomically restored ex vivo condition or in the equivalent fixed specimen. However, a 1 cm margin is to be considered narrow and therefore not advisable in patients with a large and poorly differentiated tumour. If the distal margin is 1 cm, a frozen tissue section of the distal margin nearest to the tumour or of the doughnut is recommendable [51, 54, 55].

Total mesorectal excision (TME) has become the standard procedure for mid and low rectal tumours. It results in better local control and increased disease-free survival [51, 54, 55, 149-154]. No high level evidence has been published and it is most unlikely that older techniques will be compared with total mesorectal excision. Bulow et al. published a case control study confirming the excellent results of TME versus classical anterior resection [149]. The implementation of TME also led to a decrease in the abdominoperineal resection rate. The proportion of rectal tumours treated with abdominoperineal rectum excision and definitive colostomy should be less than 30 %. If distal clearance of 1 cm can be achieved a low rectal cancer may be suitable for restorative proctectomy.

The decision to perform an abdominoperineal rectum excision needs to be made on the basis of clinical examination and imaging, before the start of neo-adjuvant treatment. If a surgeon has any doubt regarding the choice between abdominoperineal rectum excision and a sphincter saving operation, an experienced second opinion should be sought [51].

Vascular ligation is influenced by the type of resection and reconstruction that eventually has to be adapted to the anatomic and physiologic characteristics of the sigmoid colon and to the removal of a preoperatively irradiated sigmoid colon. Strong evidence is still missing about the level of vascular ligation at the inferior mesenteric artery and its role in oncological outcome. It is unclear whether high ligation of the inferior mesenteric artery with inferior mesenteric lymph node resection significantly decreases the stage migration phenomenon. If so, patients could have a better chance to benefit from adequate adjuvant therapy due to more correct staging. At present, it is advisable to ligate the inferior mesenteric artery at its origin in order to ensure best nodal staging [155, 156]. However, the hypogastric nerve should be preserved in the absence of macroscopically abnormal lymph nodes.

There is no consensus on the impact of lateral lymphatic dissection on outcome in rectal cancer patients for whom curative surgery is scheduled. The major drawback is the risk for damage to the pelvic nerves with urinary and sexual impairment [157]. Little evidence is available about lateral lymph node spread. The presence of invaded lymph nodes or micrometastasis has been confirmed especially in locally advanced pT3 and pT4 tumours. Prognosis in these cases, even after extended lateral lymph node dissection, remains poor. On the other hand, results in terms of local recurrence and survival improve after neoadjuvant radiotherapy and are not influenced by the extension of lymph node dissection.

No RCT has established the precise criteria to choose between sphincter saving or abdominoperineal resection. A higher rate of tumoral involvement of the resection margin and tumour break at APR may be avoidable by adapting the technique of "cylindrical" resection [153].

Rectal cancer in the upper third requires anterior resection with partial mesorectal excision. The latter assumptions are based on the good oncological results of large national audits published in the late nineties [51, 52, 54, 55]. No RCTs comparing these "new" techniques to classical blunt dissection have been conducted.

Efforts have been made to validate a laparoscopic approach in the treatment of colorectal cancer. Laparoscopic resection of rectal cancer was reported to be feasible and safe [54, 55, 158-164]. The resected specimen is oncologically comparable to that obtained at open surgery. The long-term oncological results of ongoing RCTs will determine the role of laparoscopy in rectal cancer surgery.

Intra-operative perforation of the tumour or the bowel wall increases local recurrence and decreases survival [153, 165-167]. It occurs more frequently during abdominoperineal rectum excision as compared with anterior resection.

Figure 3. Partial and total mesorectal excision as related to the location of rectal cancer

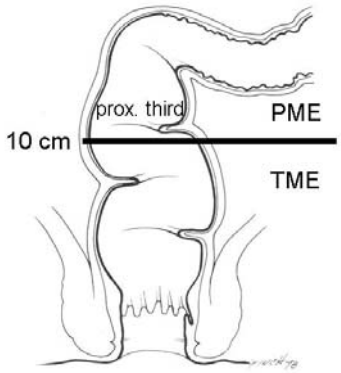
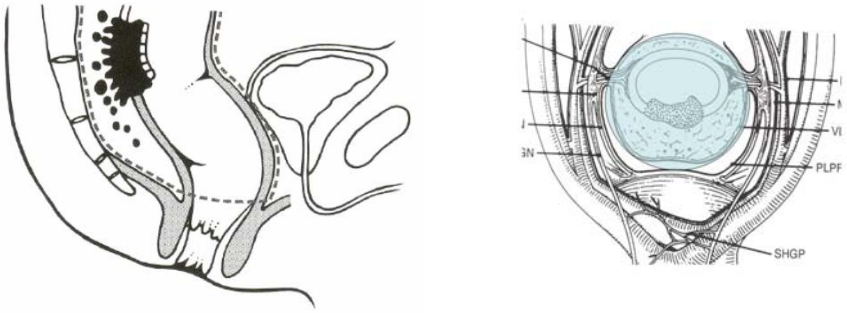


Figure 4. Total mesorectal excision for mid and low rectal cancer



Exfoliated neoplastic cells have been demonstrated in the rectal lumen or donuts after rectal stapling [168, 169]. The entrapment of neoplastic cells in the anastomosis may be one of the mechanisms of local recurrence. Some surgeons advocate mechanical elimination, while most use cytotoxic agents to kill these free intraluminal cancer cells before construction of an anastomosis. No strong evidence is available on the effect of rectal wash-out on oncological outcome.

Although an R0 with tumour free margins is the primary concern at sphincter saving surgery, the functional outcomes cannot be neglected. The functional outcome after colon pouch construction was found to be better than after straight colo-anal anastomosis in the early postoperative period [55, 170-172]. Differences reduced with longer follow-up. Results after colonic J-pouch, coloplasty or side-to-end anastomosis were comparable [173-178].

Anastomotic leakage, particularly in the absence of a defunctioning stoma, remains a strong prognostic factor of surgical mortality [55, 154, 179-181]. The effect of pelvic drainage on infraperitoneal anastomotic leakage is controversial, although the presence of a drain was not found to increase the risk of leakage [154, 182]. Construction of a defunctioning stoma limits the clinical consequences of anastomotic dehiscence after TME and low or very low re-anastomosis. Precise criteria indicating when a stoma should be constructed are absent, although the results of a recent RCT [183] suggest that a derivative stoma should be constructed systematically.

Each team should audit its clinical leak rate and adapt clinical practice as required. Ileostomy or colostomy can be used equally, but there is a tendency to use more ileostomies.

39 It is advisable to ligate the inferior mesenteric artery at its origin in order to ensure best nodal staging. However, the hypogastric nerve should be preserved in the absence of macroscopically abnormal lymph nodes (2C recommendation) [155, 156].

40 During rectal surgery for cancer, lateral lymph node dissection (iliac nodes) is not recommended in the absence of macroscopic disease (2A recommendation) [157].

41 Surgeons should aim, wherever possible and desirable, to preserve the anal sphincter. A total mesorectal excision should be performed for tumours in the middle and lower third of the rectum either as part of a restorative proctectomy, a Hartmann's procedure or an abdominoperineal resection. If distal clearance of 1 cm can be achieved, a low rectal cancer may be suitable for restorative proctectomy. For tumours in the upper rectum, the mesorectum should be divided no less than 5 cm below the lower margin of the tumour (partial mesorectal excision). Care should be taken to preserve the pelvic autonomic nerves and plexuses whenever possible (1B recommendation) [54, 55, 149-154].

42 Laparoscopic or laparoscopy-assisted surgery for rectal cancer should only be performed by experienced laparoscopic surgeons who have been properly trained, who enter their patients in a trial or audit their results very carefully in a multidisciplinary context (1A recommendation) [54, 55, 158-164].

43 During surgery for rectal cancer, great care should be taken to avoid rectal perforation or tumoral break, especially during abdominoperineal resection. The occurrence of intra-operative perforation as well as its location in relation to the tumour site should be reported in the surgical note (1B recommendation) [153, 165-167].

44 A rectal wash-out before re-anastomosis may prevent tumour cell implantation and is recommended, although strong evidence is lacking (2C recommendation) [168, 169].

45 After restorative proctectomy and total mesorectal excision, the formation of a colonic pouch, coloplasty or side-to-end colo-anal anastomosis should be considered to improve functional outcome and quality of life (1A recommendation) [55, 170-178].

46 A temporary defunctioning stoma should be considered each time the anastomosis is at risk for leakage. This is particularly true for an infra-peritoneal anastomosis after total mesorectal excision (1A recommendation) [55, 154, 179-184].

Local excision and transanal endoscopic microsurgical resection

Local excision (LE) and transanal endoscopic microsurgical resection (TEMS) are attractive because of their low morbidity and functional sequellae as compared with radical resection. However, care should be taken not to forget the primary goal of surgery, namely to cure the patient.

Local full thickness disk excision for cure classically has been restricted to low risk pT1 rectal cancer that are technically suitable for a transanal approach: located in the lower third of the rectum (or up to about 7 cm), uT1N0, less than 3 cm diameter; postoperative pT1, G1 or G2, no lymphovascular invasion and tumour free resection margins [55]. In contrast with LE, TEMS allows transluminal excision of a (small) rectal tumour at any level, i.e. up to 15 cm [185]. In case of unfavourable pathology findings or positive margins, more radical surgery with restorative proctectomy or APR should follow immediately [55].

However, local full thickness excision (i.e. LE and, by analogy, TEMS) for pT1 has become controversial in view of significantly decreased local disease control after full thickness local excision as compared with radical excision, except maybe for pT1sm1 [61-64].

Promising results have been reported after neoadjuvant treatment for early rectal cancer (up to T2) followed by TEMS [186]. TEMS could also be applied for resection and pathological examination of remaining scar tissue after clinical complete response following chemoradiation. The results of ongoing trials have to be awaited before any general recommendation on this novel approach can be made.

47 Local excision (LE) or transanal endoscopic microsurgical resection (TEMS) should not be a standard curative approach for 'early' rectal cancer outside a clinical trial. However, patients not fit for radical resection or on a palliative course can benefit from these techniques (1B recommendation) [55, 185, 186].

48 The role of local excision (LE) for pT1 rectal cancer has become controversial. LE or transanal endoscopic microsurgical resection (TEMS) can be recommended for small (< 3 cm diameter) uT1 lesions with the appearance of a villous adenoma and with negative biopsies, located below the peritoneal reflection of Douglas (7-9 cm above the anal verge in men, 5-7.5 cm in women). For pT1 sm 2 and sm 3 lesions, radical resection or adjuvant treatment should follow LE or TEMS in patients fit for further therapy. However, for pT1sm1 lesions close observation is a valid alternative (1C recommendation) [55, 61-64, 187].

49 In view of the risk of nodal metastasis and decreased disease control, all uT1 lesions located above the peritoneal reflection of Douglas deserve radical total mesorectal excision (TME) (with low risk of urogenital dysfunction) if the patient is fit for surgery (1C recommendation) [61-64, 187].

2.4.4.3 Emergency surgery

The quality of care in emergency circumstances should be as high as possible. Therefore, emergency surgery should be carried out by or under supervision of an experienced surgeon and anaesthetist. Stoma formation should be carried out in the patient's interests only. The overall mortality for emergency surgery should be less than 20%.

Intestinal obstruction in rectal cancer patients is rare. In first instance, a stoma should be constructed. Intraluminal stents have been proposed as an alternative. Originally, this endoscopic approach was developed for palliative settings (cfr. chapter 0 on palliative treatment). Many questions remain open on its use in a potentially curative setting. Although stenting as a bridge to curative surgery might be attractive, no recommendation can be made at this time.

50 In case of stenosing rectal cancer, a laparoscopic exploration and construction of a derivative stoma should be considered before starting neoadjuvant treatment. Stenting as a bridge to curative surgery can not yet be recommended. Stenting is a promising technique that should be considered for palliation in patients with extensive metastatic disease, who are not fit enough or who are unwilling to have a colostomy (2C recommendation) [54, 55].

2.4.5 Pathology

Assessment of the completeness of tumour resection and of the pathological stage of rectal cancer is important for prognosis, choice of additional treatment, and control of the quality of the surgical resection. Standardisation of data, the application of well-defined criteria, and the acceptance of an identical and unique staging system allow integration and comparison of data.

2.4.5.1 Macroscopic assessment

The mesorectal surface of a good resection specimen should be smooth without violation of the fat and with a good bulk to the mesorectum around the rectum. The distal margin should appear adequate without coning near the tumour. Defects should not be more than very superficial or 5 mm deep.

The quality of the mesorectum can be graded as complete, nearly complete, or incomplete [188]:

1. A complete mesorectum is an intact mesorectum with only minor irregularities on a smooth mesorectal surface. Defects are no deeper than 5 mm, and there is no coning toward the distal margin of the specimen. There is a smooth circumferential resection margin on slicing (cfr. infra).
2. A nearly complete mesorectum has a moderate bulk to the mesorectum, but irregularity of the mesorectal surface. Moderate coning of the specimen is allowed. At no site the muscularis propria is visible, with the exception of the insertion of the levator muscles.
3. An incomplete mesorectum has little bulk to the mesorectum with defects down onto the muscularis propria and/or very irregular circumferential resection margin on slicing (cfr. infra).

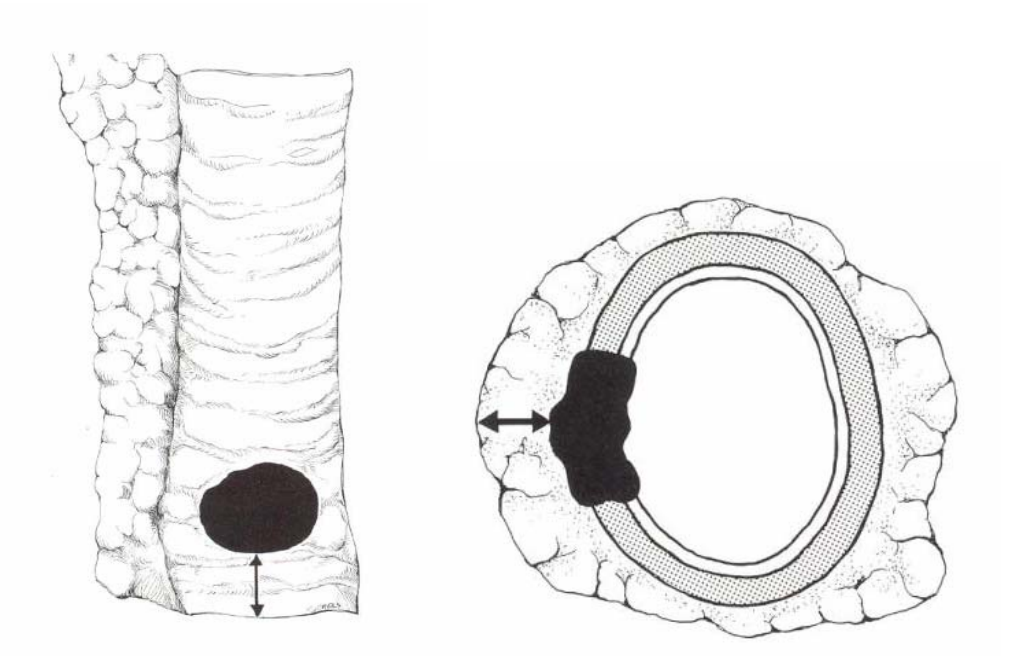
The distance between the deepest point of extension of the tumour and the surgical circumferential surface is defined as the circumferential margin, which needs to be assessed with great care. It can be measured by using a measurement device incorporated in the microscope itself (e.g. Vernier scale). Otherwise a sheet of graph paper that is photocopied onto a sheet of acetate and cut to size can be used.

51 The rectal cancer resection specimen should be delivered to the pathologist fresh (within 2 to 3 hours), unopened, and unpinned (except for local excision specimen; cf.). Administrative data, information on personal or family history, cTNM staging, the type of surgery performed, and preoperative treatment modalities should be provided by the surgeon (1C recommendation) [55, 188-193].

52 The resection specimen should be examined by the pathologist. It is mandatory to determine the exact topography of the tumour, also with reference to the serosal surface, i.e. above, at or below the peritoneal fold of Douglas. The quality of the mesorectal excision should be assessed on the unopened specimen and graded as complete, nearly complete or incomplete. Abdominoperineal rectal excision specimens require specific attention as the description of the quality of the total mesorectal excision is limited to the mesorectal surface; ideally, an abdomino-perineal resection specimen should have a monocylindrical shape. It is recommended to photograph the ventral and dorsal aspects of the specimen before inking or opening the specimen (1C recommendation) [55, 188-194].

53 After examination of the external surface, it should be inked before opening and fixating the specimen. After fixation, the specimen should be sectioned in parallel cuts of 3-4 mm perpendicular to the length of the bowel allowing to assess the deepest point of invasion and to measure the smallest distance between tumour extension and the nearest lateral surface. It is necessary to photograph the parallel cuts taken through the total mesorectal excision (TME) to document the quality of the surgical specimen and the extent of the disease and mandatory if large microscopic sections are not used. The deepest point of invasion should be sampled for microscopy, and the distance to the nearest circumferential surface should be measured and reported in mm. No distinction should be made between the various modes of involvement i.e. direct spread, involved lymph node, lymphatic or vascular spread (1C recommendation) [55, 188-195].

Figure 5. The distal and circumferential margin.



The distal margin The circumferential margin

2.4.5.2 *Sampling and microscopy*

After sectioning in parallel cuts of 3-4 mm perpendicular to the length of the bowel representative blocks will be taken from the resection specimen. These representative blocks should include at least three blocks from the tumour allowing assessment of the prognostic parameters especially the depth of invasion and the CRM [55, 194, 195]. The CRM is the most critical margin to be investigated. Most commonly the proximal and distal margin will be situated at a certain distance and may not have to be sampled. Ideally, samples should be fixed in formol, i.e. optimal trade-off between quality of fixation (and thus quality of histological features) on the one hand and the possibility of performing additional tests (immunohistochemistry, molecular pathology) on the other hand [194]. Other lesions should be sampled too.

In addition to the depth of invasion and the CRM, great care should be given to the sampling of lymph nodes [51, 55, 194, 196]. Increasing node yields increase numbers of positive lymph nodes. The pathologist should find as many lymph nodes as possible. The median number found is an indication of the quality of the pathological examination. Ideally, it should exceed 12 lymph nodes. The number of lymph nodes retrieved mainly depends on the effort of the pathologist. The lymph nodes should be retrieved by careful dissection, which is time-consuming. Alternative techniques, such as micro-dissection and flat clearance, are not recommended [194]. Under certain circumstances, it may however be difficult to find numerous lymph nodes in rectum resections, in particular after preoperative radio-chemotherapy.

54

54.1 **The number of blocks to be taken from the tumour is 3 at minimum (1C recommendation) [55, 194, 195].**

54.2 **One block at least should include the transition from the surrounding 'normal' mucosa to the tumour and at least one other should include the deepest point of invasion (1C recommendation) [55, 188-195].**

54.3 **Proximal and distal section margins do not have to be embedded if the tumour is situated at a distance of more than 3 cm from these margins. If the tumour is close to a margin, it is recommended to sample this margin and to demonstrate the relationship to the tumour by perpendicular sections. Biopsies have to be taken to assess the circumferential (radial, lateral) margin (1C recommendation) [16, 55, 188-193, 197].**

55 **Ideally, samples should be fixed in formol in order to allow additional molecular pathological examination. Frozen preserved biopsy samples may be important, especially if there are clinical arguments for hereditary nonpolyposis colorectal cancer (expert opinion) [194].**

56 **Associated lesions (polyps, inflammatory bowel disease [IBD], …) have to be sampled. In polyposis cases, a reasonable number of biopsies should be taken as well as the (proximal and distal) section margins. Proximal and distal section margins should also be embedded in IBD cases (expert opinion) [194].**

57

57.1 **All lymph nodes included in a resection specimen are considered to be regional. Distinction between paratumoral nodes and others i.e. local vs. regional lymph nodes is not requested. The number of lymph nodes analysed is important. At least 12 lymph nodes should be found and embedded. The numbers of lymph nodes retrieved depends mainly on the effort of the pathologist (1B recommendation) [55, 194, 196, 198, 199]. The number of positive lymph nodes relates to the number investigated. When less than 8 lymph nodes have been analysed, the proportion of cancers with lymph node involvement is underestimated (1C recommendation) [194, 196, 199]. However, it may be difficult to find numerous lymph nodes in rectum resections, in particular after preoperative radio-chemotherapy (1C recommendation) [194, 199] .**

57.2 **There is insufficient scientific evidence to recommend micro-dissection techniques or fat clearance (expert opinion) [194].**

57.3 **Extra-regional lymph nodes are classified as metastases and should be embedded and described separately (1C recommendation) [194].**

2.4.5.3 *The pathology report*

Histologic type according to the WHO classification:

- Adenocarcinoma: the histological grade should be mentioned either in a four or three-tiers system as well (G1), moderately (G2), poorly differentiated (G3) and undifferentiated (G4), or in a two-tiers system as low (G1,G2) grade and high (G3, G4) grade. The high grade corresponds to less than 50% of glandular structures of the surface analysed.
- Mucinous carcinoma (colloid carcinoma): a tumour composed of at least 50% of this type of proliferation. It is considered as poorly differentiated adenocarcinoma.
- Signet ring cell carcinoma: a tumour composed of at least 50% of this type of proliferation. It is also considered as poorly differentiated adenocarcinoma.
- Adenosquamous or squamous carcinoma.
- Small cell carcinoma.
- Medullary carcinoma: is considered as undifferentiated carcinoma
- Undifferentiated carcinoma (G4): corresponds to less than 5% of glandular structures of the surface analysed.

The depth of invasion should be described in function of the anatomical structures i.e. mucosa, submucosa, muscularis propria, subserosa, serosa and translated into the new TNM classification.

- Tx and To: primary tumour cannot be assessed (Tx). No evidence of primary tumour (T0).
- Tis: carcinoma in situ includes cancer cells confined within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa. The term 'high grade dysplasia' and 'severe dysplasia' may be used as synonyms for intraepithelial (in situ) carcinoma.
- T1: tumour invades submucosa
- T2: tumour invades muscularis propria without breaching
- T3: tumour invades through the muscularis propria into the subserosa, or into the non-peritonealised pericolic and perirectal tissues. The subserosa corresponds to the adipous connective tissue situated in between the outer surface of the muscularis propria and the mesothelial lining.
- T4: tumour directly invades other organs or structures, and/or perforates the visceral peritoneum. "Direct invasion" in T4 includes invasion of other segments of the colorectum by way of the serosa. Tumour that is adherent to other organs or structures, macroscopically, is classified cT4. However if no tumour is present in the adhesion, microscopically, the classification should be pT3.

Note: The 3-mm rule was introduced in TNM5. This rule stated that any mesorectal tumour deposit 3 mm in size or greater should be thought of as an involved lymph node. Any deposit smaller than 3 mm in diameter should be included in the pT. In the current edition of the TNM staging system (TNM6), the 3-mm rule has been withdrawn and the definitions of lymph-node and venous invasion revised. TNM6 states that smooth metastatic nodules in the perirectal fat should be considered as lymph-node metastases and should, therefore, be staged in the N category. Although TNM5 contains the controversial 3-mm rule that seems to lack an evidence base, this rule does at least have the advantage of being quantitative and, therefore, reproducible. Thus, it has been advocated to stick to the 3-mm rule [198].

Different systems have been developed and used to describe and to quantify regression of colorectal cancer after (chemo)radiation (ypTNM):

- the Rectal Cancer Regression Grade (RCRG) [200]. This system comprises three grades: RCRG 1 indicates "good" radioresponsiveness where the tumour is either sterilized or only microscopic foci of adenocarcinoma remain. RCRG 2 reflects marked fibrosis but with macroscopic tumour still present. RCRG 3 indicates a "poor" response with little or no fibrosis in the presence of abundant macroscopic tumour.
- the modified Mandard classification system which has been developed for oesophageal cancer initially [201]; this system uses 5 grades ranging from TRG1 (no tumour cells) to TRGR5 (no regression).
- the Dworak classification [202]; this system also uses 5 grades ranging from no evidence of any treatment effect to a complete response with no viable tumour identified. The following are characteristics of each grade:
    - GR0 or no regression;
    - GR1 or minor regression: dominant tumour mass with obvious fibrosis and/or vasculopathy (dominant tumour mass with obvious fibrosis in 25% or less of the tumour mass);
    - GR2 or moderate regression: dominantly fibrotic changes with few tumour cells or groups easy to find (dominant tumour mass with obvious fibrosis in 26% to 50% of the tumour mass);
    - GR3 or good regression: very few tumour cells (difficult to find microscopically) in fibrotic tissue with or without mucous substance (dominant fibrosis outgrowing the tumour mass; i.e., more than 50% tumour regression);
    - GR4 or total regression: no tumour cells (no viable tumour cells, only fibrotic mass).

Problems relating to the finding of mucin pools with and especially without neoplastic epithelium are described. Tumour related mucin pools represent areas throughout the bowel wall that were previously occupied by tumour and could still be depending on sampling.

58 The pathology report should be standardised, providing all important macroscopic and microscopic data.

58.1 **Mandatory macroscopic data are:**

58.1.1 **the measurements of the resection specimen, including those of adjacent structures and organs;**

58.1.2 **the localisation of the tumour in relationship to the peritoneal lining;**

58.1.3 **the proximal, distal and lateral (circumferential, radial) section margins; if the specimen can not be oriented, the section margins are described as the closest and most distant margin;**

58.1.4 **the maximal diameter of the tumour;**

58.1.5 **the macroscopic appearance of the lesion should be described as protruding/exophytic, ulcerating, infiltrating, flat;**

58.1.6 **the presence of perforation at the tumour site; the presence of peritoneal deposits.**

58.1.7 **the presence of associated lesions, e.g. synchronic cancers, polyps and chronic idiopathic inflammatory bowel disease;**

(1C recommendation) [55, 194].

58.2 **Mandatory microscopic data are:**

58.2.1 **the histological type;**

58.2.2 **the histologic grade of adenocarcinoma, using either a four or three-tiers system, i.e. well (G1), moderately(G2), poorly differentiated (G3) and undifferentiated (G4), or a two-tiers system, i.e. low (G1,G2) grade and high (G3, G4) grade; mucinous carcinoma (colloid carcinoma) and signet ring cell carcinoma are to be considered as poorly differentiated adenocarcinoma;**

58.2.3 **the depth of invasion should be described and translated into the new pTNM classification;**

58.2.4 **after irradiation (ypTNM), the grade of tumour regression should be described so that any of the existing grading systems can be applied; although scientific evidence is limited, the use of the 5-tierce Dworak classification system is recommended [200-202];**

58.2.5 **resection margins; a margin of <1 mm is considered positive;**

58.2.6 **the total number of examined and the number of involved regional lymph nodes; there is insufficient evidence to recommend semi-serial sectioning of lymph nodes or to perform immunohistochemical stains; it is recommended to report extramural tumour deposits as lymph node involvement if they measure >3 mm in diameter;**

58.2.7 **extramural deposits of tumour; defined as deposits that are not obviously within lymph nodes if they measure <3 mm in diameter;**

58.2.8 **the presence of vascular invasion into extramural veins;**

58.2.9 **the presence of perineural and/or lymphatic and/or intramural vascular invasion may be mentioned;**

58.2.10 **distant metastasis: the report should mention M1 if microscopic examination of a sample confirms the presence of a metastasis. This finding can relate to a liver biopsy or non-regional lymph nodes or peritoneal carcinomatous deposits;**

58.2.11 **cytological examination of peritoneal fluid revealing tumour cells equals M1. If the existence of distant metastasis can not be assessed, one should indicate pMx;**

(1B recommendation) [16, 52, 54, 55, 194-196, 198, 203-205].

58.3 **It is recommended to use a check-list (cfr. appendix) [54, 55, 194, 203].**

59 The results of the pathology report should be discussed in a multidisciplinary meeting, involving the pathologist, surgeon, radiologist, radiotherapist, oncologist and gastroenterologist in order to determine further treatment (1C recommendation) [194].

2.4.6 Adjuvant therapy

2.4.6.1 Adjuvant chemotherapy in patients with clinical stage II-III rectal cancer who did receive neoadjuvant (chemo)radiotherapy

From former clinical practice guidelines [55] it is known that chemotherapy during six months is prolonging survival in stage III patients. Whether adjuvant chemotherapy is prolonging survival in stage II patients is not known. The recent EORTC 22921 trial showed no survival benefit of adding chemotherapy (a regimen that actually is no more optimal) to radiotherapy for stage II and III patients, but chemotherapy, regardless of whether administered before or after surgery had a significant benefit on local control [75]. In this trial postoperative chemotherapy was given during four months. Although this trial is a RCT, there were several shortcomings (TME was not the standard surgical procedure, pathology reports were not up to present standards, e.g. no CRM assessment, and there was a poor compliance of postoperative chemotherapy).

Two clinical practice guidelines concluded that FUFA given by IV injection for 5 days every 4 weeks for 6 cycles is the regimen for which the most evidence is available and that it is clearly effective in prolonging survival in patients with stage III [55, 206].

The most recent guideline also concluded that infusional FUFA or capecitabine is more effective and less toxic, based on retrospective analysis and based on extrapolation of evidence from patients with advanced disease [55]. Two new European studies could not give new relevant information on this topic [207, 208]. There were also three new Japanese studies showing no benefit of adding one year oral 1-hexylcarbamoyl-5-fluorouracil (HCFU) to induction 5-FU [209], low dose (333 mg/m2 day 1-3 and day 6-8) versus high dose (1000 mg/m2 day 1-3 and day 6-8) induction therapy with 5-FU [210] or adding immunotherapy [211].

There is no direct evidence supporting the indication for adjuvant chemotherapy in Stage III rectal cancer patients treated with neoadjuvant chemoradiotherapy [55, 206]. However, the evidence from studies with adjuvant chemotherapy in patients with a resected stage III rectal cancer without neoadjuvant treatment suggests that further chemotherapy with 5-FU can be administered for at least 4 months (given that preoperatively already two months of chemotherapy was given). The new EORTC 22921 trial failed to show a benefit for postoperative chemotherapy if a patient already received neoadjuvant chemoradiotherapy [75], but again a regimen was used that actually is no more considered to be optimal. As there is no proven benefit of chemotherapy in patients with stage I or II disease, postoperative chemotherapy may not be indicated in case of a pathologic complete response.

Cohort studies and one published meta-analysis suggest a small but not significant survival benefit for portal vein infusional chemotherapy with 5-FU [55, 206]. The recent AXIS study could only demonstrate a benefit for curatively resected colon cancer patients (in subgroup analysis) and not for rectal cancer patients [212].

There is no direct evidence supporting the need to start adjuvant therapy within 3 months after surgery. This is a rather general recommendation based on expert opinion, in analogy with the treatment of other types of cancer and based on the oncologic rationale that adjuvant therapy is able to treat micrometastatic disease at a time when tumour burden is at a minimum.

60 Any patient with a pathological stage II or III after resection who received preoperative radiotherapy without chemotherapy, should be considered for adjuvant chemotherapy with 5-FU during four (Stage II) or six (Stage III) months (1A recommendation) [55, 75, 206].

61 Infusional FUFA or capecitabine are recommended because they are more effective and less toxic than bolus FUFA (1C evidence), which was shown to prolong survival in patients with pathological stage III disease (1A recommendation) [55, 206-211].

62 After neoadjuvant radiochemotherapy, the indication for adjuvant chemotherapy in Stage III rectal cancer can be based on the cStaging. However, the benefit of adjuvant chemotherapy (during 4 months) seems to be very limited and may not be indicated in case of a pathologic complete (or almost complete) response (2C recommendation) [55, 75, 206].

63 There is insufficient evidence to support the use of adjuvant treatment with portal vein infusion chemotherapy with 5-FU in patients with resected rectal cancer (1A recommendation) [55, 206, 212].

64 Adjuvant therapy should start within 3 months after surgery. It should not be started in the presence of pelvic septic complications (expert opinion).

2.4.6.2 Adjuvant therapy in patients who did not receive neoadjuvant therapy

In 2001, Cancer Care Ontario (CCO) performed a review of 25 randomized controlled trials, 4 meta-analyses, 2 evidence-based consensus statements on adjuvant radiotherapy and/or chemotherapy in stage II and III resected rectal cancer. [206]. Some multi-arm trials contributed to more than one of the following comparative analyses: radiotherapy versus observation, chemotherapy versus observation, chemotherapy versus radiotherapy, chemotherapy plus radiotherapy versus chemotherapy alone, and chemotherapy plus radiotherapy versus radiotherapy alone.

The resulting CCO guideline came to the same conclusion as the National Institutes of Health Consensus Development Conference 1990 [213], i.e. that patients with resected stage II or III rectal cancer should be offered adjuvant therapy with the combination of radiotherapy and chemotherapy. There was no evidence to support the use of radiotherapy alone, if the goal of adjuvant therapy is to improve survival. There was evidence that chemotherapy should include 5-fluorouracil (5-FU), but not semustine, and that intravenous infusion with 5-FU is more effective than bolus injection (6 RCTs).

Radiotherapy alone versus observation (8 RCTs) improved local control without a significant survival benefit [206]. The SIGN guideline summarized 27 RCTs and 2 meta-analyses on radiotherapy versus observation showing a 9% reduction in risk of loss of local control (Number Needed to Treat = 11) without benefit in overall survival (meta-analysis) and at the cost of a significantly worse bowel function with RT [55]. Also, the AXIS trial investigators did not observe a survival benefit in 761 patients randomized with respect to radiotherapy. Although not statistically significant, the impact on local recurrence rates in this trial was similar to that reported in the literature [212]. In an EORTC trial there was an increased toxicity without survival benefit of elective irradiation of para-aortic lymph nodes and liver in addition to postoperative pelvic radiotherapy [214].

Chemotherapy versus observation (6 RCTs and 2 meta-analyses) improved survival but not local control [206].

None of 3 RCTs comparing chemotherapy versus radiotherapy found a benefit for overall survival or disease-free survival [206].

However, this information has become less relevant since chemoradiation is to be preferred above observation (2 RCTs), radiotherapy alone (3 RCTs) or chemotherapy alone (3 RCTs) [206].

The pooled analysis of the 3 trials of chemotherapy plus radiotherapy versus radiotherapy revealed a benefit for chemotherapy plus radiotherapy for both survival (odds ratio, 0.58; 95% confidence interval, 0.37 to 0.92; p=0.019) and local control (odds ratio, 0.50; 95% confidence interval, 0.27 to 0.92; p=0.025) [206]. After this guideline was published, Cafiero et al. reported a trial in which postoperative radiotherapy was compared to radiotherapy and chemotherapy [215]. The group with combination therapy had a non-significantly increased relative risk of death, but there was an unbalance of stage II and stage III patient in the two groups, there was low adherence to chemotherapy, chemotherapy was with 5-FU and levamisole and chemotherapy and radiotherapy were not concurrent.

Pooled results from two trials showed no significant survival benefit for chemotherapy plus radiotherapy versus chemotherapy (odds ratio=0.80; 95% confidence interval, 0.48 to 1.32; p=0.37). Also, in a third trial, the addition of radiotherapy to chemotherapy did not significantly improve disease-free survival (hazard ratio, 0.99; 95% confidence interval, 0.80 to 1.22; p=0.90) or overall survival (hazard ratio, 0.98; 95% confidence interval, 0.78 to 1.24; p=0.89); however, a significant reduction in the cumulative incidence of locoregional recurrence was evident for patients randomized to combined CT+RT compared with chemotherapy alone (relative risk, 0.57; 95% CI, 0.36 to 0.92; 5% absolute decrease from 13% with CT alone to 8% with CT+RT at five years; p=0.02) [206]. Moreover, the level of evidence for adjuvant radiotherapy as monotherapy giving a better local control is high. On the other hand, it is known that adjuvant chemotherapy gives a better overall survival, most often without effect on local recurrence rate. Thus, postoperative adjuvant combined radiation and chemotherapy is to be recommended in patients who did not receive preoperative radiotherapy and who are at high risk of recurrence [55, 206].

From existing clinical practice guidelines [55] it is known that chemotherapy during six months is prolonging survival in stage III patients. Also a recent Japanese trial, the first with TME as standard surgery, showed a better relapse free survival (primary endpoint) and a better overall survival (secondary endpoint) with oral 5-FU based chemotherapy in stage III resected rectal cancer patients [216].

As we recommend to use in these patients a long course of radiotherapy together with continuous 5-FU (which counts for two months), postoperative chemotherapy during an extra four months is warranted.

Existing clinical practice guidelines concluded that further adjuvant chemotherapy is not indicated in stage II patients [55]. Thereafter, data from four recent trials on adjuvant chemotherapy have been reported. The study of Taal et al. could not show a significant survival benefit for rectal cancer patients (in subgroup analysis) because there were too few rectal cancer patients included to draw conclusions [217]. There was a tendency for a better survival in these patients, more in stage III than in stage II patients. A systematic review by Glimelius et al. did not find a survival benefit for adjuvant chemotherapy in rectal cancer patients [218]. A Japanese study by Kato et al. on the other hand showed a clear improvement in disease free survival as well for colonic cancer patients as for rectal cancer patients, but again, there were too few rectal cancer patients to draw firm conclusions [219]. A Japanese meta-analysis of the effect of adjuvant chemotherapy with oral fluorinated pyrimidines in the rectal cancer group found an overall survival benefit, but with hazard ratio=0,92, CI 95% 0,79-1,07) [220].

Although there is no trial dealing with the specific setting of pStage II rectal cancer with "unfavourable prognostic features", our recommendation is to apply the conclusions of the NIH consensus [213], i.e. to give postoperative chemoradiotherapy in stage II and III patients if they were not treated with neoadjuvant treatment.

Evidence from existing guidelines on the use of 5-FU given by a protracted venous infusion (PVI) during postoperative RT is mainly based on the results of chemoradiation in patients with high risk RC [55, 206]. There was an improved tumour response and distant control, suggesting an improved local and systemic effect with FU given by a PVI. This resulted in a benefit for overall survival in favour of PVI. The overall local control was good and slightly better in the PVI arm.

A recent American trial showed similar overall survival rates, disease free survival rates and locoregional failure rates between bolus 5-FU therapy and PVI therapy (with a non significant benefit for the PVI group) but with significantly less haematological toxicity in the PVI arm [221].

Enteritis, diarrhoea, bowel obstruction or perforation and fibrosis within the pelvis are associated with postoperative radiotherapy [206]. Delayed adverse effects from radiotherapy include radiation enteritis (4%), small-bowel obstruction (5%) and rectal stricture (5%). A greater number of haematological and non-haematological adverse effects were associated with chemotherapy plus radiotherapy than with chemotherapy, radiotherapy or observation. Postoperative chemotherapy plus radiotherapy was associated with acute gastrointestinal and rheumatologic adverse effects that may be severe or life-threatening.

A recent small study showed severe long-term anorectal dysfunction as result of a weakened, less sensitive anal sphincter and undistensible rectum with faecal incontinence in 60% vs. 8% of patients that received adjuvant radiotherapy or not [222]. Another small study demonstrated that the combination of postoperative radiotherapy with high-dose 5-FU was too toxic [223]. A detailed analysis of toxicity of a previously reported trial by the North Central Cancer Treatment Group showed that the rate of diarrhoea was significantly greater in the PVI group when compared to the bolus 5-FU group, and this effect was even more important in the group of patients that underwent an anterior resection [224].

There is no direct evidence supporting the need to start adjuvant therapy within 3 months after surgery. This is a rather general recommendation based on expert opinion, in analogy with the treatment of other types of cancer and based on the oncologic rationale that adjuvant therapy is able to treat micrometastatic disease at a time when tumour burden is at a minimum.

65 In patients with radically resected rectal cancer who did not receive neoadjuvant therapy, there is no superiority of adjuvant chemotherapy alone over adjuvant radiotherapy alone, or vice versa, with respect to overall or disease-free survival (1A recommendation) [206].

66 Although adjuvant radiotherapy alone decreases local recurrence rate and adjuvant chemotherapy alone improves survival, they are inferior to the combination of radiotherapy and chemotherapy in patients with radically resected pathological Stage II-III rectal cancer who did not receive neoadjuvant therapy (1A recommendation) [55, 206, 212, 214, 215].

67

67.1 Patients who did not receive neoadjuvant therapy and have a pathological stage III tumour of the rectum, or in whom an R1 resection (including a pCRM of <1 mm) was performed, should be considered for chemoradiotherapy, followed by 4 months of chemotherapy (1A recommendation) [55, 206, 212, 215, 216, 219].

67.2 Patients with a resected pathological stage II tumour with unfavourable prognostic features (inadequately sampled lymph nodes, perforation, T4 lesion, poorly differentiated histology), who did not receive neoadjuvant therapy, should also be considered for chemoradiotherapy (1B recommendation) [55, 206, 212, 215-220], followed by 4 months of chemotherapy (expert opinion).

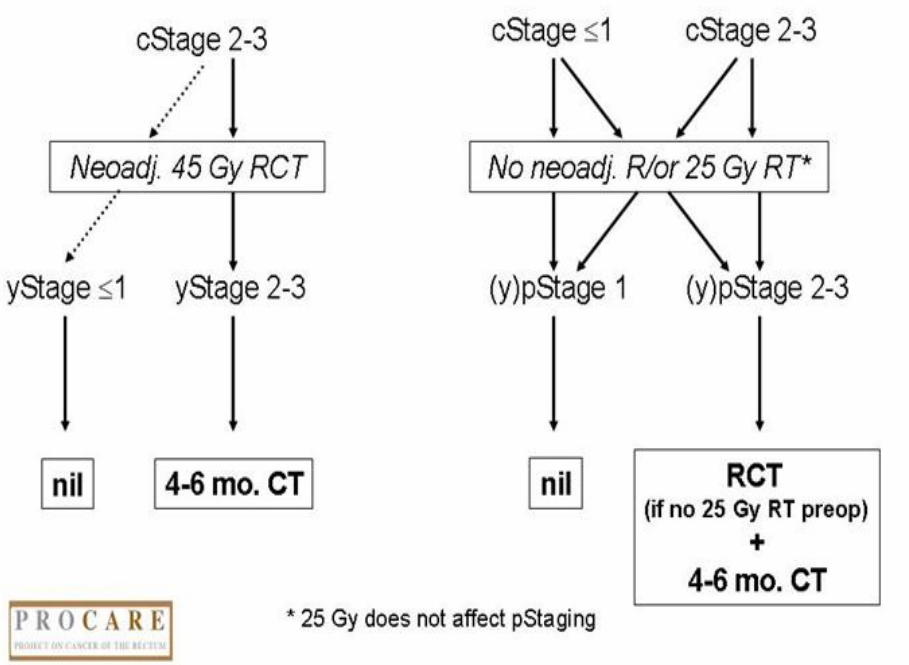
67.3 Patients with a resected pathological stage II tumour without unfavourable prognostic features, who did not receive neoadjuvant therapy, should also be considered for chemoradiotherapy. However, the evidence supporting the use of 4 months extra adjuvant chemotherapy is weak [55, 206, 215-220].

68 When chemotherapy with 5-fluorouracil is given concurrently with postoperative radiotherapy, a continuous intravenous infusion is more effective than the drug administered by bolus infusion (1A recommendation) [206, 221].

69 Patients to whom adjuvant radiotherapy or radiochemotherapy is proposed, should be informed of the potential harmful effects, most often diarrhoea and faecal incontinence, following sphincter sparing surgery (expert opinion) [55, 206, 222-224].

70 Adjuvant therapy should start within 3 months after surgery. It should not be started in the presence of pelvic septic complications (expert opinion).

Figure 6. Algorithm of adjuvant treatment after curative resection for rectal cancer.



2.4.7 Follow-up after curative treatment

The aim of follow-up is to detect local recurrence and/or metastasis at a surgically curable stage, and to detect new primary tumours. Patients that are fit for further treatment in case of recurrent disease should be offered intensive follow-up. However, intensive follow-up is not cost-effective for those unfit for liver/lung resection.

Above this, follow-up is necessary for audit and should be structured with particular reference to outcome measures. It may be facilitated by the use of a database. If 'local' databases are used, it is recommended that their field definitions match those of a larger, e.g. national, database.

Published data on follow-up are difficult to compare because of the heterogeneity of the schedules regarding both procedures and frequency with which they are carried out [74, 225, 226]. Individual randomised trials show no advantage of follow-up in terms of survival. Meta-analyses indicate that follow-up can offer survival benefit by means of earlier detection of metastatic or recurrent disease. There is some evidence that intensive follow-up does improve long-term survival for stage II and III colorectal cancer. Recurrence will be detected earlier, so treatment is often curative [74, 225, 226]. Important to remember is that a survival benefit is dependent on the joint fulfilment of many conditions (stage of colorectal cancer, variety and frequency of screening tests, compliance, co-morbidity).

Standard follow-up should contain a history and physical examination (including digital examination), laboratory testing, radiological testing and endoscopic surveillance [52, 74, 225]. Although there is no formal evidence about the necessity of the visits, including history and physical examination, they offer the opportunity to determine symptoms, to coordinate follow-up and to offer counselling [225]. There is an important psychological benefit for the patient that comes along with the regular follow-up. Quality of life aspects should be included during these visits [74]. Patients with a stoma should have ready access to nursing staff with a specific interest in stoma care. Physical examination and history should be done every three months during the first three years, in the fourth and fifth year every six months [225].

CEA is the only blood test that is supported by evidence regarding early diagnosis of recurrence. Routine blood tests (i.e. CBC, liver function tests), molecular markers or faecal occult blood testing have no prognostic or predictive value [52, 55, 225, 227]. CEA measurement should be done together with history and physical examination every three months during the first three years, in the fourth and fifth year every six months [52, 54, 55, 74, 225, 226].

Liver imaging is necessary since most metastases occur there. Ultrasound is a well-accepted imaging tool, but is less accurate than CT or MRI in diagnosing liver metastases at presentation (see chapter 2.4.2). This is likely also true for liver metastases that develop after curative surgery [68]. Above this, ultrasound is unable to assess for recurrent pelvic disease following rectal (or sigmoid) surgery. There is no obvious difference between CT and MRI for detecting recurrence, although MRI is more useful due to a higher theoretical ability to differentiate scar tissue from recurrence [68]. In patients with stage II and III rectal cancer, an abdominal/pelvic CT should be done annually during the first three years, while an ultrasound of the abdomen should be done in between the CT scans [52, 68, 225, 226].

Although there are insufficient data to recommend lung imaging, lung recurrences are as common as liver relapses in patients with rectal cancer, with the largest proportion of resectable recurrence found on thoracic CT [225]. Pulmonary recurrences are less associated with an elevated CEA [74, 225, 226]. An annual CT of the chest is therefore recommended during the first three years for patients with stage II and III rectal cancer. A chest X-ray should be done at six months after surgery and then annually for all patients. Thus, chest CT and X-ray will be done alternately at 6 months intervals during the first three years.

The endoscopic follow-up consists of a total colonoscopy in the peri-operative period and 1 year after the resection [52, 225, 227]. If this examination is normal, the next examination can be scheduled after 3 years. If this colonoscopy is normal, the interval until the next examination can be extended to 5 years. In patients with hereditary or familial predisposition, more intensive follow-up must be considered [52, 68, 74, 225, 227].

Chromo-endoscopy, magnification endoscopy and computed tomography colonography (virtual colonoscopy) are not established techniques for screening or surveillance [227]. There is also no place for EUS in routine follow-up, but EUS is a good tool for diagnosing local recurrence [52].

71 Every patient curatively treated for rectal cancer (all stages) should undergo intensive follow-up if there are no other medical conditions that limit the prognosis (1B recommendation) [74, 225, 226].

72 Every patient should undergo a physical examination and history, carcinoembryonic antigen (CEA) measurement, lung imaging (chest X-ray or CT-scan) and liver imaging (ultrasound or CT-scan). In patients at higher risk of local recurrent disease (i.e. stage II and III) a pelvic CT-scan or magnetic resonance imaging (MRI) is recommended (1B recommendation) [52, 54, 55, 68, 74, 225, 226].

73 Endoscopic ultrasound is only recommended when a local recurrence is suspected or in the follow-up after local excision/ transanal endoscopic microsurgical resection (TEMS) (1C recommendation) [52, 227].

74 A history, physical examination and carcinoembryonic antigen (CEA) testing should be done every three months for the first three years, during the fourth and fifth year every six months (1B recommendation) [52, 54, 55, 68, 74, 225, 226].

75 Patients at higher risk of recurrent disease (i.e. stage II and III) should undergo annually a CT-scan of the chest and abdomen/pelvis during the first three years (1B recommendation) [52, 68, 225, 226].

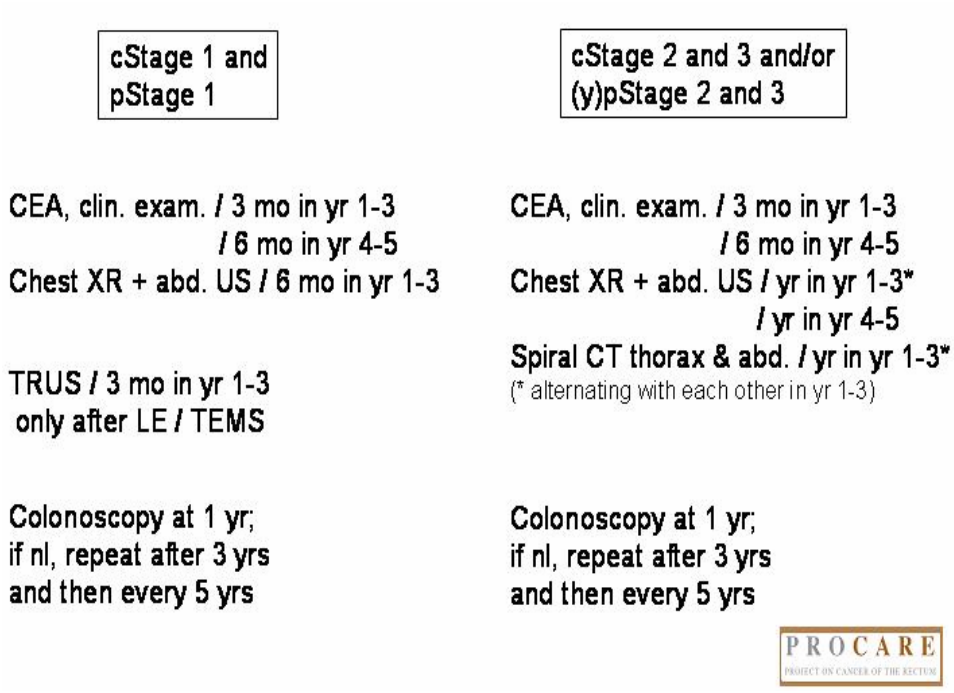
76 Liver ultrasound should be done every 6 months in the first three years (not when a CT-scan is done), annually in the fourth and fifth year (1B recommendation) [52, 68, 74, 226].

77 Chest X-ray is recommended every six months in the first three years (not if a CT thorax is done), in the next two years only yearly (1C recommendation) [74, 226].

78 Every patient should undergo total colonoscopy on a regular basis (1B recommendation) [52, 225, 227].

79 Total colonoscopy should be performed in the peri-operative period and 1 year after the resection. If this examination is normal, then the interval until the next examination should be 3 years. If that colonoscopy is normal, then the interval until the next examination should be 5 years. In patients with hereditary or familial predisposition, more intensive follow-up must be considered (1B recommendation) [52, 68, 74, 225, 227].

Figure 7. Follow-up of fit patients after curative treatment for rectal cancer.



2.4.8 Treatment of metastatic rectal cancer

The management of patients with rectal cancer and synchronous or metachronous liver metastasis is covered in these guidelines. Most of the recommendations, however, do also apply to patients with other locations of metastatic disease, in particular in the lung.

It is clear that there is a group of patients with liver (and lung) metastases who may become long-term disease-free survivors following resection [54]. Such survival is rare in apparently comparable patients who do not have surgical treatment. Further work is needed to more accurately define this group of patients.

80 Patients with liver (and lung) metastases from rectal cancer should be considered for surgery (1C recommendation) [54].

2.4.8.1 Evaluation of resectability

Although surgery for metastases is only appropriate in a minority of patients, resection can be curative and increase survival. Therefore, patients who are believed to have resectable liver metastases should be referred to a specialised liver multidisciplinary team (MDT) for an opinion about the feasibility of resection. Guidance criteria for referral are: patients in relatively good general health (ASA 1-3), after curative resection of their primary colorectal cancer or with a resectable primary tumour [54].

Percutaneous biopsy of a liver tumour may be associated with extrahepatic cancer cell dissemination and results in a reduced long-term survival even when resection of hepatic metastases is undertaken [228]. Biopsy of hepatic lesions should therefore not be performed without discussion within the multidisciplinary team.

Positron emission tomography (PET) scanning is an emerging technology and its optimum role in relation to more established imaging methods is not yet defined [54, 59]. PET is capable of identifying local recurrence, liver and other distant metastases from colorectal origin. PET is certainly useful before resection of liver metastases to exclude extra-hepatic dissemination of the disease.

Metastatic liver lesions can be characterized with MRI. This also allows evaluation of the liver volume in case a large resection is considered [59].

81 Patients who are believed, on the basis of imaging, to have resectable liver metastases should be referred to a specialised liver multidisciplinary team, for an opinion about the feasibility of resection, if they are in relatively good general health (ASA 1-3), have undergone curative resection of their primary colorectal cancer or have a resectable primary tumour (1C recommendation) [54].

82 Biopsy of hepatic lesions should not be performed without discussion with the multidisciplinary team (1C recommendation) [228].

83 In conjunction with other imaging modalities, PET can be recommended in the further staging of the extent of metastatic disease, and influences decisions on patient management. PET is useful before resection of metastases to evaluate the extra-hepatic dissemination of the disease (2C recommendation) [54, 59].

84 Magnetic resonance imaging (MRI) can be useful to characterize metastatic liver lesions and to evaluate the volume of liver in case of large resection (1C recommendation) [59].

85 The morphology of the metastatic disease must be discussed in a multidisciplinary team (MDT) to identify non-resectability and to evaluate the possibility of reversibility. If necessary, a magnetic resonance imaging (MRI) liver and/or PET scan will be performed if they would influence the management of the disease (expert opinion).

2.4.8.2 Resectability criteria

Long-term survival can be achieved in patients with hepatic metastasis from colorectal origin after radical resection of the primary cancer and appropriate local treatment for hepatic metastases. The influence of the number or location of the metastases on survival after complete macroscopic resection is controversial [228]. Duration of survival is shortened by the presence of inadequate or involved resection margins [229]. A number of studies have supported the view that poorer overall and disease free survival are associated with resection margin less than 1 cm although others have produced evidence to suggest that a lesser margin may be acceptable as long as the tumour pseudocapsule is resected during dissection [228].

It has been increasingly evident that tumours which were previously thought to be unresectable can be treated by a combination of advanced techniques with a curative intent and long term survival [230-233]. Thus, it is suggested to subdivide patients according to their metastatic status in those with resectable metastases, potentially resectable metastases, and those with metastases unlikely to ever become resectable [234].

Resectability of liver tumours requires assessment by a radiologist in conjunction with a liver surgeon experienced in the management of colorectal metastases as there is also a need to define acceptable residual functioning volume in order to avoid postoperative liver failure. Concerns regarding compromised hepatic functional reserve following extended hepatic resection have led to consider preoperative portal vein embolisation in an attempt to increase the volume of the intended residual liver [231]. Others have suggested two-stage hepatic resection [230, 232].

86

86.1 **The ability to achieve clear margins (R0 resection) should be determined by a radiologist and a surgeon in the liver multidisciplinary team (MDT);**

86.2 **The acceptable residual functioning liver volume should be taken into account;**

86.3 **Resectability may be achieved by portal vein embolisation or two stage hepatectomy to increase hepatic functional reserve and also by the combination of surgery and ablation;**

86.4 **Patients with extrahepatic disease that should be considered for liver resection include resectable/ablatable pulmonary metastases, resectable/ablatable extrahepatic sites and local direct extension of liver metastases;**

86.5 **Those patients with tumours thought to be borderline for resection may have resectable or ablatable disease and should be referred for discussion with the specialized hepatobiliary unit before treatment**

(1C recommendation) [59, 228, 235, 236].

2.4.8.3 Patients with resectable liver metastasis

Synchronous resectable liver metastasis

Long-term survival can be achieved in patients with hepatic metastasis from colorectal origin after radical resection of the primary cancer and curative local treatment for hepatic metastases. The influence of the number or location of the metastases on survival after complete macroscopic resection is controversial [228]. There is a consensus that the primary tumour should be operated, with or without neoadjuvant chemoradiation, if the tumour is symptomatic, irrespective of the resectability of the metastases. If the primary tumour is asymptomatic with resectable metastases, standard practice is to resect the primary tumour and the metastases, either at the same time or in a stepwise fashion, followed by chemotherapy [234]. The EORTC intergroup randomised phase III study 40983 evaluating the benefit of peri-operative Folfox4 chemotherapy in patients with potentially resectable colorectal cancer liver metastases, demonstrated improved progression-free survival over surgery alone in patients whose metachronous or synchronous metastases were actually resected [237]. Perioperative Folfox4-chemotherapy was proposed as the new standard of care. However, the results have not yet been published in full paper.

87 Although there is no evidence, optimal local control should be obtained in patients with a resectable primary rectal cancer and synchronous resectable metastases, including preoperative radiotherapy, radiochemotherapy, or chemotherapy. Multidisciplinary team (MDT) discussion is recommended for decision-making in this setting. A specialized liver and colorectal MDT should decide about the opportunity of synchronous resection of the primary rectal cancer and liver metastasis (1C recommendation) [228, 237].

88 Perioperative chemotherapy is recommended in patients with synchronous resectable liver metastases (1B recommendation) [237].

89 Usually, rectal cancer resection and liver resection has not been performed synchronously but management of accessible small metastases detected peri-operatively may be considered for combined resection. Simultaneous colon and liver resection has been shown to be safe and efficient when performed in high volume centres with appropriate experience in liver resectional surgery (2C recommendation) [52, 228].

90 It is also appropriate to provide recovery time after resection of the primary rectal cancer resection and to refer the patient to a specialist liver multidisciplinary team (MDT) for consideration of liver resection (1C recommendation) [228].

91 Patients with unfavourable primary pathology such as perforated primary tumour or extensive nodal involvement should be considered for chemotherapy prior to liver resection and be restaged after 3 months (1C recommendation) [228].

Metachronous resectable liver metastasis

There are only a few RCTs with low power addressing the treatment of patients with metachronous resectable metastases. More studies are needed to answer the question whether these patients should have pre- and/or postoperative chemotherapy. The EORTC intergroup randomised phase III study 40983 evaluating the benefit of peri-operative Folfox4 chemotherapy in patients with potentially resectable CRC liver metastases, demonstrated improved progression-free survival over surgery alone in patients whose metachronous or synchronous metastases were actually resected [237]. Perioperative Folfox4-chemotherapy was proposed as the new standard of care. However, the results have not yet been published in full paper.

Chemotherapy for non-resectable metastatic colorectal cancer improves survival and should be considered in all patients (cfr. infra). In some cases, initially non-resectable tumours should be considered for downsizing with chemotherapy.

In a large cohort study, combination chemotherapy with oxaliplatin, fluorouracil and folinic acid (Folfox) allowed resection in 13.5% of patients presenting initially non-resectable liver metastases; survival of these patients was similar to comparable series of operable patients treated by surgical resection [238].

Both Folfox and Folfiri therapy used and tested in phase III randomized trials provide a similar response rate, progression free survival and overall survival [239]. Both Folfox and Folfiri regimens can make unresectable patients resectable. There are arguments in favour of an oxaliplatin-based chemotherapy, which could increase the resection rate [240]. Folfox, Folfiri, Folfoxiri or the combination of 2 cytotoxics and a biological (cetuximab or bevacizumab) may lead to resection in +/- 20 % of the patients. Larger phase 3 studies report a lower resection rate. In general a correlation between the response rate and resection rate has been reported [241, 242].

92 Perioperative chemotherapy is recommended in patients with metachronous resectable liver metastases (1B recommendation) [237].

93 Patients with potentially resectable disease and who have undergone radical resection of the primary tumour should be considered for resection, with perioperative chemotherapy (1B recommendation) [59, 228, 237].

94 Neoadjuvant treatment is of interest to shrink liver metastases thought to be irresectable by a specialist liver multidisciplinary team (MDT) (1C recommendation) [52, 54, 59, 228, 240].

95 Several types of chemotherapy could be used to decrease liver metastases with the aim to increase the resection rate. The best regimen appropriate to reduce liver metastases in the hope of resection has not yet been established (expert opinion).

Adjuvant chemotherapy after metastasectomy

There are few RCTs with low power examining the use of adjuvant chemotherapy after metastasectomy. Further work is needed to determine whether the addition of adjuvant treatment results in improved survival. However, adjuvant intravenous systemic chemotherapy with 5-FU/LV significantly increases the disease-free survival in patients with completely resected liver metastases from colorectal cancer [243]. However the FOLFOX regimen is more active than the 5-FU/LV alone in patients with metastases and is considered as a better option.

Thus, perioperative Folfox4-chemotherapy, consisting of 6 cycles Folfox4 during 3 months preoperatively and the same regimen postoperatively, was proposed as the new standard of care in patients with respectable liver metastases from colorectal origin

[237]. This regimen was found to be safe and to increase the progression free survival as compared with surgery alone. However, the results have not yet been published in full paper.

Few RCTs with limited power are available on the use of intra-arterial chemotherapy in combination with systemic chemotherapy. The interest of intra-arterial chemotherapy combined with systemic chemotherapy is limited because of the complexity of the technique, the costs, and the morbidity [59].

96 After R0 resection of colorectal metastases, chemotherapy using systemic 5-FU/folinic acid with or without irinotecan or oxaliplatin is recommended (1C recommendation) [237, 243]. However, the evidence suggests that perioperative chemotherapy with FOLFOX can be recommended (cfr. supra).

97 The benefit of intra-arterial chemotherapy in combination with systemic chemotherapy is limited and not applicable outside clinical trials. Therefore, routine adjuvant hepatic arterial infusion after curative resection for colorectal cancer of the liver cannot be recommended (2C recommendation) [59].

2.4.8.4 Patients with non-resectable liver metastasis

Primary treatment of patients with synchronous non-resectable liver metastasis

The prognosis of the patients with non-resectable metastases unlikely to ever become resectable is conditioned by the metastases and not by the primary tumour itself. If the primary tumour is not symptomatic, it is reasonable to start with chemotherapy without any treatment of the primary [234]. However, there is some discussion on the indication for resection of the primary or administration of radiochemotherapy in order to prevent local complications before initiating a systemic chemotherapy. In the literature, there are few reports looking on the feasibility of non surgical treatments for rectal tumour with synchronous non-resectable metastases [244]. There is no RCT to guide the therapeutic choices. The first aim of therapy is to maintain the quality of life and avoid invasive procedures.

98 In the presence of synchronous non-resectable metastases, and without any hope of future resection, and in the absence of signs of local complication, resection of the primary tumour is not recommended (1C recommendation) [59, 228, 237].

99 In the presence of non-resectable metastases, symptoms related to the primary rectal cancer should be palliated by local therapy, such as coagulation, radiotherapy, stenting (1C recommendation) [52, 54, 55].

Chemotherapy for non-resectable synchronous or metachronous (liver) metastasis

There is evidence from two systematic reviews that chemotherapy for metastatic colorectal cancer can improve survival and should be considered in all patients not suitable for surgery [245, 246]. In advanced disease, early chemotherapy can increase survival time, reduce symptoms and improve quality of life. Good condition is required to have the greatest benefit of systemic chemotherapy. Patients should be informed of the potential benefits and morbidity of treatment and should be fully involved in decision-making. First-line chemotherapy should also be proposed to elderly patients in good condition since the benefit on survival was the same as that observed in younger patients.

FIRST-LINE TREATMENT

In first-line therapy, a combination of irinotecan with fluorouracil-leucovorin (bolus or continuous infusion) leads to significant increase in response rate, progression free survival, and overall survival compared with standard fluorouracil-leucovorin. Quality of life is comparable [247, 248]. 5-FU/folinic acid plus oxaliplatin compared with 5-

FU/folinic acid alone in first-line failed to show survival benefit, but there is improvement in response rate [249, 250].

In other words, there is good evidence to support initial combination chemotherapy for patients with metastatic CRC, but any benefit of the use of these regimens has to be set against increased toxicity compared with 5-FU/folinic acid alone.

Oral capecitabine as single agent yields higher response rates than 5-FU plus leucovorin [251, 252]. Similar median time to progression and median duration of survival were observed with capecitabine and 5-FU plus leucovorin. Therefore, oral fluoropyrimidines can be proposed as an alternative to intravenous 5-FU. Oral fluoropyrimidine in monotherapy can also be proposed as an alternative to the combination in case of contra-indication to IV therapy or increased risk of toxicity or for the patient's convenience.

The addition of bevacizumab to Irinotecan/5-FU/Leucovorin in first-line treatment of metastatic CRC has been reported to improve overall survival, progression-free survival, objective response rate, and duration of response compared with Irinotecan/5-FU/Leucovorin alone [253]. For patients with advanced colorectal cancer receiving 5-FU-based chemotherapy as first-line therapy, the addition of bevacizumab is recommended to improve overall survival in patients with no contraindications to bevacizumab.

Ralitrexed is as effective as the Mayo FU/FA regimen, but evidence concerning its toxicity is conflicting [254]. Therefore, raltitrexed is not recommended as first-line therapy, but may be considered as an alternative for patients intolerant of 5-FU regimens or for patients in whom 5-FU is contraindicated due to cardiotoxicity in monotherapy or in combination with irinotecan or oxaliplatin.

Neuropathy, one of the most important side effects of oxaliplatin, can be irreversible and decreases the quality of life of the patients. The Optimox strategy (Folfox-7) can be considered as first-line to decrease the exposure to oxaliplatin with the consequence of decreasing its side-effects [255]. Comparable median progression-free survival and survival times were observed after Folfox4 and Folfox7 (lower dose versus higher dose of oxaliplatin).

SECOND-LINE TREATMENT

Patients who have failed to respond to, or who have progressed during treatment with 5-FU/folinic acid may respond to treatment with irinotecan [256, 257]. The responses in second-line irinotecan may translate into improved survival although the benefits are modest: an increase of 10 weeks in median survival but converging survival curves at 2 years. As for first line chemotherapy, second line chemotherapy must also be proposed to elderly patients since the benefit on survival is the same as that observed in younger patients.

The addition of bevacizumab to 5-FU/LV/oxaliplatin increases the activity of the FOLFOX regimen in patients with advanced colorectal cancer receiving second-line therapy if they did not receive bevacizumab as a part of their initial irinotecan-based therapy. However, the potential toxicity of bevacizumab must be evaluated in function of the patient's condition and potential contra-indications [258]. Bevacizumab is not yet approved in this setting in Europe.

A randomised phase II study confirmed the activity of cetuximab in 329 patients with EGFR-positive, irinotecan-refractory metastatic CRC [259]. Response rate, median time to progression and overall survival were significantly better after retreatment with cetuximab and irinotecan than with cetuximab alone.

Second-line treatment with irinotecan, either alone or in combination with infusional 5-FU/LV, is supported after failure to 5-FU [256, 257].

The effectiveness of oxaliplatin as single agent in first- or second-line palliative therapy is limited [260]. Improved response rate, time to tumour progression and alleviation of tumour-related symptoms has been demonstrated with oxaliplatin in combination with fluorouracil-leucovorin in irinotecan failing patients [261].

100 Chemotherapy must be proposed to patients with non-resectable metastases in good condition (1A recommendation) [54, 55, 59, 262, 263].

101 First-line chemotherapy should also be proposed to elderly patients in good condition since the benefit on survival was the same as that observed in younger patients (1A recommendation) [264, 265].

102 Folfox or Folfiri are recommended as first-line chemotherapy for non-resectable metastases from rectal cancer (1A recommendation) [52, 262, 266].

103 Oral fluoropyrimidines can be proposed as an alternative to intravenous 5-FU. Oral fluoropyrimidine in monotherapy can also be proposed as an alternative to the combination in case of contra-indication to IV therapy or increased risk of toxicity or for the patient's convenience (1A recommendation) [55, 262, 267].

104 First-line bevacizumab in combination with a 5-FU based regimen is an option since bevacizumab increases survival in association with a 5-FU based regimen. However, the potential toxicity of bevacizumab must be evaluated in function of the patient's condition and potential contra-indications (1A recommendation) [262, 263, 268, 269].

105 Raltitrexed is not recommended as first-line therapy but may be considered as an alternative in those patients intolerant of 5-FU regimens or in whom 5-FU is contraindicated due to cardiotoxicity in monotherapy or in combination with irinotecan or oxaliplatin (1C recommendation) [55, 270].

106 The sequential (optimox) strategy can be used safely to avoid the toxicity related to the administration of oxaliplatin (1A recommendation) [255].

107 After progression under first-line chemotherapy, taking into account the benefit in survival and quality of life, second-line chemotherapy should be proposed to informed patients in good condition (1A recommendation) [55, 59, 271].

108 Second line chemotherapy must also be proposed to elderly patients since the benefit on survival is the same as that observed in younger patients (1A recommendation) [59, 272].

109 In case of disease progression several options remain valuable:

***109.1* Cetuximab is a good option in combination with irinotecan for chemotherapy-resistant patients (1B recommendation) [259, 273].**

***109.2* Shift to Folfiri for patients resistant to Folfox and vice versa, is another option (1B recommendation) [52, 262, 274].**

2.4.8.5 Patients with non-resectable rectal cancer and metastases

The aim of palliative systemic therapy is to improve survival and quality of live in patients with metastatic colorectal cancer. Fluorouracil (5-FU) with LV modulation has a marginal but positive effect on survival in these patients [245, 246]. The incorporation of irinotecan (CPT-11) and oxaliplatin for the management of metastatic colorectal cancer has generated improvement in survival. The development of oral fluoropyrimidines, mimicking continuous infusion 5-FU, is convenient to use. An additional increase in the effectiveness of systemic therapies can be expected from new agents such as anti-angiogenesis drugs, tyrosine kinase inhibitors, and epidermal growth factor blockers.

Palliative chemotherapy should be available for every patient with metastatic colorectal cancer. Older patients without clinical contraindications benefit just like younger patients and should not be excluded from treatment [265]. Infusional 5-FU was shown to be more effective than bolus 5-FU in both age groups.

Four to seven percent of the patients with rectal cancer develop bone metastases. Palliative radiotherapy has been shown to be effective for pain relief in such patients.

Therefore, a short course of radiotherapy (one to five fractions) should be available without delay for patients with metastatic disease in bones [54].

Although there is no high-quality evidence, radiotherapy can provide valuable palliation in patients with non-resectable rectal cancer and pelvic pain. However, the choice of the regimen will depend upon a number of factors including the patient's preference and general condition, and the severity of symptoms.

A systematic review on the efficacy and safety of stenting in colorectal obstruction identified 29 case series describing 598 attempted stent insertions [275]. Fifty-six percent of stent insertions were palliative. Use of a stent can avoid the need for a stoma. Expanding metal stents usually remain effective for more than a year, and in many cases provide palliation until death.

Patients who develop small or large bowel obstruction, in whom surgery is inappropriate, can be managed in most cases without intravenous fluids or a nasogastric tube. The symptoms can often be controlled for weeks using analgesic, antiemetic and antisecretory drugs parenterally [55]. Parenteral hydratation is sometimes indicated.

110 Chemotherapy must be proposed to patients with non-resectable primary and metastatic disease in good condition (1A recommendation) [54, 55, 59, 262, 263].

111 Elderly patients with non-resectable primary and metastatic colorectal cancer should also be considered for chemotherapy (1A recommendation) [264, 265].

112 Short course of radiotherapy (one to five fractions) should be available without delay for patients with metastatic disease in bones (1C recommendation) [54].

113 Radiotherapy in combination with chemotherapy should also be offered to those patients with locally recurrent or advanced rectal cancer and pelvic pain, who have not previously undergone radiotherapy (1C recommendation) [52, 54, 55].

114 Palliative surgery to relieve intestinal obstruction can have an important role in the management of patients with advanced colorectal cancer (1C recommendation) [54].

115 Stenting is a promising technique that should be offered to patients not fit enough or unwilling to undergo colostomy (2C recommendation) [52, 54, 55].

116 Medical measures such as analgesics, antiemetics and antisecretory drugs should be used alone or in combination to relieve the symptoms of bowel obstruction (1B recommendation) [55].

2.4.8.6 Patients with peritoneal carcinomatosis

The correct management of peritoneal carcinomatosis in CRC patients has to be further explored. Criteria of patient's selection are not already determined. In a recent systematic review the level of evidence was low in 13 of 14 eligible studies [276]. A limited number of studies show that cytoreductive surgery associated with perioperative intraperitoneal chemotherapy improves overall survival when compared with systemic chemotherapy. However, several studies indicate that prognosis improves in patients receiving a complete cytoreduction, achieving a median survival of 28-60 months and a 5-year survival of 22-49%.

117 Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) can be considered in a selected subset of patients with peritoneal carcinomatosis from colorectal origin, in whom a complete resection can be obtained (1B recommendation) [262, 276-281].

118 In each patient with peritoneal carcinomatosis, the decision of cytoreductive surgery should be based on a multidisciplinary discussion (expert opinion).

3 CONCLUSIONS

- **The presented PROCARE guideline offers a framework for the Professional Societies and the College of Oncology to improve the quality of rectal cancer care in Belgium.**
- **The dissemination and implementation of this guideline will be prepared by the PROCARE Steering Group, and will be done by a broad distribution of the guideline through the professional and scientific associations of hospital specialists involved in the care of rectal cancer patients, and of general practitioners.**
- **In view of the evolving evidence, an update of the guideline will be necessary within 3 – 5 years after a pre-assessment of the literature.**
- **Next, based on this guideline a set of quality indicators will be developed and pilot tested. These indicators will be used to evaluate the implementation of the guideline and the quality of rectal cancer care in Belgium.**

4 APPENDICES

APPENDIX 1: GRADE SYSTEM

Grade of Recommendation/ Description	Benefit vs. Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/ Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/ Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/ Strong recommendation, low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation, but may change when higher quality evidence becomes available
2A/ Weak recommendation, high quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/ Weak recommendation, moderate quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/ Weak recommendation, low quality evidence	Benefits closely balanced with risks and burden	Observational studies or case series	Very weak recommendation, other alternatives may be equally reasonable

Source: Guyatt et al., 2006 [44]

APPENDIX 2: IDENTIFIED GUIDELINES AND THEIR QUALITY APPRAISAL

Source	Title	Standardised Score						In/exclusion?
		I	II	III	IV	V	VI	
Cancer Care Ontario [270]	Use of Raltitrexed (Tomudex) in the Management of Metastatic Colorectal Cancer. Practice Guideline Report #2-17.	86%	65%	93%	58%	31%	38%	Included
Cancer Care Ontario [267]	Oral Capecitabine (Xeloda) in the First-line Treatment of Metastatic Colorectal Cancer: A Clinical Practice Guideline.	94%	56%	91%	83%	0%	75%	Included
Cancer Care Ontario [266]	Use of Irinotecan (Camptosar®, CPT-11) Combined with 5-Fluorouracil and Leucovorin (5FU/LV) as First-Line Therapy for Metastatic Colorectal Cancer. Practice Guideline Report #2-16b.	94%	77%	89%	69%	0%	75%	Included
Cancer Care Ontario [74]	Follow-up of Patients with Curatively Resected Colorectal Cancer. Practice Guideline Report #2-9.	94%	77%	89%	83%	11%	67%	Included
Cancer Care Ontario [274]	Use of Irinotecan in the Second-Line Treatment of Metastatic Colorectal Carcinoma. Practice Guideline Report #2-16.	94%	79%	88%	94%	0%	100%	Included
Cancer Care Ontario [282]	The Use of Preoperative Radiotherapy in the Management of Patients with Clinically Resectable Rectal Cancer. Practice Guideline Report #2-13.	92%	65%	88%	69%	6%	71%	Included
SIGN [55]	Management of colorectal cancer. A national clinical guideline.	83%	88%	86%	96%	50%	83%	Included
Garden et al. [228]	Guidelines for resection of colorectal cancer liver metastases.	86%	63%	85%	81%	36%	63%	Included
Cancer Care Ontario [263]	The Role of Bevacizumab (Avastin™) Combined With Chemotherapy in the Treatment of Patients With Advanced Colorectal Cancer: A Clinical Practice Guideline.	93%	86%	84%	75%	0%	67%	Included
Cancer Care Ontario [206]	Postoperative Adjuvant Radiotherapy and/or Chemotherapy for Resected Stage II or III Rectal Cancer. Practice Guideline Report # 2-3.	94%	81%	82%	75%	0%	100%	Included
FNCLCC [262]	Recommandations pour la pratique clinique : prise en charge par chimiothérapie palliative de première ligne des patients atteints d'un cancer colorectal métastatique.	100%	52%	81%	90%	0%	100%	Included
FNCLCC	Recommandations pour la pratique clinique : Standards, Options et Recommandations pour la prise en charge des patients atteints de cancer du côlon. Mise à jour 2003 du chapitre chimiothérapie palliative de première ligne des patients atteints d'un cancer colorectal métastatique.	100%	46%	77%	92%	3%	100%	Excluded (updated by previous CPG)
ACS [227]	Guidelines for Colonoscopy Surveillance After Cancer Resection: A Consensus Update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer.	92%	31%	74%	81%	0%	21%	Included
Lazorthes et al. [59]	Therapeutic management of hepatic metastases from colorectal cancers.	85%	47%	73%	89%	15%	44%	Included
Cancer Care	Cross-Sectional Imaging in Colorectal Cancer.	89%	44%	70%	81%	15%	94%	Included

Source	Title	Standardised Score I	II	III	IV	V	VI	In/exclusion?
Ontario [68]								
Schmiegel et al. [52]	S3-Leitlinienkonferenz "Kolorektales Karzinom" 2004.	75%	33%	69%	77%	14%	13%	Included
ASCO [225]	Colorectal Cancer Surveillance: 2005 Update of an American Society of Clinical Oncology Practice Guideline.	83%	31%	66%	65%	19%	83%	Included
NICE [54]	Improving Outcomes in Colorectal Cancers.	89%	50%	63%	96%	83%	0%	Included
ASCRS [283]	Practice Parameters for the Surveillance and Follow-Up of Patients With Colon and Rectal Cancer.	81%	21%	49%	75%	31%	38%	Excluded
ACPGBI [51]	GUIDELINES FOR THE MANAGEMENT OF COLORECTAL CANCER	78%	71%	48%	96%	67%	33%	Excluded
ASCO [284]	2000 Update of Recommendations for the Use of Tumor Markers in Breast and Colorectal Cancer: Clinical Practice Guidelines of the American Society of Clinical Oncology.	81%	13%	48%	63%	22%	25%	Excluded
Van Cutsem et al. [242]	Towards a pan-European consensus on the treatment of patients with colorectal liver metastases.	85%	44%	43%	75%	26%	67%	Excluded
NCI [285]	Guidelines 2000 for Colon and Rectal Cancer Surgery.	78%	33%	43%	94%	0%	21%	Excluded
NCCN [286]	Rectal cancer.	64%	38%	42%	100%	11%	50%	Excluded
HAS [287]	Choix des thérapeutiques du cancer du rectum.	92%	58%	38%	77%	17%	46%	Excluded
FNCLCC [196]	STANDARDS, OPTIONS ET RECOMMANDATIONS POUR LA PRISE EN CHARGE DES PATIENTS ATTEINTS D'ADENOCARCINOME PRIMITIF DU RECTUM.	50%	19%	35%	88%	22%	21%	Excluded
MOH Singapore	Colorectal cancer.	75%	54%	32%	81%	17%	8%	Excluded
ASCRS [288]	Practice Parameters for the Management of Rectal Cancer (Revised).	67%	27%	31%	67%	6%	21%	Excluded
ASGE [289]	ASGE guideline: the role of endoscopy in the diagnosis, staging, and management of colorectal cancer	86%	27%	29%	69%	0%	0%	Excluded
Scholefield et al. [290]	Guidelines for follow up after resection of colorectal cancer.	58%	8%	25%	73%	67%	33%	Excluded
ABCSG [291]	Empfehlungen zu Diagnostik und multimodaler Primärtherapie des Rektumkarzinoms 2004.	53%	23%	24%	58%	0%	17%	Excluded
ESMO [292]	ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of rectal cancer.	44%	6%	12%	60%	3%	0%	Excluded
ESMO [293]	ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of advanced colorectal cancer	53%	13%	10%	63%	3%	8%	Excluded

APPENDIX 3: SCORES OF EXTERNAL REVIEWERS

Recommendation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Mean	Median	SD	% 4 or 5
Tumours with their distal edge at 15 cm or less from the anal verge, as measured with a rigid rectosigmoidoscope, should be classified as rectal. Distances from the anal verge measured at flexible sigmoido- or colonoscopy are not reliable. The anal verge should be the usual landmark. Nonetheless, the distance between the lower edge of the tumour and the upper limit of the anal canal can be useful. The distance between the lower edge of the tumour and the anal verge is very important, since it influences the type of neoadjuvant treatment, the type of surgery and outcome. For international benchmarking, rectal tumours can be categorized according to their distal edge as "low" (up to 5.0 cm above the anal verge), "mid" (from 5.1 till 10.0 cm above the anal verge) and "high" (from 10.1 – 15.0 cm above the anal verge).	5	5	5	5	5	5	5	4	5	5	5	4	5	5	5	4,87	5	0,35	100%
A biopsy should be obtained from all rectal tumours before the start of any type of treatment (including endoscopic or local excision).	5	5	5	5	5	5	4	5	5	4	5	5	5	5	5	4,87	5	0,35	100%
Patients with rectal cancer should have a total colonoscopy with resection of concomitant polyps if possible. If total colonoscopy is judged to be too risky or if colonoscopy is refused after informed consent, a high quality double contrast barium enema should be performed.	5	4	5	5	4	5	NA	5	3	4	5	5	5	5	5	4,64	5	0,63	93%
CT-colonography can not (yet) be recommended for routine use. However, it may be useful in case of stenosing rectal cancer if the radiological equipment and expertise with audit is available.	5	4	5	5	5	5	3	5	3	5	5	5	5	5	5	4,67	5	0,72	87%
In emergency circumstances, when a total colonoscopy is not possible preoperatively, it should be performed before the start of adjuvant therapy or at least within 3-6 months after surgery.	5	5	5	5	4	5	NA	5	4	5	5	5	5	5	5	4,86	5	0,36	100%
The quality of colonoscopy should be recorded with the aim to achieve a high total colonoscopy rate with a low perforation risk.	5	5	5	NA	4	5	5	5	3	5	5	5	4	5	5	4,71	5	0,61	93%
The serum CEA level should be determined in all patients before the start of any treatment.	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5,00	5	0,00	100%
There is not enough evidence to recommend the routine use of other tumour markers.	5	5	5	5	4	5	5	5	5	2	5	5	5	5	5	4,73	5	0,80	93%
All patients with rectal cancer should have imaging of abdomen and chest for the detection of metastatic disease before elective treatment.	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5,00	5	0,00	100%
A combined thorax and abdomen/pelvis spiral contrast-enhanced CT is recommended for the detection of metastatic disease. If a contrast-enhanced CT is contra-indicated, a thorax spiral CT without contrast and a contrast-enhanced MRI of the liver can be performed.	5	5	5	5	N	5	5	5	4	3	5	5	5	5	5	4,79	5	0,58	93%
FDG-PET/CT can be recommended as an additional investigation, especially for the further staging of patients with apparently resectable metastasis, because of its high overall accuracy.	5	3	5	5	5	5	5	5	4	4	5	5	5	5	5	4,73	5	0,59	93%
In case of emergency surgery, staging for metastatic disease should be performed intra-operatively and postoperatively, if not done pre-operatively.	5	5	5	5	5	5	5	5	5	4	5	5	5	5	5	4,93	5	0,26	100%

Recommendation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Mean	Median	SD	% 4 or 5
A digital rectal examination should be performed, in particular by the surgeon, in case of a rectal tumour estimated to be located up to 10 cm from the anal verge. Information on the fixity and location of the tumour as related to the anal sphincters should be reported.	5	5	5	5	4	5	5	5	5	5	5	5	4	5	5	4,87	5	0,35	100%
Before the start of neoadjuvant treatment the distance from the lower edge of the tumour to the anal verge should be determined with rigid proctoscopy (rectoscopy). Colonoscopy is unreliable to measure this distance.	5	5	5	5	5	4	5	4	3	5	5	1	5	5	5	4,47	5	1,13	87%
If cTN staging will drive therapeutic decisions, TRUS, if performed by an experienced examiner, is recommended for all non-stenosing, resectable tumours in the middle and lower third of the rectum.	5	4	5	5	4	5	NA	5	3	4	5	5	NA	5	5	4,62	5	0,65	92%
If cTN staging will drive therapeutic decisions, any uT3/4 and any uN+ stage should be confirmed by phased array HR-MRI. The cCRM should also be determined by HR-MRI.	5	3	5	5	4	5	NA	5	3	5	5	4	NA	5	5	4,54	5	0,78	85%
If cTN staging will drive therapeutic decisions, a phased array HR-MRI is recommended for all tumours in the upper third of the rectum.	5	3	5	5	3	5	NA	5	3	4	5	4	NA	5	NA	4,33	5	0,89	75%
Diagnostic imaging and its accuracy should be discussed and audited by all (colo)rectal cancer multidisciplinary teams.	5	4	5	5	5	5	5	5	4	4	5	5	4	5	5	4,73	5	0,46	100%
uT1 rectal cancer as well as benign looking, biopsy negative villous adenomata of the rectum that might benefit from endoscopic/local excision/transanal endoscopic microsurgery should be referred to particular multidisciplinary teams with expertise in their management.	5	1	5	3	2	5	NA	4	1	2	5	5	4	5	5	3,71	4,5	1,59	64%
uT1 rectal cancer as well as benign looking, biopsy negative villous adenomata of the rectum should be assessed with rectal endosonography (TRUS) by an experienced examiner before any type of treatment (including excisional biopsy).	5	2	NA	5	5	5	NA	4	5	4	5	5	5	5	5	4,62	5	0,87	92%
Audits of diagnostic performance should be performed.	5	3	5	5	5	5	NA	5	4	5	5	4	4	5	5	4,64	5	0,63	93%
For identification of transmural penetration (T3 or more) and node positivity it is recommended to use at least 2 staging modalities (TRUS and HRMRI or TRUS and MSCT are recommended).	5	2	5	5	4	5	5	4	2	3	5	4	3	5	5	4,13	5	1,13	73%
For clinical decision making, particularly related to neoadjuvant treatment, it is recommended to take into account the highest tumour and/or nodal stage found by means of any imaging modality.	5	5	5	5	4	5	5	5	5	3	5	5	4	5	5	4,73	5	0,59	93%
Patients with resectable rectal cancer should undergo radiotherapy before TME surgery to improve local control.	3	4	5	5	5	5	5	4	1	2	5	5	4	5	5	4,20	5	1,26	80%
A long-course of preoperative radiotherapy combined with some form of 5-FU based chemotherapy (pre- or postoperative) is recommended in patients with resectable rectal cancer.	3	4	5	5	4	5	5	4	1	2	5	5	4	5	5	4,13	5	1,25	80%
A long course of preoperative chemoradiotherapy is recommended in patients with Stage II-III rectal cancer.	3	5	5	5	5	5	5	4	5	5	5	5	5	5	5	4,80	5	0,56	93%
Based on evidence from combined chemoradiation in the postoperative setting in patients with high risk rectal cancer, the use a continuous infusion of FU during preoperative pelvic radiation is recommended.	5	5	5	5	5	5	5	4	NA	4	5	5	NA	5	5	4,85	5	0,38	100%

Recommendation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Mean	Median	SD	% 4 or 5
The use of a protracted infusion of 5-FU during preoperative pelvic radiation is recommended for patients with Stage II-III rectal cancer. Oral 5-FU is an acceptable alternative to intravenous 5-FU during preoperative pelvic radiation.	3	4	5	5	5	5	NA	4	NA	3	5	5	NA	5	5	4,50	5	0,80	83%
A long course (25 times 1.8 Gy combined with 5-FU based chemotherapy) of preoperative RT is recommended for patients with resectable Stage II or III rectal cancer, because it offers the advantage of tumour downsizing and downstaging.	3	5	5	5	5	5	5	5	5	5	5	5	NA	5	5	4,86	5	0,53	93%
A short-course of preoperative RT can be an alternative in patients with a moderate to low risk for local recurrence (middle and high seated RC and/or CRM > 0,2 cm).	5	5	5	5	4	5	4	4	3	4	5	4	NA	5	5	4,50	5	0,65	93%
A long course of RT (minimum 25 x 1,8Gy) should be followed by a long interval (6 to 8 weeks) to improve tumour resectability as a result of tumour downstaging. If a short course of RT (5 x 5Gy) is used, patients should be operated within a week after the end of RT.	5	5	5	5	5	5	5	5	5	5	5	5	NA	5	5	5,00	5	0,00	100%
Higher doses of radiotherapy (> 28 x 1,8Gy) can be used in order to increase tumor response and tumor resectability, provided it is associated with an acceptable toxicity rate.	5	1	5	5	4	5	NA	4	NA	3	5	5	NA	5	5	4,33	5	1,23	83%
Brachytherapy/contact X-ray therapy is not a standard approach in resectable rectal cancer and the use should be limited to clinical trials and specialized centers with experience in these techniques.	5	5	5	5	5	5	NA	5	5	3	5	5	NA	5	5	4,85	5	0,55	92%
Actually, clinical and imaging diagnostic tools, incl. DRE, proctoscopy with biopsies, TRUS, CT, pelvic MRI and FDG-PET scan, do not allow a confident prediction of a histologic complete response. All acceptable-risk patients with a diagnosis of primary rectal cancer should undergo radical resection, regardless of their clinical response to preoperative therapy.	5	5	5	5	5	5	5	4	5	4	5	5	5	5	5	4,87	5	0,35	100%
For initially non-resectable rectal cancer, a long-course (at least 25 fractions of 1.8 Gy) of chemoradiation is recommended in order to obtain tumour downstaging and downsizing. The total dose of radiation that can be administered depends on the volume and type of normal tissues within the irradiated volume and the drugs used in combination with the radiotherapy. The target volume can be limited to the macroscopic tumour after the first 25 fractions of 1.8 Gy in order to allow a higher total dose of irradiation with optimal sparing of the normal surrounding tissues.	5	5	5	5	4	5	5	4	5	4	5	5	NA	5	5	4,79	5	0,43	100%
In the absence of specific data, mechanical bowel preparation is recommended in the context of rectal cancer surgery, although no benefit was observed in the context of colon surgery (including anterior resection).	5	5	5	NA	4	5	3	5	5	4	5	5	3	5	5	4,57	5	0,76	86%
Thromboembolism prophylaxis should be administered in the perioperative period of patients with rectal cancer using graduated compression stockings and appropriate doses of subcutaneous low molecular weight heparine, unless there is a specific contraindication.	5	5	5	NA	3	5	5	5	5	5	5	5	5	5	5	4,86	5	0,53	93%
All patients undergoing surgery for rectal cancer should have a single immediately preoperative dose of antibiotic prophylaxis. Several intravenous antibiotics appear to be effective, but only those covering aerobic and anaerobic germs should be used.	5	5	5	NA	5	NA	5	5	5	5	5	5	5	5	5	5,00	5	0,00	100%
Whenever stoma construction is planned, preoperative counselling and stoma site marking by a specialized nurse is recommended.	5	2	5	NA	5	5	2	5	5	2	5	5	5	5	5	4,36	5	1,28	79%

Recommendation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Mean	Median	SD	% 4 or 5
Surgeons should aim, wherever possible and desirable, to preserve the anal sphincter. A total mesorectal excision (TME) should be performed for tumors in the middle and lower third of the rectum either as part of a restorative proctectomy, a Hartmann's procedure or an abdominoperineal resection. In tumors of the upper rectum, the mesorectum should be divided no less than 5 cm below the lower margin of the tumor (partial mesorectal excision, PME). Care should be taken to preserve the pelvic autonomic nerves and plexuses whenever possible.	5	5	5	NA	5	5	5	5	5	5	5	5	5	5	5	5,00	5	0,00	100%
LE or TEMS should not be a standard curative approach for rectal cancer outside clinical trial. Patient in poor condition or on a palliative course can benefit from these techniques.	5	3	5	NA	4	5	4	4	5	4	NA	5	5	5	5	4,54	5	0,66	92%
The role of local excision for pT1 rectal cancer has become controversial. Local excision or transanal endoscopic microsurgical resection can be recommended for small (< 3 cm diameter) uT1 lesions with the appearance of a villous adenoma and with negative biopsies, located in the infraperitoneal rectum (7-9 cm above the anal verge in men; 5-7.5 cm in women). For pT1 sm 2 and sm 3 lesions, radical resection or adjuvant treatment should follow local excision in patients fit for further therapy; for pT1sm1 close observation is a valid alternative in these patients.	5	2	5	NA	5	5	4	4	5	4	5	5	5	5	5	4,57	5	0,85	93%
In view of the risk of nodal metastasis and decreased disease control, all uT1 lesions located in the intraperitoneal rectum deserve radical TME resection (with low risk of uro-genital dysfunction) if the patient is fit for surgery.	5	5	5	NA	4	5	5	4	5	5	5	5	5	5	5	4,86	5	0,36	100%
Laparoscopic or laparoscopy-assisted surgery for rectal cancer should only be performed by experienced laparoscopic surgeons who have been properly trained, who enter their patients in a trial or audit their results very carefully in a multidisciplinary context.	5	5	5	NA	5	5	5	4	5	4	5	5	5	5	5	4,86	5	0,36	100%
After restorative proctectomy and total mesorectal excision the formation of a colonic pouch, coloplasty or side-to-end colo-anal anastomosis should be considered to improve functional outcome and quality of life.	5	2	5	NA	5	5	3	5	5	5	5	5	5	5	5	4,64	5	0,93	86%
It is advisable to ligate inferior mesenteric artery at its origin in order to ensure best nodal staging. However, the hypogastric nerve should be preserved in the absence of macroscopically abnormal lymph nodes.	5	5	5	NA	5	5	5	5	5	5	NA	3	4	5	5	4,77	5	0,60	92%
During rectal surgery for cancer, lateral lymph node dissection (iliac nodes) is not recommended in the absence of macroscopic disease.	5	5	5	NA	5	5	5	5	5	4	NA	5	4	5	5	4,85	5	0,38	100%
During surgery for rectal cancer, great care should be taken to avoid rectal perforation or tumoral break, especially during abdominoperineal resection. The occurence of intra-operative perforation as well as its location in relation to the tumour site should be reported in the surgical note.	5	5	5	NA	5	5	5	5	5	5	5	5	5	5	5	5,00	5	0,00	100%
A rectal wash-out before re-anastomosis may prevent tumour cell implantation and is recommended, although strong evidence is lacking.	5	4	5	NA	4	5	4	5	5	4	5	4	4	5	5	4,57	5	0,51	100%
A temporary defunctioning stoma should be considered each time the anastomosis is at risk for leakage. This is particularly true for an infra-peritoneal anastomosis after TME.	5	4	5	NA	5	5	5	5	5	5	5	5	5	5	5	4,93	5	0,27	100%
Before TME, patients should be informed about the risk of urogenital dysfunction after resection for mid and low rectal cancer.	5	4	5	NA	5	5	5	5	5	5	5	5	5	5	5	4,93	5	0,27	100%

Recommendation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Mean	Median	SD	% 4 or 5
In case of stenosing rectal cancer, a laparoscopic exploration and construction of a derivative stoma should be considered before starting neoadjuvant treatment. Stenting as a bridge to curative surgery can not (yet) be recommended. Stenting is a promising technique that should be considered for palliation in patients with extensive metastatic disease, who are not fit enough or who are unwilling to have a colostomy.	4	3	5	5	3	5	NA	5	5	3	5	5	5	5	5	4,50	5	0,85	79%
If the goal of adjuvant therapy is to improve survival, there is no evidence to support the use of adjuvant radiotherapy as monotherapy. Although adjuvant radiotherapy as monotherapy decreases local recurrence rate, it is inferior to the combination of radiotherapy and chemotherapy.	5	4	5	5	5	5	4	5	5	5	5	5	5	5	5	4,87	5	0,35	100%
Patients with a resected pathological stage III tumour of the rectum should be considered for chemoradiotherapy, followed by 4 months of chemotherapy.	5	5	5	5	3	5	5	5	5	4	4	5	NA	5	5	4,71	5	0,61	93%
Patients with a resected pathological stage II tumour with unfavorable prognostic features (inadequately sampled lymph nodes, perforation, T4 lesion, poorly differentiated histology) should also be considered for chemoradiotherapy, followed by 4 months of chemotherapy.	5	4	5	3	3	5	4	4	5	3	4	5	NA	5	5	4,29	4,5	0,83	79%
Patients with a resected pathological stage II tumour with favorable prognostic features should only be considered for chemoradiotherapy.	5	4	5	5	4	5	3	4	5	3	5	2	NA	5	5	4,29	5	0,99	79%
There is no benefit of adjuvant chemotherapy alone over adjuvant radiotherapy alone in patients with radically resected rectal cancer or vice versa with respect to OS or DFS.	5	NA	5	5	4	5	NA	5	5	4	5	4	NA	5	5	4,75	5	0,45	100%
When chemotherapy with 5-fluorouracil is given concurrently with postoperative radiotherapy, a continuous intravenous infusion is more effective than the drug administered by bolus infusion.	5	NA	5	5	5	5	5	5	NA	5	5	5	NA	5	5	5,00	5	0,00	100%
FUFA given by IV injection for 5 days every 4 weeks for 6 cycles is the regimen for which the most evidence is available and which clearly prolongs survival in patients with stage III disease.	5	NA	5	5	5	5	NA	5	NA	4	5	4	NA	5	5	4,82	5	0,40	100%
De Gramont FUFA and capecitabine are more effective and less toxic than bolus FUFA.	5	NA	5	5	4	5	NA	4	NA	4	5	5	NA	5	5	4,73	5	0,47	100%
There is insufficient evidence to support the use of adjuvant treatment with portal vein infusion chemotherapy with 5FU in patients with resected rectal cancer.	5	NA	5	5	5	5	5	4	5	4	5	5	NA	5	5	4,85	5	0,38	100%
Although there is no direct evidence supporting the superiority of a combination of chemotherapy and radiotherapy over chemotherapy alone, the combination treatment is recommended because of the known advantage of adjuvant radiotherapy as monotherapy on local recurrence rate.	5	NA	5	3	4	5	5	4	5	3	5	5	NA	5	5	4,54	5	0,78	85%
Any patient with a pathological stage II or III after resection that received preoperative radiotherapy without chemotherapy, should be considered for adjuvant chemotherapy with 5FU during at least six months.	5	NA	5	5	5	5	5	4	5	3	5	4	NA	5	5	4,69	5	0,63	92%
After neoadjuvant radiochemotherapy, the indication for adjuvant chemotherapy in Stage III rectal cancer can be based on the cStaging. However, the benefit of adjuvant chemotherapy (during 4 months) seems to be very limited and may not be indicated in case of a pathologic complete (or almost complete) response.	5	NA	5	3	3	5	NA	4	3	3	5	5	NA	5	5	4,25	5	0,97	67%
Patients to whom adjuvant radiotherapy or chemoradiotherapy is proposed, should be informed of the potential harmful effects, most often diarrhea and fecal incontinence, following sphincter sparing surgery.	5	4	5	5	5	5	5	5	5	5	5	4	5	5	5	4,87	5	0,35	100%
Adjuvant therapy should start within 3 months after surgery. It should not be started in the presence of pelvic septic complications.	5	4	5	5	5	5	5	5	5	4	5	5	NA	5	5	4,86	5	0,36	100%

Recommendation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Mean	Median	SD	% 4 or 5
Patients with liver and lung metastases from rectal cancer should be considered for surgery.	5	3	5	5	5	5	5	5	5	4	5	5	5	5	5	4,80	5	0,56	93%
Patients who are believed, on the basis of imaging, to have resectable liver metastases should be referred to a specialist liver MDT (multidisciplinary team), for an opinion about the feasibility of resection, if they are in relatively good general health (ASA 1-3), have undergone curative resection of their primary colorectal cancer or have a resectable primary tumor. The members of the liver resection MDT should normally be the same as the hepatobiliary (and pancreatic) cancer MDT.	5	NA	5	3	5	5	5	4	5	5	5	5	NA	5	5	4,77	5	0,60	92%
Biopsy of hepatic lesions should not be performed without discussion with the MDT.	5	NA	5	3	3	5	5	4	5	4	5	5	4	5	5	4,50	5	0,76	86%
In conjunction with other imaging modalities, PET can be recommended in the further staging of the extent of metastatic disease, and influences decisions on patient management. PET is useful before resection of metastases to evaluate the extra-hepatic dissemination of the disease.	5	NA	5	5	5	5	5	5	5	5	5	5	5	5	5	5,00	5	0,00	100%
MRI is useful to characterize metastatic liver lesions and to evaluate the volume of liver in case of large resection.	5	NA	5	5	3	5	5	5	4	4	5	4	5	5	5	4,64	5	0,63	93%
The morphology of the metastatic disease must be discussed in a MDT to identify non-resectability and to evaluate the possibility of reversibility. If necessary, a MRI liver and/or PET scan will be performed if they would influence the management of the disease.	5	NA	5	5	5	5	5	5	4	5	5	5	5	5	5	4,93	5	0,27	100%
The ability to achieve clear margins (R0 resection) should be determined by radiologist and surgeon in the liver MDT. The acceptable residual functioning liver volume should be taken into account. Resectability may be achieved by portal vein embolisation or two stage hepatectomy to increase hepatic functional reserve and also by the combinations of surgery and ablation. Patients with extrahepatic disease that should be considered for liver resection include resectable/ablatable pulmonary metastases, resectable/ablatable extrahepatic sites and local direct extension of liver metastases. Those patients with tumours thought to be borderline for resection may have resectable or ablatable disease and should be referred for discussion with the regional hepatobiliary unit before treatment.	5	NA	5	NA	4	5	NA	5	4	4	5	5	5	5	5	4,75	5	0,45	100%
There is no evidence on the need, course of radiotherapy in the case of a resectable primary tumor with resectable metastases. MDT discussion is recommended for decision-making in this setting. A specialist liver and colorectal MDT should decide about the opportunity of synchronous resection of the primary rectal cancer and liver metastasis.	5	NA	5	5	5	NA	5	5	NA	4	5	5	NA	5	5	4,91	5	0,30	100%
Usually, rectal cancer resection and liver resection has not been performed synchronously but management of accessible small metastases detected peri-operatively may be considered for combined resection. Simultaneous colon and liver resection has been shown to be safe and efficient when performed in high volume centres with appropriate experience in liver resectional surgery.	5	NA	5	NA	5	5	4	5	5	5	5	5	4	5	5	4,85	5	0,38	100%
It is also appropriate to provide recovery time after resection of the primary rectal cancer resection and to refer the patient to a specialist liver MDT for consideration of liver resection.	5	NA	5	3	5	5	5	5	5	4	5	5	4	5	5	4,71	5	0,61	93%

Recommendation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Mean	Median	SD	% 4 or 5
Induction chemotherapy is not recommended in patients with metachronous resectable liver metastases.	4	NA	5	3	4	5	NA	4	2	4	5	4	NA	3	3	3,83	4	0,94	67%
However, there is some rationale to give some cycles of chemotherapy before going to liver surgery.	5	NA	5	3	4	5	NA	4	4	4	5	5	NA	5	5	4,50	5	0,67	92%
Patients with potentially resectable disease and who have undergone radical resection of the primary tumour should be considered for resection before consideration of chemotherapy.	5	NA	5	3	5	5	5	4	4	4	5	4	NA	5	5	4,54	5	0,66	92%
Neoadjuvant treatment for liver metastases is not recommended, but could be of interest to shrink liver metastases when thought to be irresectable by a specialist liver	5	NA	5	3	4	5	NA	4	3	5	5	5	NA	5	5	4,50	5	0,80	83%
Several types of chemotherapy could be used to decrease liver metastases with the aim to increase the resection rate. The best regimen appropriate to reduce liver metastases in the hope of resection has not yet been established.	5	NA	5	5	4	5	NA	4	5	4	5	5	NA	5	5	4,75	5	0,45	100%
After R0 resection of colorectal metastases, chemotherapy using systemic 5-FU/folinic acid with or without irinotecan or oxaliplatin is recommended.	5	NA	5	3	4	5	5	5	5	4	4	5	NA	5	5	4,62	5	0,65	92%
The benefit of intra-arterial chemotherapy in combination with systemic chemotherapy is limited and not applicable outside clinical trials. Therefore routine adjuvant hepatic arterial infusion after curative resection for colorectal cancer of the liver cannot be recommended.	5	NA	5	3	5	5	5	4	5	5	5	5	NA	5	5	4,77	5	0,60	92%
Patients with unfavourable primary pathology such as perforated primary tumour or extensive nodal involvement should be considered for chemotherapy prior to liver resection and be restaged at 3 months.	5	5	5	5	5	5	5	4	5	4	5	5	NA	5	5	4,86	5	0,36	100%
In the presence of synchronous non-resectable metastases, and without any hope of future resection, and in absence of sign of local complication, resection of the primary tumor is not recommended.	5	4	5	5	3	5	NA	4	5	5	5	5	NA	5	5	4,69	5	0,63	92%
Symptoms related to the primary rectal cancer should be palliated by local therapy, such as coagulation, radiotherapy, stenting.	5	4	5	5	5	5	4	4	5	5	5	5	NA	???	???	4,75	5	0,45	100%
Chemotherapy must be proposed to patients with non-resectable metastases in good condition.	5	5	5	5	4	5	4	4	5	5	5	5	NA	5	5	4,79	5	0,43	100%
First-line chemotherapy should also be proposed to elderly patients in good condition since the benefit on survival was the same as that observed in younger patients.	5	5	5	5	5	5	4	4	5	4	5	5	NA	5	5	4,79	5	0,43	100%
After progression under first line chemotherapy, taking into account the benefit in survival and QOL, a second line chemotherapy should be proposed to informed patients in good condition.	5	5	5	3	4	5	4	4	5	5	5	5	NA	5	5	4,64	5	0,63	93%
Second line chemotherapy must also be proposed to elderly patients since the benefit on survival was the same as that observed in younger patients.	5	5	5	3	5	5	4	4	5	4	5	5	NA	5	5	4,64	5	0,63	93%
Folfox or Folfiri are recommended as first line chemotheratpy for non-resectable metastases from rectal cancer.	5	NA	5	3	NA	5	5	4	5	5	5	5	NA	5	5	4,75	5	0,62	92%
Oral fluoropyrimidine can be proposed as an alternative to intravenous 5-FU (level of evidence high, strong recommendation). Oral fluoropyrimidine in monotherapy can also be proposed as an alternative to the combination in case of contra-indication to IV therapy or increased risk of toxicity or for the patient's convenience.	5	NA	5	5	4	5	NA	4	5	4	5	4	NA	5	5	4,67	5	0,49	100%

Recommendation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Mean	Median	SD	% 4 or 5
First line bevacizumab in combination with a 5-FU based regimen is certainly an option in first line since bevacizumab increases survival in association with a 5-FU based regimen (level of evidence high, strong recommendation). However, the potential toxicity of bevacizumab must be evaluated in function of the patient's condition and potential contra-indications.	5	NA	5	3	3	5	NA	4	5	4	5	4	NA	5	5	4,42	5	0,79	83%
Raltitrexed is not recommended as first line therapy but may be considered as an alternative in those patients intolerant of 5-FU regimens or in whom 5-FU is contraindicated due to cardiotoxicity in monotherapy or in combination with irinotecan or oxaliplatin.	5	NA	5	3	NA	5	NA	4	NA	3	5	4	NA	5	5	4,40	5	0,84	80%
The sequential (optimox) strategy can be used safely to avoid the toxicity related to the administration of oxaliplatin.	NA	NA	5	3	NA	5	NA	4	NA	3	5	4	NA	5	5	4,33	5	0,87	78%
In case of disease progression several options remain valuable. Cetuximab is a good option in combination with irinotecan for irinotecan-resistant patients.	5	NA	5	3	4	5	NA	4	5	4	5	5	NA	5	5	4,58	5	0,67	92%
Shift to Folfiri for patients resistant to Folfox and vice versa, is another option.	5	NA	5	3	5	5	NA	4	5	4	5	5	NA	5	5	4,67	5	0,65	92%
Cytoreductive surgery with HIPEC is recommended in a selected subset of patients with peritoneal carcinomatosis from colorectal orirgin. Obtaining a complete resection is of major importance for survival.	5	NA	5	NA	2	5	NA	5	5	5	5	2	NA	5	5	4,45	5	1,21	82%
In each case, the decision should be based on a multidisciplinary discussion.	5	5	5	5	5	5	5	5	5	5	5	5	NA	5	5	5,00	5	0,00	100%
Chemotherapy must be proposed to patients with non-resectable metastatic disease in	5	5	5	5	4	5	5	5	5	5	5	5	NA	5	5	4,93	5	0,27	100%
Elderly patients with metastatic colorectal cancer should also be considered for chemotherapy.	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5,00	5	0,00	100%
Short course of RT (one to five fractions) should be available without delay for patients with metastatic disease in bones.	5	5	5	5	4	5	5	5	5	4	5	5	NA	5	5	4,86	5	0,36	100%
Radiotherapy in combination with chemotherapy should also be offered to those patients with locally recurrent or advanced rectal cancer and pelvic pain, who have not previously undergone RT.	5	5	5	5	5	5	5	5	5	5	5	5	4	5	5	4,93	5	0,26	100%
Palliative surgery to relieve intestinal obstruction can have an important role in the management of patients with advanced colorectal cancer.	5	5	5	5	4	5	5	5	5	4	5	4	5	5	5	4,80	5	0,41	100%
Stenting is a promising technique that should be offered to patients not fit enough or unwilling to undergo colostomy.	5	5	5	3	4	5	NA	5	5	5	5	4	4	5	5	4,64	5	0,63	93%
Medical measures such as analgesics, antiemetics and antisecretory drugs should be used alone or in combination to relieve the symptoms of bowel obstruction.	5	4	5	NA	4	5	5	5	5	5	5	5	5	5	5	4,86	5	0,36	100%
Every patient curatively treated for rectal cancer (all stages) should undergo intensive follow-up.	5	4	5	5	5	5	5	4	5	5	5	5	5	5	5	4,87	5	0,35	100%
Every patient should undergo a physical examination and history, CEA measurement, lung imaging (chest X-ray or CT-scan) and liver imaging (ultrasound or CTscan). In patients at higher risk of recurrent disease (i.e. stage II and III) or in those who did not receive radiation therapy a pelvic CTscan or MRI is recommended.	5	5	5	5	4	5	5	4	5	5	5	5	5	5	5	4,87	5	0,35	100%
Every patient should undergo total colonoscopy on a regular basis.	5	4	5	5	3	5	5	4	5	4	5	5	NA	5	5	4,64	5	0,63	93%
Endoscopic ultrasound is only recommended when a local recurrence is suspected or in the follow-up afer local excision/TEMS.	5	4	5	5	4	5	4	5	5	3	5	5	5	5	5	4,67	5	0,62	93%
A history, physical examination and CEAtesting should be done every three months for the first three years, during the fourth and fifth year every six months.	5	4	5	5	4	5	5	4	3	4	5	5	4	4	4	4,40	4	0,63	93%

Recommendation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Mean	Median	SD	% 4 or 5
Patients at higher risk of recurrent disease (i.e. stage II and III) should undergo annually a CT-scan of the chest and abdomen/pelvis during the first three years.	5	4	5	5	5	5	5	4	5	4	5	5	4	5	4	4,67	5	0,49	100%
Liver ultrasound should be done every 6 months in the first three years (not when a CT-scan is done), annually in the fourth and fifth year.	5	4	5	5	5	5	5	4	5	4	5	5	4	3	5	4,60	5	0,63	93%
Chest X-ray is recommended every six months in the first three years, in the next two years only yearly.	5	4	5	5	4	5	5	4	3	4	5	5	4	3	5	4,40	5	0,74	87%
Total colonoscopy should be performed within one year postoperatively, 1 year after the resection (or 1 year following the performance of the colonoscopy that was performed to clear the colon of synchronous disease). If this examination is normal, then the interval until the next examination should be 3 years. If that colonoscopy is normal, then the interval until the next examination should be 5 years.	5	5	5	5	5	4	5	4	5	5	5	5	5	5	5	4,87	5	0,35	100%
The rectal cancer resection specimen should be delivered to the pathologist fresh (within 2 to 3 hours), unopened, and unpinned (except for local excision specimen; cf.). Administrative data, information on personal or family history, cTNM staging, the type of surgery performed, and preoperative treatment modalities should be provided.	5	5	5	NA	5	NA	3	5	5	5	5	5	5	5	5	4,85	5	0,55	92%
The resection specimen should be examined by the pathologist. It is mandatory to determine the exact topography of the tumor, also with reference to the serosal surface, i.e. above, at or below the peritoneal fold of Douglas. The quality of the mesorectal excision should be assessed on the unopened specimen and graded as complete, nearly complete or incomplete. Abdominoperineal rectal excision specimens require specific attention as the description of the quality of the TME is limited to the mesorectal surface; ideally, an APR specimen should have a monocylindrical shape. It is recommended to photgraph the ventral and dorsal aspects of the specimen.	5	5	5	NA	5	NA	NA	4	5	5	5	5	5	5	5	4,92	5	0,29	100%
After examination of the external surface, it should be inked before opening and fixating the specimen. After fixation, the specimen should be sectioned in parallel cuts of 3-4 mm perpendicular to the length of the bowel allowing to assess the deepest point of invasion and to measure the smallest distance between tumor extension and the nearest lateral surface. It is advisable to photograph the parallel cuts taken through the TME to document the quality of the surgical specimen and the extent of the disease and mandatory if large microscopic sections are not used. The deepest point of invasion should be sampled for microscopy, and the distance to the nearest circumferential surface should be measured and reported in mm. No distinction should be made between the various modes of involvement i.e. direct spread, involved lymph node, lymphatic or vascular spread.	5	5	5	NA	NA	NA	NA	4	5	5	NA	5	5	5	5	4,90	5	0,32	100%
The number of blocks to be taken from the tumor is 3 at minimum and 5 at maximum.	5	NA	5	NA	NA	NA	5	5	NA	5	NA	3	5	3	3	4,33	5	1,00	67%
One block at least should include the transition from the surrounding 'normal' mucosa to the tumor and at least one other should include the deepest point of invasion.	5	NA	5	NA	4	NA	5	4	NA	5	NA	5	5	5	5	4,80	5	0,42	100%
Proximal and distal section margins do not have to be embedded if the tumor is situated at a distance of more than 3 cm from these margins. If the tumor is close to a margin, it is recommended to sample this margin and to demonstrate the relationship to the tumor by perpendicular sections. Biopsies have to be taken to assess the circumferential (radial, lateral) margin.	5	NA	5	NA	NA	NA	5	4	NA	4	NA	5	5	5	5	4,78	5	0,44	100%
Ideally, samples should be fixed in formol in order to allow additional molecular pathological examination. Frozen preserved biopsy samples may be important, especially if there are clinical arguments for HNPCC.	5	NA	5	NA	NA	NA	5	4	5	4	NA	5	5	5	5	4,80	5	0,42	100%

Recommendation	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Mean	Median	SD	% 4 or 5
Associated lesions (polyps, IBD, ...) have to be sampled (level of evidence IIb). In polyposis cases, a reasonable number of biopsies should be taken as well as the (proximal and distal) section margins. Proximal and distal section margins should also be embedded in IBD cases.	5	NA	5	NA	4	NA	5	4	NA	4	NA	5	5	5	5	4,70	5	0,48	100%
All lymph nodes included in a resection specimen are considered to be regional. Distinction between paratumoral nodes and others i.e. local vs. regional lymph nodes is not requested. The number of lymph nodes analysed is important. At least 12 lymph nodes should be found and embedded. The numbers of lymph nodes retrieved depends mainly on the effort of the pathologist. The number of positive lymph nodes relates to the number investigated; when less than 8 lymph nodes have been analysed, the proportion of cancers with lymph node involvement is underestimated. However, it may be difficult to find numerous lymph nodes in rectum resections, in particular after preoperative radio-chemotherapy.	5	NA	5	NA	4	NA	5	4	5	4	NA	5	5	5	5	4,73	5	0,47	100%
There is insufficient scientific evidence to recommend micro-dissection techniques or fat clearance.	5	NA	5	NA	NA	NA	NA	3	NA	4	NA	5	5	5	5	4,63	5	0,74	88%
Extra-regional lymph nodes are classified as metastases and should be embedded and described separately.	5	NA	5	NA	4	NA	NA	4	5	4	NA	5	5	5	5	4,70	5	0,48	100%
The pathology report should be standardised, providing all important macroscopic and microscopic data. Mandatory macroscopic data are: - the measurements of the resection specimen, including those of adjacent structures and organs; - the localisation of the tumor in relationship to the peritoneal lining; - the proximal, distal and lateral (circumferential, radial) section margins; if the specimen can not be oriented, the section margins are described as the closest and most distant margin; - the maximal diameter of the tumor; - the macroscopic appearance of the lesion should be described as protruding/exophytic, ulcerating, infiltrating, flat; - the presence of perforation at the tumor site; - the presence of peritoneal deposits; - the presence of associated lesions, e.g. synchronic cancers, polyps and chronic idiopathic inflammatory bowel disease. Mandatory microscopic data are: - the histological type; - the histologic grade of adenocarcinoma, using either a four or three-tiers system, i.e. well (G1), moderately(G2), poorly differentiated (G3) and undifferentiated (G4), or a two-tiers system, i.e. low (G1,G2 - the depth of invasion should be described and translated into the new pTNM classification (cf.); - after irradiation (ypTNM), the grade of tumor regression should be described so that any of the existing - resection margins; a margin of <1 mm is considered positive; - the total number of examined and the number of involved regional lymph nodes; there is insufficient evi - extramural deposits of tumor; defined as deposits that are not obviously within lymph nodes if they mea - the presence of vascular invasion into extramural veins; - the presence of perineural and/or lymphatic and/or vascular invasion may be mentioned; - distant metastasis: the report should mention M1 if microscopic examination of a sample confirms the - cytological examination of peritoneal fluid revealing tumor cells equals M1. If the existence of distant m	5	NA	5	NA	5	NA	5	5	5	5	5	5	5	5	5	5,00	5	0,00	100%
It is recommended to use a check-list.	5	NA	5	NA	4	NA	5	4	5	5	5	5	5	5	5	4,83	5	0,39	100%
The results of the pathology report should be discussed in a multidisciplinary meeting, involving the pathologist, surgeon, radiotherapist, oncologist and gastroenterologists in order to determine further treatment.	5	5	5	5	5	NA	5	4	5	5	5	5	5	5	5	4,93	5	0,27	100%

APPENDIX 4: THE SURGICAL REPORT

The ideal surgical report in patients with colorectal cancer should include:

1. Names of surgeon(s), assistant(s) and anaesthesiologist(s).
2. Date of operation and time start/finished.
3. Mode of surgery: elective, urgent (2-24 hrs), emergency (< 2 hrs).
4. The ASA status of the patient and other data for postoperative mortality risk adjustment.
5. Preoperative treatments (including chemotherapy, radiation therapy).
6. Distance from anal verge (in cm), circumferential localisation and extension, fixity and (actual) cTNM staging.
7. The findings at operative exploration:
    a. site of the primary tumour together with size, fixity, involvement of other structures, abscess, perforation. Its relationship to the pelvic brim and the peritoneal reflection of Douglas should be specifically mentioned.
    b. presence or absence of metastatic disease (liver, peritoneum, omentum, ovaries) and non mesenteric lymph nodes (iliac, periaortic, portohepatic, eliac). A sample of ascites should be sent for cytologic examination. The report should describe any compromise of the exploration due to adhesions or concomitant diseases. Sites of biopsies of areas suspected of having metastatic disease should be mentioned. Also the rationale of not taking a biopsy specimen of metastastic disease should be mentioned.
6. The operative procedure:
    a. site of vascular ligation;
    b. the extent of resection, particularly the extent of mesorectal excision;
    c. the level from the anal verge and methods of anastomosis, including the use of a pouch or coloplasty;
    d. the use and nature of any peritoneal lavage;
    e. the use and nature of any rectal washout;
    f. a statement as to whether or not the surgeon regards the resection as curative (i.e. no residual macroscopic tumour), palliative or uncertain;
    g. site and reason(s) for stoma
    h. the use of drain(s)
7. Any departure from an en-bloc resection, perforation and its location in relation to the tumour site, or any spillage of tumour or stool and the site of placement of clips to aid in radiation therapy should be mentioned.
8. Any frozen sections submitted for examination and other interaction with the pathologist.

APPENDIX 5: PATHOLOGY REPORT CHECKLISTS BELGIAN PROJECT ON CANCER OF THE RECTUM

Patient's name: ……

Given name: ……

Date of birth: ……

Registration number (provided by the data center):
……

Hospital/Laboratory: ……

Pre-operative treatment (induction): ……

RECTAL CANCER: Distance from anal verge ……cm
cTNM staging: ……

ycTNM staging: ……

☐ Abdomino-perineal rectum excision (TME)
☐ Local (transanal) excision – use specific checklist
☐ ……

TYPE OF SURGICAL INTERVENTION

☐ Anterior resection rectum
☐ Restorative rectum resection (TME)

MACROSCOPIC EXAMINATION

☐ fresh ☐ fixed	External surface TME: ☐ smooth, regular ☐ mildly irregular ☐ severely irregular

Rectal tumor location:

☐ ventral ☐ lateral ☐ dorsal	☐ …… ☐ above peritoneal reflection ☐ below peritoneal reflection
☐ multifocal: if second location, please use separate sheet	

Depth of invasion

☐ Tx: primary tumor cannot be assessed
☐ T0: no evidence of primary tumor
☐ Tis: intra-mucosal or intra-epithelial (not beyond muscularis mucosae)
☐ T1: limited to submucosa
☐ T2: limited to muscularis propria
☐ T3: subserosal invasion (invasion beyond muscularis propria)
☐ T4: invasion of serosa or adjacent organ(s)

Length of resected specimen: …… cm
Distance tumor – resection margin:
proximal: ……cm
distal: ……cm

Surgical resection:

Longitudinal margins:

Proximal:	☐ free	☐ invaded
Distal:	☐ free	☐ invaded

Circumferential margin: …… mm remote from tumor

Rectal tumor appearance:

☐ exophytic ☐ ulcerating ☐ infiltrating ☐ flat

Extension:

	yes	no
Tumor perforation	☐	☐
Associated lesions	☐	☐
Polyp(s)	☐	☐
Synchronic cancer(s)	☐	☐
Ulcerative colitis	☐	☐
Crohn's disease	☐	☐
Familial polyposis	☐	☐

Additional samples: ☐ frozen ☐ other fixation ……

Number of lymph nodes examined: ……
Number of invaded lymph nodes: ……
Number of extramural deposits < 3 mm ……
Number of extramural deposits > 3 mm: ……

Nx	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastasis in 1 to 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes

Extramural vascular invasion:

☐ yes	☐ no

Metastasis (liver, peritoneum, …)

☐ yes	☐ no	☐ impossible to determine

HISTOLOGICAL EXAMINATION

☐ Adenocarcinoma

	☐ well ☐ moderate ☐ poorly differentiated	☐ undifferentiated ☐ low grade ☐ high grade

☐ Other: ……

Rectal cancer regression grade (RCRG):

☐ grade 0 ☐ grade 1 ☐ grade 2	☐ grade 3 ☐ grade 4

RECTAL CANCER

☐ pTNM	☐ ypTNM	☐ Tx ☐ Nx ☐ Mx	☐ T0 ☐ N0 ☐ M1	☐ Tis ☐ N1	☐ T1 ☐ N2	☐ T2	☐ T3	☐ T4	

Other classification: ……

Signature: Date:

Patient's name: ……
Given name: ……
Date of birth: ……

Registration number: ……
Hospital/Laboratory: ……
Pre-operative treatment (induction): ……

RECTAL CANCER: Distance from anal verge …… cm
cTNM staging: ……

ycTNM staging: ……

TYPE OF INTERVENTION

☐ **LOCAL (TRANSANAL) EXCISION**

MACROSCOPIC EXAMINATION

☐ fresh ☐ fixed

Rectal tumour location:

☐ ventral ☐ dorsal
☐ lateral ☐ ……
☐ above peritoneal reflection ☐ below peritoneal reflection

☐ Multifocal: if second location, please use separate sheet

Number of fragments ……
Dimensions of resected specimen: …… cm
Distance tumor – resection margin:
proximal: …… cm
distal: …… cm
lateral: …… cm
deep: …… cm

HISTOLOGIC EXAMINATION

☐ Adenocarcinoma
☐ well ☐ undifferentiated
☐ moderate ☐ low grade
☐ poorly differentiated ☐ high grade
☐ Other: ……

Depth of invasion

☐ Tis: intra-mucosal or intra-epithelial (not beyond muscularis mucosae)
- m1
- m2
- m3

☐ T1: limited to submucosa
- sm1
- sm2
- sm3

☐ T2: limited to muscularis propria

Rectal tumour location

☐ exophytic ☐ ulcerating ☐ infiltrating ☐ flat

Tumour perforation: ☐ yes ☐ No

Surgical resection:

Longitudinal margins:		
Proximal:	☐ free	☐ invaded……mm
Distal:	☐ free	☐ invaded……mm
Lateral:	☐ free	☐ invaded……mm
Deep:	☐ free	☐ invaded……mm

Additional samples:
☐ frozen
☐ other fixation

Extension:
☐ lymphatic invasion

RECTAL CANCER

☐ pTNM ☐ ypTNM

Other classification: ……

☐ T0	☐ Tis	☐ T1	☐ T2
	☐ -m1	☐ -sm1	
	☐ -m2	☐ -sm2	
	☐ -m3	☐ -sm3	

Signature :

Date :

APPENDIX 6: THE HANDLING OF THE SPECIMEN AFTER LOCAL EXCISION FOR (EARLY) RECTAL CANCER

"Early" rectal cancer can have different presentations varying from the so-called "malignant" polyp (invasive adenocarcinoma arisen in a pedunculated adenoma) up to the (de novo) infiltrating carcinoma limited to the superficial layers of the bowel wall. Compared to other segments of the gastro-intestinal tract, the colon is unique in that the colonic mucosa appears to contain very few lymphatic vessels, especially so under normal circumstances. This anatomical peculiarity underlies 1) the potential therapeutic value of local excisions and 2) the specific TNM classification : pTis = carcinoma in situ : intraepithelial (within basement membrane) i.e. non-invasive or invasion in the lamina propria (intramucosal) with no extension throughout the muscularis mucosae into the submucosa ; while pT1 equals tumour invading the submucosa. From the point of view of the pathologist the finding of an early rectal cancer can be fortuitous e.g. a malignant polyp or consist of a "first intention" therapeutic excision. There are no specific guidelines describing the handling of the latter local excision specimens, especially the local excisions of non-pedunculated lesions. The following description is mainly based on analogies with the handling of other specimens, a.o. EMR (endoscopic mucosal resection for e.g. Barrett lesions).

Assessment of the completeness of excision (R0) and of histologic features "negatively" influencing prognosis a.o. related to the risk of lymph node metastasis are important to predict prognosis and especially to assess the need for additional treatment i.e. more radical surgery. Standardisation of data, the application of well-defined criteria, and the acceptance of an identical and unique staging system allow integration and comparison of data.

Handling of the specimen

- The specimen should preferentially be received fresh, i.e. unfixed, and should be examined by a pathologist preferentially together with the clinician who performed the intervention (gastroenterologist or surgeon). The latter is mandatory if the specimen is received fragmented and (tentative) assessment of the surgical margins is aimed for.
- Administrative data, information on personal and family history, cTNM staging, type of intervention performed and if applicable preoperative treatment modalities should be provided. Additional information is needed if the specimen was received fragmented in order to aid orientation.
- It is important to inspect the specimen and to identify the lesion(s) and the margins most at risk of involvement as this will influence the orientation of the sectioning / embedding of the specimen. Usually, the lesion can be better visualized in the unfixed state.
- Macroscopic inspection of the specimen can be improved by the use of a dissection microscope.
- The margins of the specimen should be marked with ink. Different colours can be used although this is not mandatory.
- Before fixation the specimen should be pinned out – taken care not to over-stretch the specimen – on a cork or wax support. It is advisable to photograph the specimen to document the lesion.
- Ideally the specimen will be fixed in formol in order to allow molecular pathological examination. Taking frozen preserved biopsy samples may be important, especially if there are clinical arguments for HNPCC. Care should however be taken not to interfere with the assessment of completeness of excision.

- Depending on the size of the specimen it may either be entirely sectioned in parallel cuts of 2-3 mm thickness perpendicular to the most critical section margin or it may be sectioned in parallel cuts of 2-3 mm thickness from one side to the other side and additional cuts may be taken perpendicularly to assess the remaining margins. If technically feasible the first option should be preferred.
- All the cuts should be embedded. The number of cuts in one cassette should be limited. If the lesion is polypoid / villous it is likely that small fragments will get detached from the primary lesion during handling. These fragments should be embedded separately.

Pathology report

The pathology report should be standardised, providing all important macroscopic and microscopic data. As already mentioned the need for additional treatment will be based on : the completeness of excision (R0), less than 1 mm is considered positive ; the depth of invasion and especially the risk of lymph node metastasis : i.e. the degree of differentiation (G3) and the presence of lymphatic invasion (L1). The presence of "budding" has been described as a risk factor for lymph node metastasis, especially by Japanese authors. Most often "budding" is described as 1 or a few (5) cells budding of the adjacent tumoral glands at the actively invading region and invading into the stromal component. The definition, but especially the grading of budding is ill-defined. The scientific evidence for a predictive value is therefore limited. The presence of vascular invasion is related to local recurrence and distant (haematogenous) metastasis. The value of perineural invasion, which is unlikely to be seen in local excisions, is not documented in this specific setting.

- Mandatory macroscopic data are :
  - the measurement of the specimen
  - the maximum diameter of the lesion
  - localisation of the lesion in relationship to the margins
  - the macroscopic appearance of the lesion should be described as protruding/exophytic, ulcerating, infiltrating, flat
  - the presence of perforation at the site of the lesion
- Mandatory microscopic data are :
  - the layers of the bowel wall included in the specimen : mucosa, submucosa, muscularis propria, …
  - the presence of artefacts hampering interpretation (e.g. extreme coagulation artefacts)
  - the histological type of the lesion (i.e. adenocarcinoma)
  - the histologic grade of the adenocarcinoma, using a four-tiers system i.e. well (G1), moderately (G2), poorly (G3) or undifferentiated (G4) ; mucinous carcinoma (colloid) and signet ring cell carcinoma are to be considered as poorly differentiated carcinoma
  - the depth of invasion should be described and translated into the appropriate classification ; the depth of invasion of the submucosa can be expressed in relative depth (1/3 of thickness ; Kudo e.a.) or in absolute depth of invasion (µm). If the submucosa is not entirely included in the specimen the latter classification system should be used. The Haggit RC e.a. (1985) classification of colorectal carcinomas arising in adenomas has never achieved much clinical impact and should be avoided.
  - m1 : upper third of the mucosal thickness
  - m2 : middle third of the mucosal thickness
  - m3 : deepest / lower third of the mucosal thickness

- sm1 : upper third of the submucosal thickness alternatively less than 500 µm of depth of invasion into the submucosa
- sm2 : middle third of the submucosal thickness alternatively between 500 and 1000 µm of depth of invasion into the submucosa
- sm3 : deepest / lower third of the submucosal thickness alternatively more than 500 µm of depth of invasion into the submucosa
- resection margins : lateral and deep
- the presence of lymphatic invasion
- the presence of vascular invasion
- the presence of perineural invasion may be mentioned
- the presence of budding may be mentioned

- It is recommended to use a check-list.

The results of the pathology report should be discussed in a multidisciplinary meeting, involving the pathologist, surgeon, radiotherapist, oncologist and gastroenterologists in order to determine further treatment.

APPENDIX 7: RADIOLOGY: TECHNICAL RECOMMENDATIONS

Staging of rectal cancer with multi-slice CT: suggested parameters

- spiral CT of the thorax and the abdomen during the same session
  - at least four rows of detectors
  - with intravenous contrast injection
    - dose and injection rate : 120 cc 2-3 cc/sec
  - Chest CT:
    - Acquisition : 35 seconds after IV injection
    - Parameters: slice thickness 5 mm or lower
  - Abdominal CT:
    - Acquisition: 65-70 seconds after IV injection
    - Parameters : slice thickness 5 mm or lower
    - Oral contrast: 750-1000 cc of 3% Hypaque or equivalent

Imaging of rectal cancer with MRI: suggested sequences

Lymph nodes: whole pelvis

- transverse T2 - weighted spin echo without fat suppression (<= 7 mm)
- transverse true FISP (< = 7 mm)

Tumour:

- transverse T2 - weighted spin echo without fat suppression, 5 mm /0,5 mm
- transverse T2 fat suppression; 5 mm /0.5 mm
- other plan , without fat suppression
  - coronal or sagittal depending on the location of the tumour
- transverse T1 fat suppression, before and with IV contrast
  - 5 mm / 0,5 mm

Recommended MRI report:

The MRI report has to contain a T and N staging and the CRM (circumferential resection margin) estimated in mm:

- Estimation of the T category:
  - T1: The tumour is located in the submucosa, appears with a lower signal intensity than the submucosa and does not extend into the circular muscle layer.
  - T2: The tumour is located in the submucosa and in the muscular layer. There is a disappearance of the interface between the submucosa and the muscular propria. The lesion appears with an intermediate signal intensity (higher signal than muscle, lower signal than submucosa) within muscularis propria. The lesion does not extend into the perirectal fat (i.e a hypointense rim persists around the tumour).
  - T3: The tumour invades the mesorectal fat with the loss of the interface between the muscular propria and the perirectal fat tissue. The tumour bulges or has nodular projections beyond the outer muscle layer. Spiculations are more indicative of fibrodesmoplatic reaction.

  - T4: The tumour extends into adjacent organs (prostate, seminal vesicles,…) and /or perforates visceral peritoneum.
  - The limitations of MRI for the distinction between T2 and T 3 categories are well known (overstaging).
- Estimation of the N category:
  - Size of the lymph nodes : not relevant (threshold : 4 mm)
  - The shape of the lymph node has to be considered:
    - Irregular aspect
    - Signal heterogeneity
    - These signs are indicative of tumour invasion
- Circumferential Resection Margin:
  - 5 mm with MRI corresponds to 1 mm at surgery

APPENDIX 8: RADIOTHERAPY: TECHNICAL CONSIDERATIONS

Radiation dose

The radiation dose will be specified at the ICRU-50 reference point, which is to be located in the central part of the clinical target volume (CTV). This reference point is further described above. The isodose curve representing 95% of the prescription dose must encompass the entire planning target volume (PTV) which is defined above. The standard deviation of the dose within the PTV should be as small as possible and not superior to 2% (≤ 2%) provided the Dmean and Dmedian are close to each other. Each field is to be treated every day. A volumetric treatment planning CT study is required to define the CTV and the PTV. Contiguous CT slices with 3-5 mm separation of the whole pelvis should be taken. The CTV will be outlined on all appropriate CT slices and displayed using beam's eye views. The PTV is to be treated with any combination of coplanar or non-coplaner three-dimensional conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions. A planned radiotherapy volume using at least 3 or 4 beams is recommended as this reduces morbidity and mortality.

Beam energy

Radiation therapy is delivered by photon radiation generated by a linear accelerator. Megavoltage equipment is required with effective photon energies ≥ 6MV. Mixed beams are allowed with higher energy for the lateral beams compared to the posterior beam. The use of 3D conformal radiotherapy capabilities is recommended.

Dose prescription

The dose will be prescribed at the center of the target area or at the intersection of central rays of the beam.

Patient treatment position

Patients must be reproducibly immobilized. Measures should be taken to reduce the volume of small bowel e.g. by using a belly board and/or treatment of the patient with a full bladder.

Shielding and verification

The radiation target volume will be defined by shaped ports with custom-made blocks or multileaf collimation. Portal verification shall be done for all treated fields. A maximum of 0.5 cm of deviation will be accepted.

Compensating filters or wedges

In the case of a large sloping contour, wedges or compensating filters should be used. If necessary, appropriate reduction in field size must be done to avoid excessive irradiation to critical structures.

APPENDIX 9: EVIDENCE TABLES BY CLINICAL QUESTION

What method should be used for the detection of synchronous colonic lesions (polyps, cancer) in patients with rectal cancer?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	Jan 2001	Colorectal cancer	Total colonoscopy or barium enema before treatment whenever possible. Where the radiological expertise and equipment exist, a CT pneumocolon is recommended as a sensitive test for colorectal cancer, but not for polyps < 10 mm.	1 cohort study		Low
				If impossible (emergency), total colonoscopy should be performed within 3 months.	None		
NICE	[54]	March 2003	Colorectal cancer	Colonoscopy is significantly more sensitive than barium enema for the detection of both colorectal cancer and polyps, but barium enema is associated with a much lower risk of complications.	1 SR, 1 retrospective study		Moderate
				Colonoscopy should be performed by an appropriately trained examiner.	1 RCT on sigmoidoscopy only,6 uncontrolled studies, 2 audits		Low
				CT colonography discussed but no recommendation	1 SR		NA
DGVS	[52]	Unsure	Colorectal cancer	Total colonoscopy with biopsy.	3 case-series or poor quality cohort studies		Low
				If stenosing, total colonoscopy 3-6 mo postoperatively.	No refs		

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
Halligan S	[56]	4181 pts undergoing screening for CR polyps or cancer	CT colonography Colonoscopy (reference standard)	Detection of polyps Detection of cancer	Large polyps: per-patient average sensitivity 93% (95%CI 73% - 98%) and specificity 97% (95%CI: 95% - 99%) Large and Medium polyps: sensitivity 86% (95%CI: 75% - 93%) and specificity 86% (95%CI: 76%, -93%), Cancer (150 cancers) sensitivity 96% (95%CI 91% - 99%)	24 articles (1994-2003) CT colonography seems sufficiently sensitive and specific in the detection of large and medium polyps; it is especially sensitive in the detection of symptomatic cancer. Studies are poorly reported	SR Meta-analysis	low
Mulhall BP	[57]	6393 pts undergoing screening for CR polyps or cancer	CT colonography (reference colonoscopy or surgery)	Detection of polyps	Sensitivity was heterogeneous but improved as polyp size increased (48% [95% CI, 25% to 70%] for detection of polyps <6 mm, 70% [CI, 55% to 84%] for polyps 6 to 9 mm, and 85% [CI, 79% to 91%] for polyps >9 mm). Specificity was homogenous (92% [CI, 89% to 96%] for detection of polyps <6 mm, 93% [CI, 91% to 95%] for polyps 6 to 9 mm, and 97% [CI, 96% to 97%] for polyps >9 mm)	33 articles (1975-2/2005) Heterogeneity of sensitivity raises concerns about consistency of performance and about technical variability. These issues must be resolved before CT colonography can be advocated for generalized screening for colorectal cancer	Meta-analysis	low
Purkayastha	[294]	563 pts undergoing screening for CR polyps or cancer	MR Colonography Colonoscopy (reference standard)	MRC accuracy	All lesions: Sensitivity 75% (95% CI 47-91) Specificity 96% (95% CI 86-98) DOR 52.82 CRC: Sensitivity 91% (95% CI 79-97) Specificity 98% (95% CI 96-99) DOR 576.41	8 articles Wide range of techniques (confounder) Low accuracy for polyps Must be compared with CTcolonography No data related to cancer location (data not available in articles) In development, not ready for routine use	SR	very low

Are tumour markers useful staging tools in patients with rectal cancer?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
DGVS	[52]	Unsure	Colorectal cancer	CEA obligatory	3 references	CEA is an independent prognostic factor (extrapolation from colorectal cancer series)	Moderate
Locker GY 2006	[58]	1999	Colorectal cancer	CEA is not recommended as a screening test for colorectal cancer.	?		Low
				CEA may be ordered preoperatively in patients with colorectal carcinoma if it would assist in staging and surgical treatment planning. Although elevated preoperative CEA (> 5 mg/mL) may correlate with poorer prognosis, data are insufficient to support the use of CEA to determine whether to treat a patient with adjuvant therapy.	?		Low
				Present data are insufficient to recommend CA 19-9 for screening, diagnosis, staging, surveillance, or monitoring treatment of patients with colorectal cancer.	?		Low
				Neither flow cytometrically derived DNA ploidy (DNA index) nor DNA flow cytometric proliferation analysis (% S phase) should be used to determine prognosis of early-stage colorectal cancer.	?		Low
				Present data are insufficient to recommend the use of p53 expression or mutation for screening, diagnosis, staging, surveillance, or monitoring treatment of patients with colorectal cancer.	?		Low
				Present data are insufficient to recommend the use of the *ras* oncogene for screening, diagnosis, staging, surveillance, or monitoring treatment of patients with colorectal cancer.	?		Low

What imaging technique(s) can be recommended for the detection of metastatic disease in patients with rectal cancer?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	Jan 2001	Colorectal cancer	All patients undergoing elective surgery for colorectal cancer should have preoperative imaging of the liver and chest. Liver CT or MRI more sensitive than abdominal US Intraoperative US + palpation most accurate	1 systematic review 2 observational studies		Low
				In patients requiring emergency surgery intraoperative liver ultrasound or postoperative imaging is acceptable.	No refs		Very low
				Intraoperative ultrasound is appropriate if a preoperative diagnosis of liver metastases would not alter the need for operative intervention.	No refs		Very low
FNCLCC	[59]	2001	Colorectal cancer patients with suspicion of liver metastases	CT chest and abdomen, with IV injection	Multiple observational studies	These guidelines relate to the evaluation of patients with (mainly metachronous liver) metastasis	Low
				MRI if CT not possible			
				MRI if CT with Injection doubtful			
				Pet when resection of liver Met is considered in patients with high risk of extrahepatic disease			
NICE	[54]	March 2003	Colorectal cancer	Intra-operative US (incl. at laparoscopy) more accurate than CT	1 cohort study (from 1996) (RCT)	Due to heterogeneity (one high level study and 3 observational studies with serious limitations)	Moderate

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				CE-CT more sensitive than abdominal US	1 comparative study; 2 non-comparative studies		Low
				FDG Pet is the most sensitive non-invasive imaging modality for the diagnosis of hepatic metastases from colorectal cancers	MRI and Pet FDG discussed in a separated chapter in the metaanalysis of Kinkel, 2002		High
DGVS	[52]	Unsure	Colorectal cancer	Abdominal US obligatory if suspected lesion: abdominal spiral CT or MRI	Not given	No refs	Very low
				Thorax X-ray obligatory if suspected lesion: thorax spiral CT			
CCO	[68]	2004	Patients with a colorectal cancer	Prior to surgery patients with rectal cancer should have full staging including adequate images of the chest (i.e., an X-ray), abdomen and pelvis.	8 cases series; 4 comparative studies	US: - sensitivity 48-75 % - specificity 91-100 % CT: - sensitivity 76-100 % - specificity 79-100 %	Low
				CT or MRI scanning of the abdomen is recommended over ultrasound for detecting liver metastases.			

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
Bipat 2005	[60]	3187 patients with colorectal cancer	CT, MR imaging, or FDG PET. Reference standard: histopathologic analysis (surgery, biopsy, or autopsy), intraoperative palpatation, US and/or follow-up US.	Assessment of liver metastases on per-patient and per-lesion bases.	Sensitivity estimates on a per-patient basis: nonhelical CT 60.2% helical CT 64.7%, 1.5-T MR imaging 75.8%, FDG PET 94.6% Sensitivity estimates on a per-lesion basis: nonhelical CT 52.3%, helical CT 63.8%, 1.0-T MR imaging 66.1%, 1.5-T MR imaging 64.4%, FDG PET 75.9%. Estimates of gadolinium-enhanced MR imaging and superparamagnetic iron oxide (SPIO)-enhanced MR imaging were significantly better, compared with nonenhanced MR imaging (P = .019 and P < .001, respectively) and with helical CT with 45 g of iodine or less (P = .02 and P < .001, respectively). For lesions of 1 cm or larger, SPIO-enhanced MR imaging was the most accurate modality (P < .001).	Thorough search Specificity not evaluated Slice thickness at CT should not be lower than 5 mm	Meta-analysis	Moderate

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
van Erkel 2002	[295]	Pts with colorectal carcinoma	Medline 1994 – 1/2001. 47 pts with colorectal carcinoma and having surgery , intraoperative liver palpation + US (355 lesions; 252 malignant and 103 benign)	To determine the size of hepatic metastases, the standard of reference and the reported detection rate in pts with colorectal cancer	Hepatic metastases of colorectal cancer are frequently smaller than 20 mm. When the standard of reference is suboptimal, many small metastases are excluded from the analysis and detection rate are therefore inflated.		Observational study + meta-analysis	Low
Dietrich 2006	[296]	131 pts with extrahepatic primary tumours and an indication for diagnostic assessment of possible liver metastases 44 with colorectal carcinoma	CE-US (Sonovue) conventional US triphasic CT Reference: combination of all available information from imaging (CT and MRI) + histology (17), surgery (8) and other clinical examinations (4) except results from US (being a test method).	Accuracy of CEUS versus US, CT and MRI	Conventional US Sensitivity: 84,6 % specificity: 78 % accuracy: 81,4 % Contrast enhanced US sensitivity: 88,5 % specificity: 94 % accuracy: 91,2 % Spiral CT sensitivity: 92,3 % specificity: 86 % accuracy: 89,2 % MRI : Sensitivity, Specificity, Accuracy not specified in the paper	Mixed population Multicentric study	Observational study	Low

What imaging techniques can be recommended for the locoregional cTN staging of patients with rectal cancer?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	Jan 2001	Colorectal cancer	Preoperative imaging of primary rectal cancer may clarify operability and aid decisions regarding chemotherapy or radiotherapy delivered preoperatively (neoadjuvant chemo-radiation).	1 SR (Kwok), 1 exploratory cohort (MRI)	4 (expert opinion); GPP. EL of individual studies not (clearly) given	Moderate
NICE	[54]	March 2003	Colorectal cancer	Muscle penetration (T3): TRUS more accurate than MRI or CT. MRI more accurate than CT (but wide variability, overlap and not entirely consistent, no good quality comparative studies; the technology used to be considered out-of-date)	CT and/or MRI and/or TRUS: 1 SR (Kwok), 1 comparative study and 12 non-comparative studies TRUS or EUS for differentiating benign tumours from early rectal cancers: 1 SR (Kwok), 26 cohort studies		Moderate
				Patients with invasive rectal cancers for whom surgery is being considered should have MRI scans before treatment begins, to determine the precise location and extent of the tumour and clarify who might benefit from adjuvant therapy and who is likely to be adequately treated by surgery alone.			Moderate
				Nodal involvement: TRUS more accurate than MRI; MRI more accurate than CT			Moderate
CCO	[68]	Sept 2004	Colorectal cancer	If T and N category determinations will drive decisions on the use of neoadjuvant therapy, transrectal ultrasound or MRI with endorectal coil is recommended. Operator skill is more likely to influence the accuracy of transrectal ultrasound versus MRI with endorectal coil. It is likely that advances in technology will demonstrate similar	1 SR (Kwok), 22 case series		Moderate

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				staging accuracy for routine MRI versus MRI with endorectal coil.			
DGVS	[52]	Unsure	Colorectal cancer	Obligatory examinations are: TRUS (certainly before local excision) Useful in some patients can be: Pelvic CT or MRI (for T3/4 and N+ tumours) Anal manometry Gynaecologic examination cystoscopy		Operator dependent; impossible if stenosis MSCT promising; HR-MRI for CRM	Moderate to very low

Can TRUS distinguish between a pT1 and a pT0 in patients with a benign looking, biopsy negative villous adenoma of the rectum?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
DGVS	[52]	Unsure	Colorectal cancer	Local (full thickness) excision can be sufficient in pT1 carcinoma wit a diameter up to 3 cm, good or moderately differentiated, without lymphatic vessel invasion (low-risk histology) with negative section margins (R0)	1 SR 1 observational study		High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
Worrell S 2004	[65]	258 pts biopsy negative for cancer rectal villous adenoma	Biopsy only Biopsy + TRUS Histology as the reference standard	Prediction pT1 vs pT0	Prevalence of pT1 = 24% (62/258) False negative biopsy in 24% TRUS sensitivity 81% CI 69-90 (50/62) TRUS specificity 88%CI 83-92 (172/196) TRUS accuracy 86% (222/258) TRUS PPV = 68% (50/74) TRUS NPV = 93% (172/184)	5 articles (1986-2003) TRUS false + results can be reduced by performing TRUS before snare excision, by using higher freq, higher resolution US probes Expertise is required!	SR	Moderate
Kneist W 2004		286 pts with adenomas (175) or pT1-3 (111) up to 15 cm. Excised by TEMS or LE	DRE TRUS (1 examiner)	Prediction pT2-3 vs pT0-1	Prevalence pT2-3 = 15% (43/286) DRE sensitivity 78% DRE specificity 58% DRE PPV 85% DRE NPV 51% TRUS sensitivity 62% (25/43) TRUS specificity 93% (230/243) TRUS accuracy 89% (255/286) TRUS PPV 66% (25/38) TRUS NPV 93% (230/248)	TRUS is more performant than DRE and essential before TEMS or LE. The authors consider 'low risk' T1 as an appropriate indication for TEMS/LE Does not answer the question	Cohort study	Very low
Kulig J 2006	[297]	29 patients with uT1	TRUS	pT2 vs. T1	sensitivity 50% specificity 92.3% accuracy 89.2% PPV ? NPV ?	Retrospective Small series Single center N of pT0 patients = ? Does not answer the question	Cohort	Very low

What imaging technique should be used to identify transmural invasion in a patient with rectal cancer?

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
Bipat S 2004	[298]	3187 patients with colorectal cancer	TRUS CT MRI Histology as the reference standard	Summary estimates of sensitivity and specificity for invasion of perirectal tissue and adjacent organs Summary receiver operating characteristic (ROC) curves for perirectal tissue invasion	T3 or more vs. T2 or less TRUS sensitivity 90 (88-92) > CT sensitivity 79 (74-84) and MRI sensitivity 82 (74-87) TRUS specificity 75 (69-81), CTspecificity 78 (73-83) and MRI specificity 76 (65-84) T4 vs. T3 or less Sensitivity EUS 70 (62-77) = CT 72 (64-79) = MRI 74 (63-83) Specificity EUS 97 (96-98) = CT 96 (65-97) = MRI 96 (95-97)	90 articles (1/1985-12/2002) with >20 pts EUS better than CT or MRI for perirectal invasion (more understaging with CT or MRI than with EUS), but comparable overstaging in about 25%. EUS, CT and MRI equally performant for adjacent organ invasion (with 25-30% understaging, but almost no overstaging)	Meta-analysis	Moderate
Marusch 2002	[299]	499 non-consecutive pts with RC, 422 analysed: pT1 67 pts pT2 132 pts pT3 196 pts pT4 27 pts	TRUS versus histology of resection specimen	Diagnosis of T3-4 vs. T1-2	sensitivity 83.4% (186/223) specificity 70% (139/199) accuracy 77% (325/422) PPV 76% (186/246) NPV 79% (139/176) Accuracy highly variable even between high volume hospitals (>30/yr): 58%-82.9%)	49/75 hospitals performed TRUS for RC. TRUS was performed in 34% of RC (more frequently in the distal 2/3 of the rectum) in these 49 hospitals. Accuracy of TRUS used as a routine examination is lower than that reported in the literature. TRUS may aid decisions relevant to treatment only when used by well-trained investigators with a large case load of rectal carcinoma patients. Centralization of TRUS service is mandatory if a high level of quality is to be achieved with this method.	Observational cohort (non-consecutive, multicenter, prospective)	Very low
Knaebel HP 2005	[73]	First period: 424 pts with cancer	TRUS by 4 experienced	Accuracy	TRUS: T staging: 81%	Retrospective Single center (Heidelberg)	Cohort	Very low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
		Second period: 332 pts with tumour (incl. adenomas)	surgeons EUS as routine (6 examiners)		N staging 76% EUS: T staging 71.7% (76% after excl. post CRT pts) 22.9% T overstaging 42.2% overstaging of T2 as more advanced	(full paper not available) Accuracy decreases when performed by less experienced operators and after chemoradiation. Main problem is overstaging (overtreatment).		
Poon FW 2005	[300]	42 pts with T2-4 RC (6 had CRT)	MRI pelvic phased-array coil 1.5 T. T2-weighted fast spin echo (FSE).	Diagnosis of T3-4 vs. T2	Sensitivity 86% (25/29) Specificity 68% (5/13) Accuracy 60% (25/42). PPV 83% (25/30) NPV 67% (8/12) All post CRT were correctly staged.	Retrospective 1 radiologist Blinding not mentioned Moderate diagnostic accuracy Difficulty in distinguishing T2 from early T3	Cohort (retro, non-consecutive)	Very low
Tatli 2006	[301]	51 non-consecutive pts with resected RC	MRI pelvic phased-array coil + endocoil. 1.5 T. T2-weighted FSE	T3 vs T0-2 (0 after CRT) Stage II-III vs. Stage I Interobserver agreement	MRI pelvic phased-array coil + endocoil: sensitivity 93% (14/15) specificity 86% (31/36) accuracy 88% (45/51)(96% if no CRT) PPV 74% (14/19) NPV 97% (31/32) Highly predictive to exclude T3 1.5 T. T2-weighted FSE: Sensitivity 95% (18/19) Specificity 75% (15/20) accuracy 85% (33/39) PPV 78% (18/23) NPV 94% (15/16) Interobserver agreement for T3 prediction excellent (k = 0.85)	1 MRI radiologist evaluated images retrospectively without knowledge of histology. 7 radiologists interpreted MRI pre-treatment. The added value of endocoil can not be assessed	Non-consecutive cohort	Very low
Kulinna C	[302]	63 non-consecutive	EUS	Accuracy for	TRUS	Only data of pts who had both	Cohort	Very low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
2004		pts with RC	DCMSCT	T3-4 vs. T1-2	Sensitivity 63% Specificity 59% Accuracy 60% PPV 48% NPV 72% DCMSCT Sensitivity 87% Specificity 85% Accuracy 86% PPV 84% NPV 88% Accuracy was not significantly influenced by CRT	exams are presented DCMSCT performs significantly better for T1/2 vs T3/4, for N0 vs N+ and for Stage I vs Stage II/III, but TRUS performance was lower than in many other studies. More than 50% of pts had chemoradiotherapy, a potential confounder.	retrospective, non-consecutive (comparative)	
Mathur P 2003	[303]	36 pts RC T1-4	Helical CT scanner MRI 1.0 T body coil	T3-4 vs T1-2	CT: Sensitivity 41% (9/22) Specificity 77% (10/13) Accuracy 54% (22/35) PPV 75% (8/12) NPV 43% (10/23) MRI: Sensitivity 73% (16/22) Specificity 46% (6/13) Accuracy 63% (22/35) PPV 70% (16/23) NPV 50% (6/12)	Body coil 1.0 T MRI No data on N stage Preliminary study and no agreement between MRI and CT (k=0.21) Covered in CCO evidence table but wrongly reported	Cohort – comparative study	Very low
Brown G 2003	[11]	99 pts pT1 6 pT2 22 pT3 59 pT4 11 pN+ 40	MRI pelvic phased-array high resolution 1.5 T	T3/4 vs T1/2	Sensitivity 91% (64/70) Specificity 71% (20/28) Accuracy 86% (84/98) PPV 89% (64/72) NPV 77% (20/26)	No comparator Rather an exploratory study	Observational study (consecutive)	Low
Branagan	[304]	40 pts (from 72	MRI 1 T, pelvic	T stage	Correlation with pathologic T	Although 'experienced', the	Observational	Very low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
2004		consecutive cases) ; preop RT excluded pT1 3 pT2 17 pT3 18 pT4 2 pN+ 17	phased-array high resolution (with rectal air insufflation) 1 experienced examiner	T3/4 vs T1/2	stage :poor (kappa:0.18) Sensitivity 40% (8/20) Specificity 70% (14/20) Accuracy 55% (22/40) PPV 57% (8/14) NPV 54% (14/26)	authors illustrated a learning curve for T staging! Small number of pts	study	

What imaging technique should be used to identify nodal involvement in patients with rectal cancer?

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
Bipat S 2004	[298]	90 articles 1/1985-12/2002 with >20 pts and histology as the reference standard	TRUS CT MRI	N+ vs. N0 Bivariate random-effects analysis for summary estimates of sensitivity and specificity for lymph node involvement Summary receiver operating characteristic (ROC) curves were fitted for lymph node involvement	TRUS sensitivity 67% (60-73) = CT sensitivity 55% (43-67) = MRI sensitivity 66% (54-76) TRUS specificity 78% (71-84) = CT specificity 74% (67-80) = MRI specificity 76% (59-87)	EUS, CT and MRI equally performant for nodal involvement (with 35% underrstaging and 25% overstaging for all modalities)	Meta-analysis	High
Lahaye MJ 2005	[69]	75 articles from 1985-8/2004 in English, with >20 pts, histology as standard	TRUS or CT or MRI	DOR (measure for the diagnostic performance of a test, which combines sensitivity and specificity into one measure)	EUS DOR 8.83 CT DOR 5.86 MRI DOR 6.53 ROC indicate that high sensitivity cannot be reached without unacceptably high false + rates	23 refs more than in SR by Bipat et al, but 12 others excluded Criteria for N+ not discussed EUS slightly, but not significantly, better for N+/N0 than MRI or CT N staging remains a problem	SR	Moderate
Tatli 2006	[301]	39 non-consecutive pts with resected RC (excl 12 only LE). 14 mriStageII-III had CRT and surgery (after 14 wks), 25 mriStageI had surgery (after 3 wks)	MRI pelvic phased-array coil + endocoil. 1.5 T MRI.	N+ vs. N0 (also after CRT) Interobserver agreement	sensitivity 85% (11/13) specificity 69% (18/26) 6/8 'overstaged pts had CRT accuracy 74% (29/39) PPV 58% (11/19) NPV 90% (18/20) good interobserver agreement for N+ (k=0.80)	N staging has limitations 1 MRI radiologist evaluated images retrospectively without knowledge of histology. 7 radiologists interpreted MRI pre-treatment. The added value of endocoil can not be assessed	Non-consecutive cohort	Very low
Knaebel HP 2005	[73]	First period 424 with cancer	EUS by 4 experienced surgeons	Accuracy	N staging 76%	Retrospective Single center (Heidelberg)	Cohort	Very low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
		Second period 332 with tumour (incl. adenomas)	EUS as routine (6 examiners)		N staging 71% (73% after excl. postCRT pts)	(full paper not available) Accuracy decreases when performed by less experienced operators and after chemoradiation. Main problem is overstaging (overtreatment).		
Bianchi PP 2005	[305]	49 consecutive pts with RC (1/1999-1/2004)	EUS 7.5 MHz, lat position. 1 endoscopist. 1.0 T MRI body coil (28) or pelvic phased-array (21). 1 blinded radiologist for MRI	N+ accuracy of EUS vs MRI body coil or MRI pelvic phased-array	EUS sensitivity 47% specificity 80% accuracy 63% (95% CI 50-80) PPV 67% NPV 64% Body coil MRI sensitivity 62% specificity 80% accuracy 64% (95% CI 47-82) PPV 73% NPV 71% PAMRI sensitivity 63% specificity 80% accuracy 76% (95% CI 58-94) PPV 75% PAMRI NPV 77%	No data (N of patients) on pStages Most RC in upper and mid rectum No significant differences. PAMRI seems to be the best single method for local staging	Cohort (retrospective) comparative	Very low
Kulinna C 2004	[302]	63 non-consecutive pts with RC (who had both EUS and DCMSCT). 35/63 had CRT	EUS 7.5-10 MHz rotating probe 2-5 cm focal length. 2 examiners in consensus. DCMSCT 2 examiners in consensus.	EUS vs DCMSCT accuracy for N+ vs N0	TRUS Sensitivity 71% Specificity 55% Accuracy 65% PPV 74% NPV 50%	Only data of pts who had both exams are presented DCMSCT performs significantly better for T1/2 vs T3/4, for N0 vs N+ and for Stage I vs Stage II/III	Cohort retrospective, non-consecutive; compara	Very low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
					DCMSCT Accuracy 81% Sensitivity 85% Specificity 75%* PPV 85% NPV 75%* Accuracy was not significantly influenced by CRT		tive	
Fuchsjager MH 2003	[71]	39 pts with RC (9 had CRT) pT1 4 pT2 11 pT3 18 pT4 6 N+ 16 N0 23	TRUS feasible in 28 pts (11 too high/stenotic) 10-MHz endoanal probe MRI in all (1.0 T or 1.5 T) using a whole-body coil	Accuracy for N+ vs N0 (N+ = visible N)	TRUS Sensitivity 92% (12/13) Specificity 71% (10/14) accuracy 81% (22/27) PPV 75% (12/16) NPV (91% (10/11) DCMRI Sensitivity 81% (13/16) Specificity 62% (13/21) accuracy 70% (26/37) PPV 62% (13/21) NPV 81% (13/16)	TRUS and MRI data not from same pts TRUS feasible in 28/39 pts. If feasible TRUS is more accurate DCMRI is method of choice for proximal or stenotic tumours Covered in CCO evidence table but percentages on MRI are different	Cohort prospect ive	(low)
Hsieh PS 2003	[306]	59 pts with radical resection	TRUS	Accuracy N staging	N accuracy 73% N sensitivity 77% N specificity 70%	Full text not available	Validatin g cohort	?
Branagan G 2004	[304]	40 pts (from 72 consecutive cases) ; preop RT excluded pT1 3 pT2 17 pT3 18 pT4 2 pN+ 17	MRI 1 T, pelvic phased-array high resolution (with rectal air insufflation) 1 experienced examiner	N stage N + vs N0	correlation with path N stage: poor (kappa 0.38) Sensitivity 76% (13/17) Specificity 61% (14/23) Accuracy 68% (27/40) PPV 59% (13/22) NPV 78% (14/18)	Although 'experienced', the authors illustrated a learning curve for T staging! Small number of pts	Observat ional study	low
Will O 2006	[67]	38 articles from 269	MRI with and without	Nano-particle-	Summary ROC curve	Significant heterogeneity was noted	Meta-	moderate

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
		abstracts until 10 may 2005	ferumoxtran-10, with histological diagnosis after surgery or biopsy.	enhanced MRI and assessment of lymph node metastases	analysis for per-lymph-node data showed an overall sensitivity of 0·88 (95% CI 0·85–0·91) and overall specificity of 0·96 (0·95–0·97) for ferumoxtran-10-enhanced MRI. Overall weighted area under the curve for ferumoxtran-10-enhanced MRI was 0·96 (SE 0·01), DOR 123·05 (95% CI 5·93–256·93). Unenhanced MRI had less overall sensitivity (0·63 [0·57–0·69]) and specificity (0·93 [0·91–0·94]), with an overall weighted area under the ROC curve of 0·84 (SE 0·11) and DOR of 26·75 (95% CI 8·48–84·42). Metaregression analysis confirmed the significant effect of ferumoxtran-10 in the diagnostic precision of MRI (p=0·001).	for studies reporting enhanced MRI and unenhanced MRI. Only 1 article (with 12 pts) on rectal cancer included in this SR.	analysis	

What imaging technique should be used to evaluate the cCRM (lateral margin) in patients with rectal cancer?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[68]	September 2004	Colorectal cancer	CT or MRI of the pelvis should be done to assess mesorectal margin status.	3 case series + expert opinion		low
DGVS	[52]	Unsure	Colorectal cancer	Pelvic CT or MRI useful for uT3/4 and N+ tumours	5 observational studies (2 comparative)	MSCT promising; HR-MRI for CRM	low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
Lahaye MJ 2005	[69]	7 articles from 1985-1/2005 in English, with >20 pts, histology as standard	MRI	cCRM accuracy	MRI is the only modality used (SPIralCTinREctal cancer study ongoing) and rather accurate sensitivity 80% (range 60-88) specificity 80% (range 73-100) = 20% false + (may be related to CRT downsizing!)	Limited N of articles available Neoadjuvant CRT may be (is) a confounder ('inducing' 20% false +) Criteria for cCRM+ not discussed Large CI	SR	high
Strassburg J 2004	[307]	715 pts with RC from 11 European centers between 1/2002-10/2003	MRI	Equivalence of MRI and histology MRI prediction of (y)pCRM+	no data mriCRM- 91.3% correct	Preliminary and incomplete data of MERCURY study (cf.) TME quality is a confounder	Cohort multicenter (preliminary and partial results)	NA (cfr. MERCURY)
Branagan 2004	[304]	40 pts (from 72 consecutive cases) ; preop RT excluded pT1 3 pT2 17 pT3 18 pT4 2 pN+ 17	MRI 1 T, pelvic phased-array high resolution (with rectal air insufflation) 1 experienced examiner	CRM involvement CRM + vs CRM -	correlation with path CRM involvement: good (kappa 0.66) Sensitivity 50% (1/2) Specificity 100% (38/38) Accuracy 98% (39/40) PPV 100% (1/1) NPV 97% (38/39)	Small number of pts Only 2 pts with pCRM+ (low prevalence)	Observational study	Very low
Burton	[72]	298 pts with RC	MRI	CRM positive rate:		Multidisciplinary discussion	Observational	low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
2006				evaluation after MD discussions		of MRI results in significantly reduced positive CRM	study	
Mercury Study group	[70]	408 pts	MRI vs histology cCRM + = tumour at 1 mm or less from the mesorectal fascia	pCRM + versus – no chemoradiation (excl. 1 pt with extended surg) After chemoradiation	 Sensitivity 42% (15/36) Specificity 98% (269/274) PPV 75% (15/20) NPV 93% (269/290) Accuracy 92% (284/310) Sensitivity 94% (17/18) Specificity 73% (58/79) PPV 45% (17/38) NPV 98% (58/59) Accuracy 67% (65/97)	MRI - accurate technique and reproductible technique - useful for multidisciplinary team discussion for predicting failure of surgery	Mutlicenter study	Moderate

Can preoperative radiotherapy improve the outcome in patients with resectable rectal cancer compared to surgery alone?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[282]	January 2004	Adult pts with clinically resectable rectal cancer	Recommendations: preop RT is an acceptable alternative to the standard practice of postop RT for pts with stage II and III resectable RC. Both pre- and postop RT decrease LR but neither improves survival as much as postop RT combined with CT. Therefore, if preop RT is used, CT should be added postop, at least for pts with stage III disease. Qualifying statement: Patients who choose preop RT as a treatment option instead of postop combined CRT need to be made aware that, pathologic stage is unknown until SX is performed, many pts who will not benefit from treatment will be exposed to the risk of RT-induced morbidity and mortality.	Results of 3 MA (CCO, Camma C 2000, CCCG 2001) LOCAL FAILURE AR 8,6% [3,1%-14,2%], significant OVERALL MORTALITY AR 3,5% [1,1%-6%], significant Conclusion: early results of Dutch trial [Kapiteijn E et al., 2001] confirm decrease in LR with preop RT after TME. Improved results of recent trials can be explained by better pts selection, and radiation prescription.		High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	January 2001	Colorectal cancer	Adjuvant RT Preoperative RT planned with 3 or 4 fields, should be considered in patients with operable RC	LOCAL CONTROL 27 RCT [?] 2 MA [Camma C, 2000 ; Munro AJ, 2002] adjuvant RT improves LC in pts undergoing potentially curative TR absolute RR in loss of LC 9% (NNT=11) SURVIVAL MA [no reference] no overall benefit RCT [SRCT, 1997; Dahlberg M, 1998]: absolute RR of 10% (NNT=10), but at cost of increased late toxicity NON CANCER DEATH MA (CCCG, 2001): increase in first year after RT RCT [Cedermark B 1995, Holm T, 1996]: excess mortality is related to RT technique: outmoded regimens with large target volumes and 2 field technique RCT [Kapiteijn E, 2001]: 3 or 4 field plans to more conservative target volumes fail to show any increase in non-cancer deaths	RCT not referenced	High High High; moderate High High High
NICE	[54]	March 2003	Colorectal cancer	Recommendations: each Cancer Network should develop evidence	1. results from MA <u>MORTALITY</u> 2 MA [CCCG 2001, Munro AJ 2002]:	all MA included trials that used: - non-standardized conventional SX; - various RT techniques	High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				based policy on RT for RC, which should be agreed and implemented by all RT Units and colorectal cancer multidisciplinary teams (MDTs) in the Network. This may specify either routine pre-operative RT or selective post-operative RT, as in the Medical Research Council (MRC) CR07 trial; The potential benefits and risks of pre-operative RT (including both short- and long-term effects on bowel and sexual function) should be discussed with all patients with RC, so that they can make an informed choice about whether to accept it.	pre- or postop RT: no sign difference, but fewer pts deaths if ≥30Gy preop RT 1 MA [Camma C, 2000]: preop RT sign reduced 5Y overall mortality compared to SX alone <u>RC MORTALITY</u> 3 MA [CCCG 2001, Munro AJ 2002, Camma C, 2000]: preop RT: sign fewer deaths, but only sign for BED ≥30Gy <u>NON RC MORTALITY</u> 3 MA [CCCG 2001, Munro AJ 2002, Camma C, 2000]: higher if preop RT, greatest for BED ≥30Gy <u>LOCAL RECURRENCE</u> 3 MA [Camma C, 2000, CCCG 2001, Munro AJ 2002]: sign lower if RT is added to SX (pre- or postop) 1 MA [Munro AJ, 2002]: only sign reduction (50%) if BED ≥30Gy 1 MA [CCCG, 2001]: similar reduction in LR if preop RT >7d vs <7d <u>ISOLATED LR</u> 1 MA [Munro AJ, 2002]: smaller effect of RT ≥30Gy if longer course (>5d) vs short course (≤5d) of preop RT (NS) <u>DISTANT RECURRENCE</u> 1 MA [Camma C 2000]: no sign difference	- inadequate BED (<30Gy) 2 MA [CCCG 2001, Munro AJ 2002]: significant trial heterogeneity for local recurrence	

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					Conclusion: MA show that the addition of RT significantly reduces LRR. Preop RT produces a greater proportional reduction in LR than postop. Preop RT also leads to a significant reduction in mortality among pts who receive BED ≥ 30Gy Anticipated benifits: Pre-operative RT more than halves the risk of local recurrence and may improve five-year survival rates. However, these benefits are balanced by significant morbidity, so it is essential that those pts who are most likely to benefit should be clearly identified. 2. results from RCT Kapiteijn E, 2001 (RT+SX vs SX) LR: 2,4% vs 8,2%, p<0,001 OS: NS (2Y) DM: NS in hospital mortality: NS postop mortality: NS no. reinterventions: NS no. complications: NS Conclusion RT given before TME also reduces LR, but no reduction in mortality has been shown after 2Y follow-up 3. results from sub-analysis from RCT [Dahlberg M, 1998] long term AE (RT+SX vs SX)	5x5Gy + TME	High

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					Conclusion: modern RT techniques (MV and min 3 field plans) to deliver RT to smaller volumes reduce toxicity. However, even this form of RT is likely to cause long-term problems with bowel function.	only 220/1168 patients were included; short course (5-7d), high dose (37,5Gy) RT using modern techniques (3 or 4 beams) eligible patients (patients with curative anterior resection) were sent a questionnaire (median 80days after surgery) concerning their bowel function	Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
Martling A 2001	[308]	Operable rectal cancer not planned for local excision, <80y	Preoperative RT (272) vs surgery alone (285) RT: 5 x 5 Gy – 4 field box technique – supine position – anal sphincter in RT field SX: conventional	Local recurrence first event total incidence in curative operated (total) in curative operated D-A D-B D-C	 12% vs 25%, RR 56%, p<0.001 14% vs 27%, RR 54%, p<0.001 RR 57%, p<0.001 6% vs 9%, p=0.5 16% vs 34%, p=0.02 21% vs 37%, p=0.02	Conclusion: preop short term RT reduces risk of LR by approximately 50% in RC without any significant increase in postop mortality. In addition, it can improve survival after curative SX (not in analysis of all random pts). RT reduced also RC related death both after curative SX and when all pts were analyzed. However, the postop mortality was increased after RT (not significantly) and an increased risk of intercurrent death was observed after RT, which may reduce the benefit especially in elderly pts.	High
				Distant metastases	Not different (p=0.8)		
				Overall survival - after curative SX - cause spec S (RC) All Cur SX - intercurrent death All Cur SX CV death	39% vs 36% SX, p=0.2 46% vs 39%, p=0.03 RR 25%, p=0.02 RR 40%, p<0.001 19% vs 12% SX, NS (only significantly different during 6 months after SX and mainly in >68y) 21% vs 13%, p=0.1 13% vs 7%, p=0.07		
Holm T 2001	[309]	Patients from the Stockholm 2 trial that were treated with preoperative RT and a potentially curative	Preoperative RT (241) vs surgery alone (216) RT: 5 x 5 Gy – 4 field	Local recurrence and TL ≤ 5 cm 6-10 cm > 10 cm	 25% 19%	Conclusion: with conventional surgical techniques, preop RT plays an important role in RC irrespective of the location of the tumour. To irradiate only pts with	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
		procedure, in whom the distance between the tumour and the anus was reported	box technique – supine position – anal sphincter in RT field SX: conventional TL was assessed by rigid simoidoscopy	≤ 5 cm 6-10 cm > 10 cm Test of interaction between RT and TL	13%, p=0,08 30% vs 20%, p= 0,3 HR 0,7 [0,4–1,4] 25% vs 11%, p=0,03 HR 0,4 [0,2-0,9] 21% vs 5%, p=0,01 HR 0,2 [0,1-0,7] NS	tumours in the lower rectum and to omit this treatment for pts with tumors in the mid and upper rectum cannot be recommended. Whether this statement is valid with standardized TME SX is not known. Until this knowledge is available, the current indications for preop RT should probably also used with TME SX. Comments: Groups (3) were well balanced according to age, sex, tumour size and treatment group	
Pollack 2006		Patients originally treated with LAR in the Stockholm I and 2 trials and alive at time of analysis (2002) 119 pts treated with low AR and alive, 64 alive without stoma and participated	Preoperative RT (21) vs surgery alone (43) RT: 5 x 5 Gy Stockholm I: 2 field technique – supine Stockholm II: 4 field box technique – supine in both studies: anal sphincter in RT field, SX: conventional	Anorectal function fecal incontinence gas incontinence soiling stool freq/week anal incontinence and anastomotic height anal incontinence and RT regimen anal incontinence during first year	57% vs 26%, p=0,01 71% vs 46%, p=0,03 38% vs 16%, p=0,04 20 vs 10, p=0,02 no correlation (but mean height was 10 cm and 9 cm (=high!) no difference in continence impairment between 2 RT regimens (I&II) in both groups: gradual improvement	Conclusions: short-course RT, including the anal sphincters, impairs anorectal function and increases GI symptoms permanently when the anal sphincters are irradiated. Poor long-term outcome could be due to end-to-end anastomoses (all) Need for improved follow-up for anal incontinence after AR.	Moderate

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				Anorectal manometry MRP (mm Hg) MSP (mm Hg) FSF (mL) MTV (mL) RAIR(Yes/No)	 35 vs 62, p<0,001 104 vs 143, p=0,05 57 vs 51, p=0,34 105 vs 97, p=0,26 17/4 vs 36/3		
				Anal sphincter defect scarring	 2 vs 1 pt (all had incontinence symptoms) 33% vs 13%, p=0,03 (nearly all had varying symptoms of incontinence)		
				Faecal incontinence QoI (no vs focal incontinence) lifestyle coping depression embarrassment faecal incontinence QoI	 p<0,01 p<0,01 p<0,01 p<0,01 no diff between RT+ and RT-		
Folkesson J 2005	[310]	Pathological and surgical curatively resected rectal cancer pts	Preoperative RT (454) vs surgery alone (454)	Survival OS (13Y) stage sex Crude survival analysis (1168 pts)	 38% vs 30%, p=0.008 no difference women better OS in both groups 31% vs 20%, p=0.009	Conclusion: preoperative RT with 25Gy in 1 week before curative SX for RC is beneficial for OS and CSS and LRR after long term follow-up. Comments: local benefit of RT for stage I is striking, but there could	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				CSS stage sex	 72% vs62%, p=0.03 no difference women better CSS overall	be a risk of stage migration due to less radical surgery and pathology reports that were not up to present standard (CRM examination, sufficient no. LN examined).	
				Disease recurrence Local recurrence ST I ST II ST III T≤ 5cm T 6-10cm T≥11cm sex time from LR to death Distant metastasis stage sex	 9% vs 26%, p<0.001 4.5%vs14%, p=0.009 6%vs22%, p<0.001 23%vs46%, p<0.001 10% vs 27%, p=0.003 9% vs 27%, p<0.001 8% vs 12%, p=0.3 No difference median 295d vs 398d, p<0.001 34%, no difference no difference no difference		
Birgisson H 2005	[311]	Pts with curative SX and hospital admission for primary rectal cancer	Preoperative RT (454) vs surgery alone (454)	HOSPITAL ADMISSIONS <u>< 6 months</u> •Infections •GI <u>> 6 months</u>	RT+SX: 357 SX: 304, p<0.01 RR 1.07 [0.91-1.26] Number of person-years at risk for admission higher in RT group RR 1.64 [1.21-2.22] RR 7.67 [1.76-33.39] RR 2.57 [1.55-4.26]	Conclusion: GI disorders, resulting in hospital admissions, seem to be the most common adverse effect of short-course preoperative RT in pts with RC. Bowel obstruction was the diagnosis of potentially greatest importance, which was more frequent in the irradiated than in the non-irradiated pts.	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				•all diagnoses (ICD) •infections ↳non specific •CV ↳arrhythmias •GI ↳obstruction ↳nausea ↳abdominal pain ↳inguinal hernia RT shielding •insufficient •optimal RT technique •AP beams •3/4 beams	RR 0.95 [0.80-1.12] RR 1.34 [0.96-1.87] Trend RR 8.06 [1.02-63.69] RR 0.88 [0.71-1.11] RR 0.57 [0.36-0.91] RR 1.23 [0.97-1.56] Trend RR 1.88 [1.10-3.20] RR 4.04 [1.16-14.06] RR 1.92 [1.14-3.23] RR 0.26 [0.07-0.96] no significant difference trend for more bowel obstruction with AP beams vs 3 or 4 beams		
Graf W 1996		Patients from 2 RCT: SRCT: 1168 pts with resectable rectal cancer, < 80y, and Pahlman 1990: 471 patients with operable rectal or rectosigmoid cancer	Preoperative RT (632) vs no preop RT (684) (postop RT or SX alone) RT: 25,5Gy [Pahlman] or 25Gy [SRCT]; 5fr, 5-7d, 3	Determinants of tumour size (TS) student's t-test preoperative RT gender M+ single regression	RT: 4,2cm vs NO RT: 4,8cm; p<0.0001 ♂: 4,63cm vs ♀: 4,43cm; p=0.04 NS	Conclusion: short course preoperative RT results in a downstaging effect which should be considered in the interpretation of RT trials and in the recruitment of pts for further postoperative treatment. Several factors affect TS of which TL and RT were the most important,	Moderate

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
		total: 1639 patients, analyzed: 1316 pts	or 4 fields SX: standard SX procedures, not specified, Time interval between RT and SX: mean 10,5d;	tumour level (TL) age <u>multiple regression</u> preop RT gender M+ tumour level age <u>Only preoperative RT pts</u> Time interval (TI) RT – SX multiple regression Determinant of nodal status <u>χ^2 test</u> Preop RT TI ≤10d vs >10d Gender M+/M- Age <u>student's t-test</u> TL TS <u>multivariate logistic regression</u> TS Preop RT (Yes/No)	TS=4,97-0,053(TL), p<0.00002 TS=5,40-0,013(age), p<0.02 p<0.000001 NS NS p<0.00004 NS p=0.04, TS = 4.45 - 0.022 (TI) Inversely related, p=0.053 33% vs 42%, p<0.001 45% vs 4% NS, p=0.38 65% vs 36%, p<0.0001 NS, p=0.23 NS, p=0.82 N+: 4,88cm vs N-: 4,34cm, p<0.00001 OR 1.14, p<0.00001 OR 0.73, p=0.008	followed by age and sex to a lesser degree. RT affected TS, but also had a direct effect on risk for nodal spread. Comments: groups were well balanced except for age	

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
Petersen S 1998	[312]	Primary resectable RC 94 pts entered, 77 pts had R0 resection Median fup: 3,86y (0,2y-8,3y)	Preoperative RT (47) vs surgery alone (46) Preoperative RT: 5 x 3,3Gy, 2 lateral opposed fields, 9 MeV SX: within 48h Postop RT if T4-St III a/o pT4-St II or St III a/o R1/R2: 59,8Gy/1,8-2Gy if no preop RT or 41,4Gy/1,8Gy if preop RT, 3-field plan	Disease recurrence Local recurrence in R0 in R0 T3 in T4 LR or DM time to LR	 13% (5/40) vs 24% (9/37), p=0,08 8% (2/25) vs 25% (4/16) 43% (3/7) vs 35% (5/14) 25% 10/40 vs 43% (16/37) median 1,9y vs 3,0y	Conclusion: this study indicates an improved local tumour control of RC after preoperative RT. The 5-year survival rate was significantly better after preoperative RT than after SX alone. Comments: although patients were randomized, risk factors were not equally distributed among both treatment arms, due to the small sample sizes.	Moderate
				Survival OS (5y) R0 all Stage I-II-III-IV Stage I vs II Stage II vs III Stage II vs IV type of SX	 49% vs 28%, p=0,027 p=0,025 38% 70%-52%-19%-0% p=0,33 p=0,0001 p=0,006 APR 36% vs AR 44%, p=0,39		
				Prognostic factors for (multivariate analysis) LC UICC stage preop RT T stage Survival age	 p=0.0003 p=0.07 p=0,08		

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				R resection UICC stage preop RT only R0 age N stage preop RT	< 60 vs > 60, p=0,0003 p=0,01 p=0,001 p=0,078 p=0,0001 p<0,001 p=0,14		
				Postop complications death within 30d anastomotic problems wound healing problems	 3 vs 2 4 vs 5 only minor problems		
Kapiteijn E 1999	[313]	Pts with operable RC (not fixed) with tumour level ≤15 cm from AM/S1-2 This analysis included the first 500 randomized patients of the Dutch TME trial; 472 pts were eligible and 462 pts were analyzed (TME)	Preoperative RT (219) vs surgery alone (243) RT: 5x5 Gy SX: TME, median interval RT-SX: 4d [1-55], trial was conducted with the use of standardization and quality control measures to ensure the consistency of the RT, SX and pathological techniques	Toxicity	acute skin/lower GI/GU toxicity: 16%, neurotoxicity: 10%, other toxicity: 19%	Conclusion: short term preoperative RT is safe even in combination with TME. Apart from more preoperative blood loss and a higher infective complication rate in the RT group, there were no significant differences between in postoperative complications and mortality. Comments: 100% RT compliance in 96% of pts in the RT group	High
				Surgical complications type operation intraoperative complications type of anastomosis type of stoma operation time blood loss Postoperative complications overall infective anastomotic leak in LAR hospital volume	 NS NS NS NS NS 1200mL vs 800mL, p<0.001 NS 36% vs 27%, p=0.04 NS		

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				re-operation	NS NS		
				Pathology R0 R1 R2 Involved CRM LN examined	 NS NS NS NS Median: 7.0 vs 9.0, p<0.001		

Kapiteijn E 2001	[45]	Pts with operable RC (not fixed) with tumour level ≤15 cm from AM/S1-2	Preoperative RT (897) vs surgery alone (908) RT: 5x5 Gy SX: TME, within 1 week after RT trial was conducted with the use of standardization and quality control measures to ensure the consistency of the RT, SX and pathological techniques	Postoperative morbidity blood loss perineal complications Postoperative mortality	 1000 ml (RT) vs 900 ml (SX), p<0.001 26% (RT+APR) vs 18% (APR), p=0.05 no significant difference	Conclusion: TME (with extensive instructions and quality control of the surgical technique) can significantly decrease the risk of LR of resectable RC; the addition of short-term preoperative RT further reduces the risk of LR in pts with RC who undergo a standardized TME	High
				Events death intercurrent death CS death PO death recurrence LR LR only LR+DR LR after DR DR only	 20% (of 1805) 13% (of 1805) 3% (of 1805) 5.3% (of 1748) 2.6% (of 1748) 1.6% (of 1748) 0.8% (of 1748) 13.5% (277/1679 no M+at SX)		
				Survival OS *HR for SX vs RT*	 82% vs 81.8%, p=0.84 HR 1.02 [0.83-1.25]		
				Recurrence LR *HR for SX vs RT* DR *HR for SX vs RT*	 2.4% vs 8.2%, p<0.001 HR 3.41 [2.05-5.70] 14.8% vs 16.8%, p=0.87 HR 1.02 [0.80-1.30]		

				OR *HR for SX vs RT*	16.1% vs 20.9%, p=0.09 HR 1.21 [0.97-1.52]		
				Predictors for LR <u>Univariate analysis</u> treatment-group assignment TL TNM <u>Multivariate regression analysis</u> treatment-group assignment TL TNM type of resection <u>Univariate subgroup analysis</u> TL and LR TNM and LR	 p<0.001 p=0.003 p<0.001 p<0.001 p=0.03 p<0.001 p=0.90 Test for interaction: NS TL ≤5cm, HR 2.78, p=0.05 TL 5.1-10cm, HR 2.13, p<0.001 TL 10.1-15cm, HR 1.0, p=0.17 ST I HR 1.00, p=0.15 ST II HR 3.44, p=0.01		

					ST III HR 9.69, p<0.001 ST IV HR 16.2, p=0.25		
Marijnen CAM 2001	[79]	Pts with operable RC (not fixed) with tumour level ≤15 cm from AM/S1-2	Preoperative RT (602) vs surgery alone (719) RT: 5X5 Gy SX: TME, within 1 week after RT	Pathology T size (cm) T stage Total number LN number of LN+ N stage TNM stage ST III differentiation grade: poor T type	 mean ∅ 4.0 vs 4.5, p<0.001 NS mean 7.7 vs 9.7, p<0.001 mean 1.6 vs 1.9, NS 39% vs 42%, NS similar distribution 34% vs 38%, NS 35% vs 23%, p<0.001 Mucinous 13% vs 7%, p<0.001	Conclusion: short-term preoperative RT (5x5Gy) does not lead to downstaging in RC if the interval between start of RT and SX does not exceed 10d. There is a decrease in TS and no. of recovered LN after RT, but there is no change in tumour and node classification. The authors suggest that the disappearance of negative LN is caused by rapid apoptosis of lymphocytes in contrast to tumour cells. Review of RCT (RT+SX) on downstaging (fraction size, total dose, OTT, TNM, TS, LN, histology). Most trials with interval > 4w demonstrated less D-C in the RT group. Most trials with short term RT did not detect downstaging	High
Marijnen CAM 2002	[77]	1861 randomized, 1530 Dutch pts analyzed, 1414 assessable	Preoperative RT (695) vs surgery alone (719)	Acute RT toxicity any G1 G2/3 neurologic toxicity G1/2/3 Surgery	 26% 19% 7% 53 pts 	Conclusion: preop SC-RT is a safe procedure in pts treated with TME SX, despite a slight increase in complications compared to TME SX alone. Lumbosacral plexopathy was a major cause of concern!	High

				median SX time median hospital stay total blood loss LAR APR SX type conversion non SSS → SSS SSS → non SSS Per-operative complications overall bleeding unintended organ injury Postoperative complications overall perineal wound healing in APR anastomotic leakage in LAR diverting stoma vs no stoma end-to-end anastomosis pouch reconstruction side-to-end anastomosis influence of age	180' vs 180', NS 15d vs 14 d, NS 1100 ml vs 1000 ml, p<0,001 1025 ml vs 800 ml, p<0,001 NS 20% vs 19%, 9% vs 7% no difference 13% in A&B 8% vs 7% 48% vs 41%, p=0,008 29% vs 18%, p<0,01 11% vs 12%, NS 8% vs 16%, p=0,001 16% 9%		

				influence of TL Re-interventions in LAR vs APR Hospital mortality Postoperative mortality correlation with age	12% no no 15% vs 14% no difference 4% vs 3,3%, NS 3,5% vs 2,6%, NS p<0,001		
Marijnen CAM 2003	[78]	1530 pts included in trial, 1318 pts analyzed	Preoperative RT (662) vs surgery alone (656)	Local recurrence CRM > 1 cm CRM >2mm CRM 1-2mm CRM ≤1mm	 0% vs 3.3%, p=0.0002 0.9% vs 5.8%, p<0.0001 0% vs 14.9%, p=0.02 9.3% vs 16.4%, NS	Conclusion: preop hypofractionated RT has a beneficial effect in pts with a wide (>2mm) or narrow (1,1-2mm) resection margin, but cannot compensate for microscopically irradical resections (≤1mm) resulting in positive margins. Effect of postop RT: no effect on LR in patients with positive CRM (no postop RT: 15,7% vs 17,3% with postop RT). Postop RT no independent prognostic factor for LR in patients with positive CRM (multivariate analysis). In patients with a positive margin, pre-or postop RT does not prevent LR.	High
Marijnen CAM 2005	[80]	1861 rand, 1530 analyzed for HRQL, 990 evaluable (no LR/DM in first 2y)	Preoperative RT (497) vs surgery alone (493)	Health related quality of life (HRQL) VAS score Activity score	 NS	Conclusion: short-term preop RT leads to more sexual dysfunction, slower recovery of bowel function, and impaired daily activity postop. However, this does not seriously	High

				at 3 months Physical symptom scale Defecation scale faecal incontinence Psychological distress scale Voiding scale <u>Sexual functioning</u> Sexual activity ♀♂ Sexual functioning ♀ ♂ <u>HRQL by SX type</u> activity level physical problems psychological problems voiding problems sexual activity in ♂ sexual activity in ♀ erection disorders in ♂ dyspareunia in ♀	p=0.04 p=0.006 NS NS at 24 mts: 51% vs 37%, p=0.02 NS, significant improvement postop NS, significant deterioration decline compared to baseline, more in RT+ p=0.01 at 2y p=0.06 at 2y worse for RT+ at all time points, p<0.001 deteriorated more for RT+ esp. ejaculation problems, p=0.002 NS APR fewer, p=0.004 APR fewer, p=0.007 APR more, p=0.007 LAR more active, p=0.03 LAR more active p=0.01 worse for APR, p<0.001 worse for APR,	affect HRQL. The comparison between LAR and APR patients demonstrates that the existence of a permanent stoma is not the only determinant of HRQL. HRQL improved over time (24 mts after SX) RT+ did worse for VAS score and physical symptom scale at 3 months; RT- did better. This difference no longer existed after 6 months; so it takes RT+ pts longer to recuperate from Sx. Pattern between RT+ and RT- did not differ for either APRA or LAR pts from the pattern of all pts together, also for voiding problems. Similar overall outcome for APR and LAR compared to all patients together. VAS score constantly somewhat lower in LAR, p=0.04	

					p=0.006		
Sebag-Montefiori D 2006	[47]	1350 pts with operable non-metastatic rectal cancer median follow-up: 3y	SC preoperative RT (674) compared to LC postoperative RT in high risk pts (+CRM) (676) RT: short course RT: 25Gy/5 fractions long course CRT: 45Gy/25fractions + 5-FU SX: TME The trial included a prospective pathological assessment and reporting of resection of the surgical specimen Postoperative CT was received in 85% of pts with stage III RC cfr. previous	LR (3Y) TL 0-5cm 5-10cm >10cm DFS (3Y) OS (3Y)	4.7% vs 11.1%, HR 2.47 [1.61-3.79] HR 2.00 HR 2.14 HR 4.97 79.5% vs 74.9%, HR 1.31 [1.02-1.67] 80.8% vs 78.8%, HR 1.25 [0.98-1.59]	Conclusion: These preliminary results indicate that routine short course pre-operative radiotherapy results in a significant reduction in local recurrence and improved disease free survival at 3 years when compared with a highly selective post operative approach. Comments: SC-RT: 595 received allocated treatment. LC-RT: 51/73 pts with +CRM received CRT	High
Quirke P 2006	[81]	cfr previous plane of SX (PoS) was defined as: Grade1: muscularis plane, Grade2: intra-mesorectal plane; Grade3: mesorectal plane	cfr. previous	*+CRM vs –CRM* LR DFS OS *PoS: Gr1 vs Gr2 vs Gr3* LR DFS *PRE vs selective POST* LR DFS	18% vs 7% 50% vs 81% 57% vs 84% p<0.001 p=0.05 Gr1: 9% vs 29%, HR 2.76 Gr2: 6% vs 12%, HR 2.02 Gr3: 1% vs 6%, HR 4.47 Gr1: 79% vs 65%, HR	Conclusion: the results indicate a strong association between the quality of surgery and the rates of local recurrence and disease-free survival, as well as a clear benefit from the addition of PRE to all grades of surgical dissection. Thus for patients with rectal cancer short-course pre-operative radiotherapy and good quality surgery can almost completely eliminate local recurrence. Comments: cfr previous	High

					1.75 Gr2: 78% vs 75%, HR 1.13 Gr3: 87% vs 80%, HR 1.53		

Is a long course of preoperative chemoradiotherapy better than a long course of preoperative radiotherapy alone in the outcome of patients with resectable rectal cancer?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[282]	January 2004	Adult pts with clinically resectable rectal cancer	Preop RT is an acceptable alternative to the standard practice of postop RT for pts with stage II and III resectable RC. Both pre- and postoperative RT decrease LR but neither improves survival as much as postop RT combined with CT. Therefore, if preoperative RT is used, CT should be added postop, at least for pts with stage III disease	2 RCT 1. Boulis-Wassif S, 1984 [ ] OS 5Y 59% vs 46%, p=0,06 LF 15% vs 15%, p=NS Liver M+ marginally sign decrease if preop RT (p=0,006) 2. Buijko K, 2003, abstract [ ] intervention: CRT long course vs RT short course outcome: significant difference in distal intramural margin spread favouring CRT (p=0,006)	arm1: 15x2,3Gy (121) arm2: 15x2,3Gy + FU bolus for 4d during w1 of RT (126); 2w interval between RT and SX 27% of cases ineligible or not evaluable! CRT: 28x1,8Gy + FU/LV w1,w5 RT short course: 5x5Gy	Moderate Moderate
SIGN	[55]	January 2001	Colorectal cancer	Chemotherapy should be given synchronously with the RT using one of the following 3 regimens: - intermittently infused FUFA (Bosset) - continuous FU (Lokich) or bolus FUFA	2 prospective cohort studies (Bosset JF, 1993; Rich TA 1995): CRT increases pCR and tumour resectability in more advanced tumours; intermittently infused FUFA (Bosset) [ ] or continuous FU (Lokich) have been widely and safely used	applies only to long course RT	Moderate

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					3 RCT [no references]	low quality and incomplete reporting	
NICE	[54]	March 2003	Colorectal cancer	If CRT is used, it should be an established regimen.	1 RCT Frykholm GJ, 2001: RESECTABILITY: not different LOCAL CONTROL sign improved if CRT OS not significant ACUTE AE higher after CRT Conclusion: addition of CT to long-course preoperative RT for non-resectable RC does not improve resectability but produces a significant reduction in LR. Moreover, CRT causes more acute toxicity than RT alone.	Study was cited for a recommendation on the use of combined chemoradiation in all cases, but the study only included patients with non resectable RC, Study compared a long course of preoperative RT (46Gy/2Gy, 10Gy/w, 2x2 Gy/day D1,D2 + 1x2Gy D3; 4 weeks) with or without chemotherapy (sequential methotrexaat, 5-FU (bolus followed by continuous infusion) and Leucovorin (8x)), TME was standard surgical technique Study was underpowered (fewer pts included than planned) and the RT regimen was not optimal	Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
Bosset JF 2004	[105]	T3-T4 resectable RC, <15cm from AM, <80y, 1011 pts randomized,	Group A/ 405 pts arm1: RT+SX arm3: RT+SX +CT Group B/ 404 pts	Preop toxicity Group A vs Group B any G ≥2	 38% vs 54%, p<0.005 17 vs 34%, p<0.005	Conclusion: at the doses recommended in the protocol, the addition of 5-FU-LV to preoperative RT slightly	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
		809 pts analyzed, Group A/B: 398/400 started treatment, no Sx in 10 (G-A) vs 7 (G-B) pts	arm2: CRT+SX arm4 :CRT+SX+CT RT: ≥ 8MV, ¾ fields, 45 Gy/1.8Gy CT : 5-FU/LV, on W1,5 of RT, short infusion 1h before SX: recommended to perform SX as planned before start RT and TME	diarrhea other toxicities toxic death	NS 1 vs 2	increased the amount of acute toxicity. However, the compliance with the radiation protocol or the feasibility of SX did not decrease	
				Postoperative *Group A vs Group B* complications mortality within 30 days from SX	 22% vs 23%, NS 3 vs 5 pts		
				Early deaths preoperative or up to 30d from SX *Group A vs Group B*	 5 vs 9 pts		
Bosset JF 2005	[106]	T3-T4 resectable RC ,within 15 cm of AM, <80y, clinical T staging 1011 pts randomized	cfr previous Group A/ 505 Group B/ 506, Resection in 949 pts, R0 resection in 918 pts In 69% of pts in group A and 67% of pts in Group B: no info on TME	SX type Group A vs Group B resection R2 AR TME	 476 vs 473 21 vs 10 52% vs 56%, p=0.05 21 % vs 24%*	Conclusion: addition of CT to RT decreases TS, pTN stage, no. recovered LN (may mask correct pN stage), specific invasion; increases pT0 (x2,5) (but not pT0N0) and mucinous tumour, slightly increases AR. Comments: no central review of pathology, no quality control of SX	High
				Pathology *Group A vs Group B* Tumour size T stage T0 T0N+ T1 T2 T3	 median 30mm vs 25mm, p<0.0001 5.3% vs 13.7% OR 2.84 [1.75-4.59], p<0.0001 3/25 (12%) vs 6/65 (9%), NS 7.6% vs 10.4% 29.6% vs 33% 48.9% vs 37% OR 1.79 [1.38-2.32], p<0.0001 5.3% vs 3.8% 42% vs 57%,		

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				T4 <T3 Nodes total examined LN+ N0 N1 N2 Nx M stage at SX M0 M1 Mx	 mean 9 vs 7, p<0.05 mean 1.52 vs 0.86, p<0.0001 60.5% vs 71.9% 22.7% vs 17.8% 12% vs 7.2%, p<0.001 4.8% vs 3.2% 92.9% vs 92.2% 4.2 vs 4.7% 2.9% vs 3.2%		
				Histology *Group A vs Group B* tumour type adenoca mucinous specific invasion lymphatic venous perineural	 87% vs 77%, 4% vs 8%, p<0,001 17% vs 11%, p=0,008 14% vs 9%, p=0,008 14% vs 8%, p=0,001		
Bosset JF2006	[75]	T3-4 resectable RC, within 15 cm of AM, <80y, clinical T staging 1011 pts randomized and analyzed	*cfr previous* arm 1: RT+SX : 252 : 2 no RT, 13 no TR arm 2:	Acute preop toxicity *Group A vs Group B* G2 ≥G3 diarrhea ≥G2	 30% vs 38% 7% vs 14%, p<0,001 17% vs 38%, p<0,001	Conclusion: in pts with resectable T3/4 RC treated with preop RT, adding FU based CT pre- or postop has no effect on survival. Regardless of timing, CT provides a significant	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
		Median fup: 5,4y	CRT+SX: 253, 1 no RT, 2 no CT, 9 no TR arm 3: RT+SX+CT: 253: 1 no RT, 9 no TR, 72 no CT arm 4: CRT+SX+CT: 253: 0 no RT, 3 no CT, 13 no TR, 64 no CT	Surgery *Group A vs Group B* SSS postop mortality postop complications	 51% vs 53% 1,2% vs 2,4% 23% vs 23%	benefit to LC. - adding CT to preop RT slightly increases acute toxicity, but no influence on tumour resection rate, compliance to RT, postop CT, postop complications - adding CT to preop RT increases downsizing and –staging, changes in pathology, is associated with lower LRR but no improvement on OS/PFS - compliance to postop CT was poor! - no evidence that giving both pre- and postop CT is beneficial for LC	
				Pathology *Group A vs Group B* TS T stage N stage N examined LVI, PNI	*(reported previously)* smaller in G-B, p<0,001 less advanced T and N stage in G-B, p<0,001 fewer in G-B, p=0,05 less frequent, p=0,008		
				Acute postop toxicity *Group A vs Group B* any grade diarrhea ≥G2 vomiting neutropenie infection death	 58% 54 pts 25 pts 19 pts 13 pts 0 pts		
				Late toxicity *Group A vs Group B* diarrhea ≥G2 faecal incontinence anastomotic stricture SX for SB complications	no difference 4 arms 10% 9% of SSS 31 pts 1,4%		
				Survival			

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				5Y OS *Group A vs Group B* *arm1+2 vs 3+4* 5Y DFS *Group A vs Group B* *arm1+2 vs 3+4*	 65% vs 66%, p=0,84 HR 1,02 [0,83-1,26] 63% vs 67%, p=0,12 HR 0,85 [0,68-1,04] 54% vs 56%, p=0,52 HR 0,84 [0,78-1,13] 52% vs 58%, p=0,13 HR 0,87 [0,72-1,04]		
				Local recurrence 5Y LR LR and TL *≤5cm vs ≥5cm*	 arm1: 17%; arm2: 9%; arm3: 10%; arm4: 8%; arm 1 vs 2,3,4 : p=0,002 p=0,74		
				Distant recurrence 5Y DM *Group A vs Group B* *arm1+2 vs 3+4*	 34% p=0,14 p=0,62		
Gérard 2006	[76]	primary resectable RC accessible to DRE and stag T3-4, <75y 762 pts randomized, 742 pts eligible Median Fup: 81m	preop RT: 367 pts preop CRT: 375 pts preop RT+SX: 360 pts preop CRT+SX: 359 pts RT: 45Gy/1,8Gy, 5w, 3 or 4 fields, ≥8MV, prone, post pelvis preop CT: 5-FU	Preop toxicity *CRT vs RT* G3/4	 15% vs 3%, p<0,0001	Conclusion: preoperative CRT in T3-4 resectable RC of low/middle rectum increases moderately acute toxicity, increases pCR, does not modify SSS, OS or PFS, but increases LC Comments: limitations to this study include: long inclusion period, CT regimen (bolus), no standard SX, no routine TME, no	High
				Surgery *CRT vs RT* R0-1 R2 postop death complications	 94% vs 93% 4% vs 6% 2% vs 2% 21% vs 27%		

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
			350mg/m² IV bolus + LV 20mg/m² IV w1+w5 SX: 3-10w after (C)RT, type = surgeon's decision, TME recommended postop CT: 4 x 5-FU/LV, 4w interval	fistula after AR	7% vs 8%	standardized pathology	
				Pathology *(375 pts vs 367 pts)* pCR few residual cells ypN0 ypN1-2 pts with R0-1 *(338pts vs 336pts)* ypT0 ypT1 ypT2 ypT3 CRM- CRM+	 11% vs 4%, p<0,0001 19% vs 10% 67% vs 65% 33% vs 34% 12% vs 4%, p<0,0001 4% vs 8% 29% vs 25% 54% vs 62% 55% vs 56% 6% vs 7%		
				Survival *CRT vs RT* 5Y OS 5Y PFS	 67% vs 68%, HR 0,96 [0,73-1,27] 60% vs 56%, HR 0,96 [0,77-1,20]		
				Local recurrence *CRT vs RT* 5Y LRR SX 1993-1998 SX 1999-2003	 25 LR vs 49 LR, 8% vs 17%, p=0,004 RR 0,5 [0,31-0,80] favour of CRT, p value NR 15% vs 5%, p=0,007		

Is preoperative (chemo)radiotherapy better than postoperative (chemo)radiotherapy in the outcome of patients with resectable rectal cancer?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[282]	January 2004	Adult pts with clinically resectable rectal cancer	Preop RT is an acceptable alternative to the standard practice of postop RT for pts with stage II and III resectable RC. Both pre- and postop RT decrease LR but neither improves survival as much as postop RT combined with CT. <u>Qualifying statement</u>: cfr above	3 RCT 1. Pahlman, 1990 [ ], Frykholm, 1993 [ ] OS 5Y (arm1 vs 2) 43% vs 37%, p=0,43 Local failure 22% vs 33%, p=0,012 LR if radical TR 11% vs 22%, p=0,02 Postop complications (early, late) more frequent after postop HD RT <u>Conclusion</u>; short-course of high-fraction preop RT is preferable to a standard course of postop RT. Preop RT is better in reducing LRR and associated with lower morbidity 2. Sause, 1994 [ ] OS 5Y: 43% vs 32%, p=NS LF: 32% vs 32%, p=NS 3. Hermann, 1999 [ ] OS 5Y: 49% vs 37%, p=NS LF: 25% vs 39%, p=0,142 *Multivariate analysis for LR* Staging: p<0,001 preop RT: p=0,08 T4 stage: p=0,07	operable RC, arm1; RT(5x5,1Gy)+SX (263) vs arm2: selective postop RT (54x1,1?) in ST II and III (235) arm1; RT(1x0,5Gy)+SX (175) vs arm2; selective postop RT (45-51Gy) in ST II and III (178) Preop RT dose was small and shown to be ineffective arm1: RT(5x3,3Gy)+SX	Low Low Low

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					Multivariate analysis for OS Age: p<0,001 UICC: p=0,001 residual disease status: p=0,01 preop RT: p=0,078 Conclusion: 2 last trials indicate that selective postop RT annuls any potential benefit of preop RT in low dose.	(48) vs arm2: selective postop RT (41,5Gy if preop RT and 59,8-51Gy if no preop RT) in high risk pts (T4 or R1-2 or intraoperative tumour perforation (56)	
SIGN	[55]	January 2001	Colorectal cancer	Preoperative RT planned with 3 or 4 fields, should be considered in pts with operable RC Postop RT should be considered in pts with RC who did not receive preop RT and who are at high risk for LR	1 RCT Frykholm 1993 1 SR Glimelius 1997 Preop RT is more effective than postoperative RT; the magnitude of benefit is similar, but preop trials used BED ≤40Gy, where postop trials used BED ≥40Gy	study with high risk of bias and wide CI (cannot support recommendation) Indirect evidence	Low Moderate
NICE	[54]	March 2003	Colorectal cancer	Routine pre-operative RT or selective postoperative RT is recommended. Postoperative RT should be reserved for pts who are judged after SX to be at high risk of recurrence	1. results from MA <u>MORTALITY</u> 2 MA [CCCG 2001, Munro AJ 2002]: pre- or postop RT: no sign difference, but fewer pts deaths if ≥30Gy preop RT 1 MA [Camma C, 2000]: preop RT sign reduced 5Y overall mortality compared to SX alone <u>RC MORTALITY</u> 3 MA [CCCG 2001, Munro AJ 2002, Camma C, 2000]: preop RT: sign fewer deaths, but only sign for BED ≥30Gy	all MA included trials that used: - non-standardized conventional SX; - various RT techniques - inadequate BED (<30Gy) 2 MA [CCCG 2001, Munro AJ 2002]: significant trial heterogeneity for local recurrence	-

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
					NON RC MORTALITY 3 MA [CCCG 2001, Munro AJ 2002, Camma C, 2000]: higher if preop RT, greatest for BED ≥30Gy LOCAL RECURRENCE 3 MA [Camma C, 2000, CCCG 2001, Munro AJ 2002]: sign lower if RT is added to SX (pre- or postop) 1 MA [Munro AJ, 2002]: only sign reduction (50%) if BED ≥30Gy 1 MA [CCCG, 2001]: similar reduction in LR if preop RT >7d vs <7d ISOLATED LR 1 MA [Munro AJ, 2002]: smaller effect of RT ≥30Gy if longer course (>5d) vs short course (≤5d) of preop RT (NS) DISTANT RECURRENCE 1 MA [Camma C 2000]: no sign difference Conclusion MA show that the addition of RT significantly reduces LRR. Preop RT produces a greater proportional reduction in LR than postop. Preop RT also leads to a significant reduction in mortality among pts who receive BED ≥ 30Gy Anticipated benefits: Postop RT can reduce LR rates by a third but is less effective than preop RT and causes more adverse effects.		

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
Sauer 2004 [82]		operable primary RC, stage II or III 823 pts randomized, 799 pts in full analysis pCR 8% Median fup: preop CRT group: 45m (5m-101m) , postop CRT group: 49m (3m-102m)	RT+SX: 415 SX+RT: 384 RT: 50,4 Gy/1,8Gy + boost 5,4Gy/1,8Gy (if postop RT) CRT: 5-FU PVI w1,w5 CT: bolus 5-FU, 5d, q4w, 4 cycles interval SX-RT : within 4w SX: interval RT-SX : 4-6 weeks	SX type R0 SSS all APR->SSS	RT+SX vs SX+RT NS NS 39% vs 19%, p=0.004	Conclusion: although no survival benefit, preoperative chemo-radiotherapy is the preferred treatment as compared to postoperative chemoradiation for pts with locally advanced RC, because it is associated with a superior overall compliance rate, an improved LCR, reduced toxicity and an increased rate of SSS in pts with low-lying tumours.	High
				Postop complications in hospital mortality postoperative complications overall anastomotic leak delayed sacral wound healing postop bleeding ileus	0.7% vs 1.3%, NS 36% vs 34%, NS 11% vs 12%, NS 10% vs 8%, NS 3% vs 2%, NS 2% vs 1%, NS		
				Toxicity acute G3-4 AE any diarrhea hematologic dermatologic late G3-4 AE Any GI strictures at anastomosis	 27% vs 40%, p=0.001 12% vs 18%, p=0.04 NS NS 14% vs 24%, p=0.01 NS (chronic diarrhea and obstruction) 4% vs 12%, p=0.003		

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				bladder problems	NS		
				Survival & LR survival Overall (5Y) DFS (5Y) recurrence local distant	 76% vs 74%, HR 0.96 [0.70-1.31] 68% vs 65%, HR 0.87 [0.67-1.14] 6% vs 13%, p=0.006, RR 0.46 [0.26-0.82] 36% vs 38%, RR 0.97 [0.73-1.28]		
Rödel C 2005	[314]	operable primary RC, stage II or III 421 randomized to RT+SX, 385 assessable for TRG, 344 assessable for DFS Median fup: 41m	Preoperative RT TRG 0: no regression TRG 1: minor regression (dominant tumour mass with fibrosis in 25% or less of the tumour mass TRG 2: moderate regression, fibrosis in 26% to 50% of tumour mass TRG 3: good regression (dominant fibrosis outgrowing the tumour mass, more than 50% tumour regression) TRG 4: complete tumour regression	TRG & preop factors Age/Sex/T-stage/N stage	NS	Conclusion: TRG 4 (complete TR) was associated with better control of disease in LN (ypN+ 10%), and finally resulted in sustained local control (100%) and a minor risk to develop DM (DFS 86%). Pts with tumours showing intermediate TR (TRG2+3) also had an intermediate risk of LN involvement (ypN+ 32%) and yielded an intermediate prognosis (DFS	Moderate
				TRG & postop factors ypT3+4 ypN+ TNM stage St III+IV grade lymph invasion venous invasion time RT-SX completeness resection	TRG 0+1 vs TRG 2+3 (vs TRG4) 70% vs 57%, p=0.03 40.7% vs 31.9% vs 10%, p=0.001 43% vs 35% vs10%, p<0.001 NS NS 10% vs 4%, p=0.03 NS 92% vs 98% TRG4: 100%		
				Univariate analysis prognostic factors for DFS			

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				age/sex ypT ypN TNM stage grade lymph invasion venous invasion TRG grouped TRG prognostic factors for MFS age/sex ypT ypN TNM stage grade lymph invasion venous invasion TRG Grouped TRG prognostic factors for RFS age/sex ypT ypN TNM stage grade lymph invasion venous invasion TRG/grouped TRG	NS p<0.0001 p<0.0001 p<0.0001 p=0.02 p<0.0001 p=0.03 p=0.04 p=0.006 NS p<0.0001 p<0.0001 p<0.0001 p=0.02 p<0.0001 p=0.03 NS p=0.009 NS p=0.015 p<0.0001 p=0.0008 NS p=0.002 NS NS	75%). Poor TR (TRG0+1) was associated with adverse pathologic features, such as more advanced ypT stages, higher incidence of LN+ (ypN+ 42%), and predicted for an unfavourable outcome (DFS 63%) Comments: this study was an initially unplanned exploratory; ie. a hypothesis generating analysis	
				Multivariate analysis prognostic factor for DFS MFS	 ypT, p=0.016 ypN, p<0.0001 ypT, p=0.014		

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				RFS	ypN, p<0.0001 ypN, p<0.0001		
Hyams D 1997	[315]	pts with operable Dukes B or C RC. 116 pts entered, 89 pts were evaluable for toxicity, 82 pts were evaluable for postoperative complications	Preoperative RT (59pts - G1) vs postoperative RT (57pts - G2) Regimen: G1: CT(1x)-rest (3w)-CRT-RT(3w)-CRT-rest(<8w)-SX-rest(<4w)-CT(4x) G2: SX-rest (<4w)-CT(1x)-rest (3w)-CRT-RT(3w)-CRT-rest(<8w)-CT(4x) CT: high-dose weekly FU + LV; CRT: 5-FU IV bolus W1&5 of RT + low-dose LV RT: 45Gy + 5.4Gy	Toxicity overall *G1 vs G2* none Gr1 Gr2 Gr3 Gr4 death Diarrhea ≥G3 C1-3 C4-7	diarrhea = principal toxicity; next most common toxicity: leucopenia, stomatitis and vomiting (< 10% in both arms during whole treatment) 0% vs 5% 14.3% vs 7.5% 32.7% vs 37.5% 20.4% vs 25% 28.6% vs 22.5% 4% vs 2.5% 39% vs 23% G1 > G2 G2 > G1	Conclusion: preoperative chemoradiotherapy is, at least, as safe and tolerable as standard postoperative treatment. There is a trend to tumour downstaging and sphincter preservation for preoperative CRT. Whether survival, LC and reduction of therapeutic sequelae can be improved with preop CRT vs standard postop CRT awaits the completion of this trial. Comments: study limitations: limited patient accrual, trial designed to	Low
				Surgery type *G1 vs G2* *intended → actual* APR → APR APR → LAR LAR → LAR LAR → APR LE → LE LE → LAR SSS → SSS	 22 → 16 vs 26 → 26 22 → 6 vs 26 → 0 9 → 9 vs 10 → 10 9 → 0 vs 10 → 0 1 → 1 vs 3 → 2 1 → 0 vs 3 → 1 31% → 50% vs 33% → 33%		

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				Postop complications *G1 vs G2* pelvic/perineal anastomosis urinary retention abdominal wound ileus/obstruction	similar 33% vs 31% 6% vs 10%, NS 9% vs 4%, NS 3% vs 2%, NS 3% vs 2%, NS 3% vs 6%, NS	detect a 33% reduction in death rate in preoperative arm and required sample size of 900	
				Surgical staging *G1 vs G2* No residual T CR or PR SD R+	 8% vs 0% 44% (17/39) 26% (10/39) 0% vs 7%		
Roh MS 2001 (abstract, cfr previous)		267 pts randomized, 256 eligible results report status of pts 1 year after randomization	Preoperative RT (130pts - G1) postoperative RT (137pts - G2) *cfr previous*	cCR / pCR (G1) SSS and NED Non SSS and NED Alive with disease death DFS (1y) Postop complications G4 diarrhea	23% / 10% *G1 vs G2* 44% vs 34% 39% vs 44% 6% vs 16% 10% vs 6% 83% vs 78%, NS 25% vs 22%, NS 24% vs 12%	Conclusion: larger proportion of preop RT pts had SSS and had NED at 1 year, which must be balanced by the increase in toxicity and slight increase in early deaths Comments: study limitations: limited accrual, idem as in Hyams et al., 1997	Low
Roh MS 2004 (oral presentation, cfr previous)	[316]	267 pts randomized, 253 eligible Median fup: 78 m	Preoperative RT (130pts - G1) postoperative RT (137pts - G2) *cfr previous*	Toxicity *G1 vs G2* Death TR death Sepsis GI toxicity (≥G3 diarrhea)	 9 (3.3%) 4 vs 3 pts 7% vs 4% 34% vs 26%	Conclusion: CR to preop CRT is associated with significant improved DFS and OS. There is a	Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				Tumour response cCR / pCR cPR LN NEGATIVE *G1 vs G2* ≥ 4 positive LN CTR AND DFS cCR/cPR/cSD CTR AND OS cCR/cPR/cSD PTR AND DFS pCR/pSD PTR AND OS pCR/pSD	 25% / 17% 44% 68% vs 55%, p<0.07 13% vs 27%, p<0.02 95%/72%/66%, p<0.03 100%/83%/71%, p<0.05 94%/72%, p<0.09 94%/82%, p<0.28	suggestion that preop CRT results in nodal downstaging, increased rate of SSS and prolonged DFS and OS. Comments: study limitations: limited accrual, idem as in Hyams et al., 1997 []	
				outcome LR SSS DFS OS	 9% vs 5%, p<0.5 48% vs 39%, p<0.17 64% vs 53%, p=0.08 74% vs 66%, p=0.14		

Is 5-FU continuous infusion superior to bolus 5-FU in combination with preoperative radiotherapy in the outcome of patients with resectable rectal cancer?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	January 2001	Colorectal cancer	Chemotherapy should be given synchronously with the RT using one of the following 3 regimens: - intermittently infused FUFA (Bosset) - continuous FU (Lokich) or bolus FUFA	prospective cohort studies intermittently infused FUFA (Bosset JF, 1993) or continuous FU [Lokich JJ, 1989] have been widely and safely used	applies only to a long course of RT	Low

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE	[54]	March 2003	Colorectal cancer	If CRT is used, it should be an established regimen.	NO EVIDENCE	-	-

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
O'Connell 1994	[86]	RC with R0 resection, stage II or III, tumour level at or below promontory or ≤12 cm from anal margin Med fup 46 months average dose of FU: 6516mg/m² vs 2499mg/m²	680 pts randomized, 660 pts eligible, 328 PVI FU/RT 332 bolus FU/RT schedule: CTw1 - CTw6 -CRTw10-15 - CTw20 - CTw25 CT: 114/328 and 112/332 received FU + semustine 214/328 and 220/332 received FU alone CRT: FU bolus (w10,w15) or PVI + 45Gy/1,8 + 5,4Gy/ 1,8 boost ± 3,6Gy boost	Outcome PVI vs bolus FU TRR DMR LRR survival prognostic factors for survival and time to relapse multivariate analysis acute toxicity PVI vs bolus FU ≥G3 diarrhea ≥G3 leukopenia SB obstruction (SX) RT interruption treatment related death	 37% vs 47%, p=0,01 31% vs 40%, p=0,03 p=0,11 p=0,005, 31% reduction in death rate, 4Y OS 70% vs 60% increased age greater LN+ greater depth of tumour invasion higher tumour grade 24% vs 14%, p<0,01 2 vs 11%, p<0,01 3% vs 2%, NS 10 pts vs 7pts, NS 1	Conclusion: a protracted infusion of FU during pelvic irradiation improved the effect of combined treatment postoperative adjuvant therapy in patients with high risk rectal cancer. The reduction in DM rate suggests that FU given by PVI has an improved systemic effect on micrometastases. Although not significant, the LRR was decreased by PVI (low LRR). The beneficial effect of PVI may simply have been the result the much higher total doses of drug that could be safely delivered by PVI (average FU doses 6516mg/m² with PVI and 2499mg/m² with bolus infusion). PVI requires CV access and an ambulatory infusion pump, which increase the complexity and cost of therapy. Semustine plus FU (as systemic CT before and after RT) was not more effective than a higher dose of systemic FU given alone.	Low

Are intravenous 5-FU and oral 5-FU equivalent in the outcome of patients with resectable RC?

CPG	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	January 2001	Colorectal cancer	Chemotherapy should be given synchronously with the RT using one of the following 3 regimens: - intermittently infused FUFA (Bosset) - continuous FU (Lokich) or bolus FUFA	NO EVIDENCE	-	-
NICE	[54]	March 2003	Colorectal cancer	If CRT is used, it should be an established regimen.	NO EVIDENCE	-	-

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
Kim NK et al., 2001 [ ] aim: to compare IV 5-FU with oral doxifluridine with respect to tumour response (TR), toxicity and quality of life. Level of evidence:		pts with RC, T3N1/T4, <70y 28 pts entered partial tumour response: >50% diminution of the tumour volume complete response: no residual microscopic disease or RT fibrosis	CRT IV+SX : 14 CRT PO+SX: 14 CRT-IV : 5-FU/LV IV bolus for 5d in w1 and w5, CRT-PO: doxifluridine/LV PO continuously with RT RT: 50,4Gy/1,8 Gy, 3 field box	Tumour response CRT IV vs CRT PO no partial response complete response overall TR downstaging T3 -> T0 T4 -> T0	 29% vs 43%, p=0,247 50% vs 43%, p=,235 21% vs 14%, p=0 ,168 71% vs 52% 2 vs 1 1 vs 1	Conclusion: although limited no. of pts., oral doxifluridine did not show any significant advantages over IV 5-FU Comments: study limitation: limited number of patients, bolus 5-FU is compared to continuous oral FU!!	
				Quality of life CRT IV vs CRT PO poor fair and good	 4/11 vs 4/12, NS 7/11 vs 8/12, NS		

moderate		replaced the tumour mass.	PR: downstaging or >50% diminution of TV	Toxicity CRT IV vs CRT PO leucopenia G1-2 leucopenia G3 diarrhea G1-2 stomatitis G1	 14% vs 21% 7% vs 7% 14% vs 36% 7% vs 0%		
				Recurrence CRT IV vs CRT PO Local Systemic	 0 vs 1 1 vs 2, p=0,307 (all liver M+)		

Is a long course of preoperative (chemo)radiation better than a short course of preoperative radiation in the outcome of patients with resectable rectal cancer?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE	[54]	March 2003	Colorectal cancer	If CRT is used, it should be an established regimen.	NO EVIDENCE	-	-

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
Bujko K 2004	[109]	T3-4 resectable RC, palpable on DRE, no sphincter involvement, 316 pts randomized 305 pts underwent SX clinical complete remission (cCR): no tumour palpable on DRE	Short-course (SC) preoperative RT (155 pts) vs long-course (LC) preoperative CRT (157 pts) (150 and 139 pts received allocated intervention) SC-RT: 5 x 5 Gy, SX within 1 week,	Post RT acute toxicity SC RT vs LC CRT sudden death all complications G3-4	 0 vs 2 24% vs 85%, p<0,001 3% vs 18%, p<0,001	Conclusion: despite significant downsizing, CRT did not result in increased sphincter preservation rate in comparison with short-term preoperative RT. The surgeons' decisions were subjective and based on pre-treatment tumour volume at least in clinical complete responders	Moderate
				Surgery *SC RT vs LC CRT* SSS Intended SX† APR APR/SSS SSS TL > 6 cm	 61% vs 58%, p=0.57 26% vs 21%, p=0,61 68% vs 61%, p=0,4 85% vs 87%, p=0,73		

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
			LC-CRT: 50.4Gy/ 1.8 Gy, CT: 2 x 5-FU/LV, SX after 4-6w SX = TME for low RC, PME for mid RC, type of SX based on post RT tumour status Intended SX†: SX as intended before start radiotherapy Postop CT: optional Note: no central quality control for simulator films, RT plans, TME technique, pathology reports, CT	SSS APR SSS & TL‡ 2-3 cm 4-5 cm 6-7 cm > 7 cm Postoperative complications death all severe *(death or requiring re-intervention)*	47% vs 42%, p=0,40 46% vs 51%, NS 12% 45% 82% 96% 3 (1%) 23% vs 15%, p=0,12 12% vs 9%, p=0,38	The authors explain the absence of a difference in SSS as: 1: randomization error, 2: surgeon decision was not based on post-RT status (APR in cCR) There was a poor correlation between cCR and pCR	
				Tumour response *SC RT vs LC CRT* cCR APR pCR microsc pCR macrosc	 2% vs 13%, p<0,001 28% in LC-CRT 1% vs 16%, p<0,001 1% vs 15%, p<0,001		
				Pathology *SC RT vs LC CRT* Tumour size +CRM distal margin T stage T0 T1 T2 T3-4 N stage N0 N+	 4,5 cm vs 2,6 cm, p<0,001 13% vs 4%, p=0,017 2 cm in both groups 1% vs 16%, p<0,001 2% vs 9% 37% vs 37% 60% vs 38%, p<0,001 52% vs 68% 48% vs 32%, p=0,007		

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				no. LN found	Mean 11,4 vs 7,6, p<0,001		
Bujko K 2005	[108]	*cfr previous*	Short-course (SC) preoperative RT (155 pts) vs long-course (LC) preoperative CRT (157 pts) *cfr. previous* Postoperative complications were analyzed with respect to the assigned schedule of pre-operative radiotherapy. Intention-to-treat analysis.	Postop complications *SC RT vs LC CRT* <u>All</u> no. pts no. events <u>Severe complications</u> *(30-day postop death or complications requiring surgical reintervention)* no. pts no. events 30d postop death anastomotic leak other complications <u>Complications not requiring re-intervention</u> perineal wound healing	 27% vs 21%, p=0,27 31% vs 22%, p=0,06 10% vs 11%, p=0,85 12% vs 11%, p=0.85 1,3% vs 0,7%, p=1.0 11% vs 9%, p=0,76 NS	Conclusion: the study did not demonstrate a statistical significant difference in the rate of postoperative complications after short-course preoperative RT compared with full course chemoradiation. The trend towards more postop complications in SC-RT should be weighed against higher post-RT acute toxicity in LC-CRT	Moderate

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				delay or infection others <u>OTT according to complications</u> SC-RT LC-CRT <u>Complications according to OTT</u> OTT<10d vs OTT>10d OTT<78d vs OTT>78d	29% vs 21%, p=0,36 NS median 8d vs 8d, p=0,5 median 84dvs78d, p=0,054 27% vs 27% 12% vs 28%		
Bujko K 2005	[317]	cfr previous The pathological reports of patients who fulfilled entry criteria and had preoperative RT followed by transabdominal SX were analysed Response to RT: (1) few cancer foci in < 10% of the surface of slices; (2) partial response: cancer cells in 10-50% of the surface of slices; (3) no response: cancer cells in > 50% of the surface of slices	Short-course (SC) preoperative RT (147 pts) vs long-course (LC) preoperative CRT (138 pts) cfr. previous	pN stage pN+ ypT0 ypT1 ypT2 ypT3-4 ypT2N+ few cancer foci partial response no response	 49% vs 33%, p=0,007 0% vs 5%, NS 0% vs 8%, NS 28% vs 26%, p=0,83 64% vs 55%, p=0,37 20% 31% 40%	Conclusion: for patients with tumours downstaged by chemoradiation to ypT0 and ypT1 full thickness local excision may be considered as an acceptable approach, because the risk of mesorectal lymph nodes metastases is low. Even in patient with a few cancer foci seen in the bowel wall, the rate of N+ for the ypT2 category remained high. Study limitations: central quality control for pathological examinations was not performed, small sample size of analyzed subgroups, which resulted in large 95% CI.	Moderate

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
Bujko K 2006	[89]	cfr previous Median fup: 48m (31m-69m); 98% of pts: >3y, 15% of pts: >5y	Short-course (SC) preoperative RT (155 pts) vs long-course (LC) preoperative CRT (157 pts) cfr. previous pts receiving allocated intervention: SC-RT: 143, LC-CRT: 135 postop CT: more in SC-RT 46% vs 30%, no diff in pts with postop CT for N+; no pts with postop CT for pCR RT: better compliance for SC-RT (98%) vs LC-CRT (69%) Note: 21% of SSS had stoma not related to LR!	Post RT acute toxicity SC RT vs LC CRT deaths G3-4	 0 vs 2 3% vs 18%, p<0,001	Conclusion: Neoadjuvant chemoradiation did not increase survival, local control or late toxicity compared with short-course RT alone. The present trial demonstrated a downstaging effect, with higher rates of both complete tumour response and negative circumferential margin after CRT compared with those observed after short-course RT. Since local control and survival were not statistically different between the groups, the degree of downstaging, rate of complete tumour response and rate of R0 surgery should not be used as surrogate endpoints to compare the efficacy of preoperative RT ot CRT regimens with schedules that have a different interval between the beginning of irradiation and surgery. This is because cancer cells damaged after radiotherapy need time to undergo necrosis26, and non-viable cancer cells may look morphologically intact	Moderate
				Surgery SC RT vs LC CRT SSS postop complications	 no TR in 8 vs 8 61% vs 58%, NS no difference (reported previously)		
				Pathology *SC RT vs LC CRT* pCR ypT1/2 ypT3/4 ypN+ CRM+ distal spread	 0,7% vs 16% 40% vs 46% 60% vs 38% 48% vs 32% 13% vs 4%, p=0.02 no sign difference *(reported previously)*		
				Survival *SC RT vs LC CRT* 4Y OS 4Y DFS	 67% vs 66%, NS HR 1,01 [0,69-1,48] 58% vs 56%, NS HR 0,96 [0,69-1,35]		
				Recurrence *(295 pts with R0/1)* *SC RT vs LC CRT* crude rate LR 4Y LRR	 9% vs 14%, NS 11% vs 16%, NS HR 0,65 [0,32-1,28]		

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				crude rate LF *(LF= LR+R2+noR)* crude rate DM	14% vs 19%, NS 31% vs 35%, NS	shortly after irradiation. Study limitations: study is unlikely to detect small differences, as it has been powered to detect differences of 15% or more; duration of fup is not long enough; postop CT more administered in short-course group (related to downstaging effect of CRT, which resulted in decreasing no. pts for whom this treatment was considered beneficial (LN+), high rate of pT1/T2 in short-course RT may imply that this group included more favourable cases, however, tumours were stratified by character, no quality control of TME; no central quality control for pathological examinations.	
				Late toxicity - crude rate *SC RT vs LC CRT* overall severe late toxicity permanent stoma	 28% vs 27%, NS RR 1,05 [0,72-1,53] 10% vs 7%, NS RR1,43 [0,67-13,07] in SC-RT: 50% small/large intestine; in LC-CRT: 30% skin toxicity 57% vs 52%, NS RR 1,10 [0,9-1,35]		

Is a long treatment interval between preoperative (chemo)radiation and surgery better than a short interval in the outcome of patients with resectable rectal cancer?

CPG ID	Ref	Search	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[282]	January 2004	Adult pts with clinically resectable rectal cancer	no recommendation	1 RCT (François Y, 1999) OS 3Y (LI vs SI): 73% vs 78%, NS LF: 9% vs 9%, NS TUMOUR RESPONSE: (PR+CR) 72% vs 53%, p=0,007 DOWNSTAGING (p): 26% vs 10%, p=0,005	RT : 13 x 3,3Gy (17d) LI : 6-8 weeks SI : 2 weeks operable RC accessible to DRE (low seated), stage T2-3, Nx, M0	High
NICE	[54]	March 2003	Colorectal cancer	If CRT is used, it should be an established regimen.	NO EVIDENCE	-	-

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
François Y 1999	[90]	resectable RC, stage T2-3 – Nx – M0, accessible on DRE 210 pts were entered, 201 were analyzed Median fup: 33,5m (1-79)	preoperative RT followed by a short interval (SI) compared to a long interval (LI) between completion of RT and SX. Preop SI: 102 pts Preop LI: 99 SI: short interval = within 2 weeks after	Clinical response overall RR cPR cCR	LI vs SI 71.7% vs 53.1%, p=0.007 65 vs 49 6 vs 2	conclusion: a long interval between preoperative RT and SX provides increased tumour downstaging with no detrimental effect on toxicity and early clinical results. When sphincter preservation is questionable, a long interval may increase the chance of a successful sphincter-saving SX (5th or 6th week after completion of	High
				Pathologic results pCR few residual cells residual tumour pT0-1 pN0	 14% vs 7%, NS 12% vs 3%, p<0.03 74% vs 87%, p=0.005 29% vs 15%, p<0.03 76% vs 67%, NS		

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
			completion of RT LI: long interval = 6 to 8 weeks RT: 13 x 3 Gy (17d), prone, 18MV SX: 144 pts conservative SX/ 67 pts APRA The surgeon made a decision about SSS at the time of SX, based on the clinical response assessed by comparing the tumour size with the initial tumour size before RT. Surgery with curative intent was defined as a locally gross complete resection without evidence of distant metastasis. The operative specimen was classified as a pathologic complete response (CR) when no cancer cells were found or as "a few residual cells" when only a small cluster of cells was detected	pN2-3	5% vs 16%, p<0.02	RT). authors suggestions: in pts with tumours located more than 6 cm from the anal verge or in pts with tumours very close to the anus or involving it (APRA required), the interval between RT and SX probably has NO influence on the type of SX. The date of operation could be decided according to the surgeon's or patient's preference, but it is our current practice to delay SX for 4 weeks after completion of RT. Comments: study limitations are: no standardized surgery	
				SX Type SSS T≤5 cm Intended vs actual SSS - SSS non SSS - SSS	 78% vs 76%, NS 41% vs 23%, NS 99 pts -> 94 44% vs 43%		
				Postop complications mortality *(within 2 m after SX)* morbidity hospital stay re-operation anastomotic complications ↳ re-operation covering stoma in SSS	 4% vs 3% NS 16d vs 18d 17% vs 17% 17% vs 18%, NS 10% vs 13% re-operation more frequent in pts without protective stoma (20/87 vs 3/57, p=0.01) 30/77 vs 27/67		
				Survival and LR OS (2y) OS (3y) LC & curative Sx LR & SSS LR & APR LR and TL TL<15mm LR and conversion from non-SSS to SSS	 81% vs 83%, NS 73% vs 78%, NS 82/102 (80%) vs 78/99 (79%), NS 11.8% (9% vs 9%, NS) 1.5% 7/43 (16%) 16% vs 12% (3/17 vs 1/17)		

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				Toxicity anal function	 normal in 64/82 (35/43 vs 28/39)		
Glehen O 2003	[318]	cfr. previous Median fup: 6,3y (6,1-7,2)	cfr. previous	Postop complications Postop mortality Postop morbidity anastomotic complications	LI vs SI 4% vs 3% NS NS, 17% vs 18%	Conclusion: delaying surgical resection until the fifth or the sixth week after the end of RT increases downstaging and may improve the feasibility of SSS without any detrimental effect, in terms of mortality, morbidity, LR, survival and functional status.	High
				Survival OS at 5Y after SSS/APR	 66% vs 69%, NS 71% vs 57%, p=0.02		
				LRR TL<15mm TL>15mm after SSS/APR LRR after SSS requiring stoma	10% vs 13%, NS 21% (9/43) 9% (7/76) 21/144 (15%) vs 2/57 (4%), p? 9/50 vs 5/44, NS		
				Anal function excellent or good	 24/30 vs 25/30		

Is there any benefit from alternative regimens of preoperative (chemo)radiotherapy compared to the standard regimen of (chemo)radiotherapy (short course or long course) in the outcome of patients with resectable rectal cancer? What is the role of brachytherapy/contact X-ray therapy in the preoperative treatment of resectable rectal cancer?

CPG ID	Ref	Search	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[282]	January 2004	Adult pts with clinically resectable rectal cancer	no recommendation	Gérard et al, Lyon R96-02, 2003, abstract significant more sphincter preservation in boost group, no difference in 2Y OS, LC or postop complications after 35 months fup	arm1: EBRT: 13x3Gy (17d) (43) arm2: EBRT + X-ray boost: 85Gy/ 3 fractions in 21d (45)	moderate
NICE	[54]	March 2003	Colorectal cancer	If CRT is used, it should be an established regimen.	NO EVIDENCE	-	-

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
Gérard JP 2004	[91]	90 pts included, 88 eligible, T2-3 (EUS) with inferior edge ≤ 6 cm from AM, accessible for CXR (not > 2/3 circumference)	Preop EBRT: 43 Preop EBRT + boost (endo-cavitary CXR): 45 EBRT : 13 x 3 Gy Boost: 85 Gy in 3 fractions (35Gy, 30 Gy and 20Gy) RT: 3-field, prone, 18MV, CXR: 20Gy/min, 2w before EBRT, 3 fractions on D1,8,21 (D21 = end W1 EBRT)	TUMOUR RESPONSE cCR pCR few residual tumour cells TS N stage CRM+ Distal M+	EBRT+bst vs EBRT 11 vs 1, p<0.05 8/38* vs 3/43*, p<0.05 15 vs 12, p<0.05 Mean 2.6 vs 3.2, p<0.05 NS 0 vs 3 1 vs 0	conclusion: a dose escalation with endocavitary irradiation provides increased tumour response and sphincter preservation with no detrimental effect on treatment toxicity and early clinical outcome. This trila brings data in favour of the use of high-dose preoperative RT and delayed surgery to increase anorectal SSPs in the management of low rectal cancer study limitations: only 88 patients, some patients received adjuvant chemotherapy (equally distributed	Moderate
				SURGERY AND SSS RT alone (cCR) LE LAR APRA SSS	 6 vs 0 3 vs 0 24 vs 19 11 vs 24, p=0.004 76% vs 44%, p=0.004		

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
			BT: if cCR, 25Gy over 24-36h with interstitial Iridium-192 implant * examined operative specimens	multivariate	OR 3.2 [1.2-9.6], p<0.04	in both arms), the decision to perform brachytherapie was arbitrary, CXR has a limited clinical applicability (50kV machine)	
				TOXICITY SX complications postop death early acute AE anorectal function in SSS BT	 NS 0 vs 1 NS, within range NS no ≥G3 late anorectal AE		
				SURVIVAL AND TUMOUR RELAPSE OS (2Y) deaths CR deaths LRFS pelvic LR	mean fup of 35 months NS, close to 90% 5 vs 9 3 vs 7 92% vs 88% 1 vs 3		

Is restaging after preoperative treatment useful in patients with resectable rectal cancer?

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
Guillem 2005	[119]	94 pts with T3/4 or N1 – prospective study 15% (14/94) achieved pCR = ypT0N0 clinical response: five categories: (1) progression (2) minimal regression (3) moderate regression (4) significant regression (5) near complete or complete response=cCR SX med 48d after CRT	pts evaluated with DRE and sigmoidoscopy before CRT and with DRE ± endoscopy after CRT (same surgeon, just before resection) aim: ability of surgeon to assess response after CRT using DRE	ycT vs pT pCR p stage I p stage II p stage III p stage IV cCR vs pCR ACCURACY SENSITIVITY SPECIFICITY PPV NPV	overall accuracy 22% DRE correct in 3/14 (21%) DRE correct in 5/25 (20%) DRE correct in 7/20 (35%) DRE correct in 6/26 (23%) DRE correct in 0/9 49% 24% 56% 19% 61% 25% of cCR were pCR	Conclusion: Clinical examination underestimates the extent of rectal cancer response to preoperative CMT (DRE underestimates the response in 73 (78%)). There were no clinical overestimates of response. Given the inaccuracy of DRE following preoperative CMT, it should not be used as a sole means of assessing efficacy of therapy nor for selecting patients following CMT for local surgical therapies.	Moderate
Hiotis 2002	[120]	488 pts with ≥uT3 or uN+ after CRT, 10% (50/488) had ypT0N0 definition of cCR = absence of detectable tumour on preoperative DRE and proctoscopy SX 6-12 wks after CRT	clinical staging with DRE + proctoscopy 6 wks after CRT pathological staging on all resected specimens	ycT0 vs ypT SENSITIVITY SPECIFICITY ACCURACY PPV NPV ycN0 vs ypN SENSITIVITY SPECIFICITY ACCURACY PPV NPV	25% of cCR were pT0 46% (23/50) 84% (368/438) 80%(391/488) 25% (23/93) 93% (368/395) 82% of cCR were pN0 21% (74/353) 86% (101/117) 37% (175/470) 82% (74/90) 27% (101/279)	Conclusion: Clinical complete response to preoperative therapy as determined by preoperative digital rectal examination and proctoscopy or EUA is not an accurate predictor of pathologic complete response. A significant percentage of clinical complete responders have persistent deep tumours or nodal involvement (15% of pT0 had N+). We do not recommend making treatment decisions based solely on the absence of clinically palpable or visible tumour after chemoradiation. Our data suggest that all acceptable-risk patients with a diagnosis of primary	Very low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
					sens, spec, PPV and NPV are calculations by SR	rectal cancer should undergo resection, regardless of their response to preoperative therapy.	
Bedrosian I 2004	[110]	219 pts with T3 or T4 (by EUS) RC treated with preoperative CRT pCR in 20% (43/219) pCR= absence of viable tumour cells in specimen clinical response on proctoscopy: (1) mucosal ulceration (2) scar / induration (3) no visible changes SX med 48-49d after CRT	one of the aims was to assess the correlation between clinical appearance on proctoscopy after CRT (just before SX) and pathologic response	<u>primary tumour</u> - pCR 43 SENSITIVITY SPECIFICITY - gross residual disease 114 - microscopic disease 59 SENSITIVITY SPECIFICITY	 mucosal ulceration in 24 scar/induration in 17 no visible changes 2 (19 correct) 44% 92% mucosal ulceration in 113 scar/induration in 1 (113 correct) mucosal ulceration 47 scar/induration in 11 no visible changes 1 (47 correct) 92% 44%	60% of cCR (scar/induration/no visible abnormalities) were pCR Conclusion: Despite the high response rate to preoperative CRT, the tumour response in the bowel wall and nodal basin is not uniform, and nearly 20% of patients with pT0–2 tumours have residual extramural disease. In addition, accurate presurgical assessment of the pathologic response remains challenging. Radical surgery, therefore, remains the standard of care for patients downsized by neoadjuvant CRT.	Very low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
Benzoni E 2005	[111]	58 pts with RC treated with preoperative CRT pCR in 9% (5/58) pCR: no detectable tumour PR: partial response = 50% reduction of major dimension of tumour SD: stable disease = lack of 50% reduction PD: progressive disease = 25% increase in TV SX 3 weeks after CRT	DRE + proctoscopy + pelvic CT + EUS before and DRE + proctoscopy + pelvic CT immediately after CRT	ycT vs ypT cCR vs pCR cPR vs pPR cSD vs pSD cPD vs pPD PPV/NPV for cCR PPV/NPV for cPR PPV/NPV for cSD PPV/NPV for cPD	 100% cCR were pCR 45% of cPR were pPR 3.5 % of cPR were pPD 34.5% of cSD were pSD 3.5% of cSD were pPD 5.2% of cPD were pPD 100%/100% 93%/100% 91%/100% 100%/20%	Conclusion: Good correlation between cCR and pCR; whereas the clinical evaluation overestimated PR and SD and underestimated PD. PPV and NPV for PR and SD of clinical evaluation were not high enough to consider clinical staging accurate enough for treatment decisions. Limitations: SX only 3 weeks after CRT!! too early for downsizing	Low
Houvenaghel 1993	[121]	34 pts with rectal cancer (uT2-4 by EUS) 32 TRUS and 31 DRE examinations were performed after RT pCR in 15% (5/34)	clinical examination and TRUS before and after (15d) preoperative RT (RT: 36.5 Gy) aim: to evaluate the value of clinical and endosonographic examinations for staging of rectal adenocarcinomas after RT	<u>T stage</u> DRE vs pT TRUS vs pT <u>N stage</u> DRE vs pT TRUS vs pN	 correct in 13/31 underst in 10, overst in 7 correct in 17/32 underst in 6, overst in 7 correct in 23/31 underst in 7, overst 1 correct in 22/32 underst in 5, overst 5	Conclusion: Since RT alters TRUS staging of rectal cancer, this staging should be included in survival studies Time of SX is not reported!!	Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
Romagnuolo J 2004	[126]	18 pts with stage T2-3 operable RC, 13 cN0, 5 cN+ Brachytherapy (BT) pCR in 39% (7/18) pathology as reference standard	EUS at 4-8 weeks after BT, within 2 wks before surgery Pathologist blinded to EUS results.	ycT vs ypT SENSITIVITY SPECIFICITY PPV NPV ACCURACY uCR /pCR	predictive value for ypT 82% 29% 64% 50% 44% (8/18) 11/7	Conclusion: RC T-staging by EUS post-BT is inaccurate, and although it appears sensitive in predicting the presence or absence of residual tumour after preoperative BT, the low PV in this setting limit its utility at this time. EUS tends to overstage due to fibrotic changes Limitation: not stated how many of cCR were pCR in abstract	Low
Maor Y 2006	[125]	pts with rectal cancer G1: no preop CRT (66) G2: preop CRT (25) pCR in 8% (2/25) in G2	G1: SX 14-30d after EUS G2: EUS 30-45d after CRT and SX 7-14d after EUS	<u>T staging in G2</u> <u>N staging in G2</u>	accurate in 72% overstage (4/25) in 16% understage (3/25) in 12% overstage in 8% (2/25) understage in 12% (3/25)	Conclusion: EUS staging after CRT is inaccurate ; the detection of pCR is insufficient for selection of patients for limited surgical intervention cCR SENS=100%, SPEC=91%, PPV=50%, NP=100%	Low
Vanagunas 2005	[127]	82 pts with locally advanced rectal cancer treated with preoperative CRT. control group without CRT (36 pts) pCR 19% (16/82)	EUS staging before and after (4-6 wks) CRT SX (time NR)	<u>T staging</u> (EUS vs pT) <u>N staging</u>	EUS correct in 39/82 (48%) *overst 38%, under 14%* accurate in 77% *underst15%, overst 8%*	Conclusion: EUS for restaging after CRT is inaccurate. Surgical therapy should therefore be based on the original uTN staging of the rectal cancer and although overstaging is the most common error, 6/16 uT0 were UNDERstaged	Very low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
				control group T staging accuracy N staging accuracy	81% *underst 11%, overst 8%* 89% *underst 3%, overst 8%*	uCR SENS=91,3%, SPEC=100%, PPV=100%, NPV=91,6%	
Bernini 1996	[112]	43 patients with T3 or N+ (by EUS) RC received long course preoperative (C)RT 21 had restaging with EUS pCR 10% (2/21)	(1) impact of (C)RT on tumour regression (43 patients) and (2) predictive value of EUS for T and N staging after (C)RT (21 pts)	T stage (TRUS vs path) PPV NPV N stage PPV NPV	EUS correct in 13/21 (62%) *overst in 8, underst in 0* 72% 100% EUS correct in 16/21 (76%) *overst in 4, underst in 1* 56% 82%	Conclusion: EUS after neoadjuvant treatment is of lesser predictive value chiefly because of overstaging uCR SENS=50%, SPEC=100%, PPV=100%, NPV=95,2%	Low
Gavioli 2000	[118]	29 pts with rectal cancer treated with preoperative RT pCR in 14% (4/29)	TRUS before and after RT SX 6-8 weeks after RT; TRUS few days before SX	T stage (TRUS vs path) pT0 N stage	correct in 21/29 (72%) *overstaged in 8* correct in 0/4 (0%) *overstaged as T2 (2) and T3 (2)* correct in 19/29 (70%) *overst in 3, underst in 5*	Conclusion: The authors comment that, from the tumour staging point of view, six to eight weeks after radiotherapy, ERUS no longer stages the tumour, but rather the fibrosis that takes its place. However, post-radiation ERUS is a valid toot, because the extent of fibrosis in the rectal wall is a direct indication of the depth of residual cancer. A residual tumour, when present, is always inside the fibrosis. Finally, however, as regards	Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
						the capacity of ERUS to exclude or indicate complete sterilization of the lesion, the actual significance of the echo-pattern changes we observed needs to be assessed further by studies on a large number of cases. uCR SENS=0%, SPEC=100%, PPV=0%, NPV=86%	
Williamson 1996	[128]	16 patients with uT3/4 that completed preoperative (C)RT pCR 31% (4/13)	13/16 patients had ERUS restaging within 1 week before SX (6-8 weeks after RT) 1/16 patient was inoperable	T stage (ERUS vs path) N stage	correct in 7/12 *over in 4, under in 1* correct in 7/12 (58%) *overst in 2, underst in 3*	Conclusion: Although ERUS offers a method for assessing degree of shrinkage and downstaging of T3 and T4 lesions after CRT, presently it does not closely predict pathologic results. Results are strongly related to experience of the ultrasonographer. The ability to distinguish tumour from RT-induced changes to perirectal tissues is under continued investigation, and a new method of interpreting the data obtained by ERUS after CRT will need to be established. uCR (Tstage) SENS=0%, SPEC=100%, PPV=0%, NPV= 66,6%	Low
Liersch T 2003	[124]	61 pts with ≥T3/N+ (by EUS/CT) rectal cancer G1(61): postoperative CRT G2(41): preoperative CRT	G1: staging with EUS/CT before SX G2: staging with EUS/CT before and after CRT	T staging in G2 EUS/CT vs pT N staging in G2	accuracy EUS/CT 6%/51% *underst EUC/CT 2%/22%* *overst EUC/CT 32%/27%* accuracy EUS/CT 68%/76% *under EUC/CT 20%/17%* *overst EUC/CT 12%/7%*	Conclusion: EUS offers higher (but not significantly) accuracy for detection of residual tumour after CRT compared to CT (T stage) and assessment of complete remission. Identical staging by EUS and CT increased accuracy of T staging to 90%	Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
		SX: 4-6 wks after CRT restaging: 3-4 wks after CRT pCR 20% (8/41)		downstaging by EUS/CT vs pathology	T downstaging by more than 1 stage was correctly assessed by EUS in 15/20 (75%) and 20/20 (100%) by CT; N downstaging by EUS in 17/19 (89%) and by CT in 10/12 (83%)	and 83 % for N staging EUS-CR SENS=25%, SPEC=100%, PPV=100%, NPV= 84,6% CT-CR SENS=50%, SPEC=88%, PPV=50%, NPV= 88%	
Fleshman JW 1992	[117]	19 pts with rectal cancer pCR 5% (1/19)	CT and TRUS before and TRUS after CRT to assess accuracy of TRUS for predicting pathologic stage after RT	T staging (TRUS vs path) LN involvement (TRUS vs path)	accuracy 58% (11/19) *overst TRUS 42% (8/19)* accuracy 68% (13/19) *underst TRUS 1/19* *overst TRUS 5/19* PPV after RT 50% NPV after RT 88%	Conclusion: Preop RT makes TRUS less effective as staging techniques. The absence of LN on TRUS after RT is reliable. TRUS-CR: SENS 0%, SPEC 100%, PPV 0%, NPV 95%	Low
Kuo LJ 2005	[123]	36 pts with LARC (T3-4/N+) SX 6-8 wks after CRT pCR in 5/36 (12%)	staging with MR before and 4 weeks after CRT	T staging (MR vs pT) N staging (MR vs pN)	overall accuracy 17/36 (47%) *overst 17, under 17 (47%)* overall accuracy 23/36 (64%) *overst 28%, under 8%*	Conclusion: MR is commonly used in staging of pelvic malignancies because of its fine resolution, but chemoradiotherapy may decrease its accuracy. Thickening of the rectal wall after radiation by marked fibrosis, and peritumoral infiltration of inflammatory cells and vascular proliferation may contribute to overestimation of stage.	Very low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
						By contrast, pathologic residual cancer beneath normal mural structure after chemoradiation therapy may result in understaging of rectal cancer. MR-CR (T-stage) SENS=20%, *SPEC=100%, PPV=100%*, NPV= 88,5%	
Chen 2005	[116]	50pts with cT3/4 or N+ M0 low or middle RC pCR 24% (12/50)	staging with MR before and after preoperative CRT SX 4-8 weeks after CRT restaging time NR	<u>T staging</u> (MR vs pT) <u>N staging</u> (MR vs pN)	overall accuracy 52% overall sensitivity 52% overall specificity 88% *overstaging 38%, understaging 10%* overall accuracy 60% overall sensitivity 68% overall specificity 68% *overstaging 24%, understaging 8%*	Conclusion: Poor agreement between post-CCRT MRI and pathologic staging was observed in both T and N stages. Most of the inaccuracy in T and N stages was caused by overstaging, especially with T0–T2 tumours. We believe that the problem of MRI is that it cannot completely differentiate fibrosis from viable residual tumours pT0: SENS 25%, SPEC 97%, PPV 75%, NPV 80%	Low
Kahn H 1997	[122]	25 pts with pT0pN0 rectal cancer after preoperative CRT	to assess the ability of DRE (25), CT (13), MR (1) and TRUS (6) to predict absence of disease after preoperative CRT SX 6-8 weeks after CRT clinical restaging one or two weeks before SX	<u>pT0N0</u> DRE CT TRUS MR	SENSITVITY 24% 6/25 correct *overst: T3(4)/T2(8)/T1(7)* 23% 3/13 correct, *overst: T3(4)/T2(4)/T1(2)* 17% 1/6 correct *overst: T2(1)/T1(4)* 0% 0/1 correct *overst: as T2(1)*	Conclusion: The ability to assess local eradication of rectal cancer following radiation therapy remains poor. Conventional imaging and clinical examination techniques are unable to safely predict which patients do not require surgical excision following curative radiation therapy for rectal cancer.	Very low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Level of evidence
Capirci C 2004	[113]	81 pts clinical stage II-III after CRT ypCR 34,5% (28/81) *PET positivity* defined as: intense FDG uptake if SUV_{max} > 6, moderate if 3-2.9 or mild if 1.5-2.9. *PET negativity* defined as faint FDG uptake (SUV_{max} 1-1.4) and diffuse uptake or absent uptake	clinical staging: DRE + proctoscopy and biopsy + CT + pelvic MRI 4 wks after CRT FDG-PET staging 4 wks after CRT SX at 8-9wks after CRT	ycT vs ypT <u>yPET- vs ycT0</u> SENSITIVITY SPECIFICITY ACCURACY PPV NPV <u>yPET- vs ypT0</u> SENSITIVITY SPECIFICITY ACCURACY PPV NPV	NR: 12 pts had cCR but it is not reported how many were pCR 10 pts with PET CR and cCR 83% 41% 20% 93% 79% 45% 56% 43% 80%	1 mo interval between restaging and pathology!! *PET vs TRG score not in table* low sensitivity due to limited tumour mass after CRT? 51 PET positive, 30 PET negative	Low
Capirci C 2006	[115]	88 pts clinical stage II-III after CRT ypCR 34% (30/88) 58 had p-stage 0-I (66%) pCR = no cancer cells found PET positivity defined as intensity of FDG uptake: intense SUV max > 6: moderate: 3-2.9 or mild: 1.5-2.9. PET negativity defined as faint (SUVmax 1-1.4) and diffuse uptake or absent uptake.	DRE + proctoscopy and biopsy + CT (75) + pelvic MRI (23) at diagnosis and 6-7 weeks after CRT FDG-PET at 7 wks after CRT SX at 8-9 wks after CRT	ycTN vs ypTN <u>yPET+ vs ypT+</u> SENSITIVITY SPECIFICITY ACCURACY <u>PET as predictor of downstaging by CRT</u> SENSITIVITY SPECIFICITY ACCURACY	NR: 12 pts were ycCR, 30 pts were pCR (T0/TisN0) and 1 pt pT0N+, not reported how many of ycCR were ypCR 47% 77% 57% 61% 74% 70%	Conclusion: diagnostic performance of FDG PET after CRT was poor; FDG PET as predictor for downstaging after CRT was not absolute. Pathologic stage and FDG PET findings after CRT ware independent prognostic factors for OS/DFS, as well as the combination of variables. *Note SR: 20pts PET neg, in Table: 54 pts PET neg ???*	Low

What is the role of (chemo)radiotherapy in patients with unresectable rectal cancer?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	January 2001	Colorectal cancer	Recommendations: RT to convert inoperable RC into operable disease should be combined with CT. Suitable regimens include intermittent infusional 5-FU/FA (Bosset), continuously infused 5-FU (Lokich) or bolus 5-FU/FA For pts with totally inoperable RC, and who are fit for an aggressive approach to treatment, CRT should be offered as for potentially resectable RC note: - the use of higher doses of RT, in conjunction with CT should be considered - it is essential that the harms as well as the benefits from an aggressive approach should be carefully discussed with the patient - the presence of liver M+ is not on itself a contra-indication to the radical treatment of the primary tumour	RT for advanced disease 1. improving the operability in unresectable disease Clinical trials: Habr-Gama A, 1998 [], Chari RS, 1995 [] Minsky BD, 1992 [] Conclusion: response rate increases if CT is added to preop RT Clinical trials: Bosset JF, 2000 [] Ngan SY, 2001 [] Janjan NA, 2001 [] Conclusion: regimens using intermittently infused 5-FU/FA (Bosset) or continuously infused 5-FU (Ngan, Janjan) have been widely and safely used 2. curative treatment of totally inoperable disease NO EVIDENCE	no evidence from RCT Habr-Gama: potentially resectable low RC Chari: large RC (T3) + control group (no CRT) Misky: unresectable RC preop CRT vs resectable RC postop CRT Bosset: 62% circumferential/tethered Ngan: resectable RC JanJan: locally advanced RC	 low moderate low low low low
NICE	[54]	March 2003	Colorectal cancer	Longer courses of pre-operative RT are appropriate for selected	1 RCT Frykholm GJ, 2001:	study was cited for a recommendation on the use of combined chemoradiation in all	moderate

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				patients with invasive tumours, where shrinking the tumour would facilitate curative resection.	RESECTABILITY: not different LOCAL CONTROL sign improved if CRT OS not significant ACUTE AE higher after CRT <u>Conclusion</u>: addition of CT to long-course preop RT for non-resectable RC does not improve resectability but produces a significant reduction in LR. Moreover, CRT causes more acute toxicity than RT alone.	cases, but the study only included patients with non resectable RC study compared a long course of preoperative RT: 46Gy/2Gy, 10Gy/w, 2x2 Gy/day D1,D2 + 1x2Gy D3; 4 weeks with or without chemotherapy (sequential methotrexaat, 5-FU (bolus followed by CI) and LV (8x)) TME was the standard surgical technique study was underpowered (fewer pts included than planned) and the RT regimen was not optimal	

Can urinary or sexual dysfunction be avoided by good quality TME sphincter saving or abdominoperineal resection in rectal cancer patients for whom curative surgery is scheduled?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	January 2001	Colorectal cancer	Mesorectal excision is recommended for most rectal cancers where the patient is fit for radical surgery. The mesorectal excision should be total for tumours of the middle and lower thirds of the rectum, and care should be taken to preserve the pelvic autonomic nerves wherever this is possible without compromising tumour clearance.	Prospective clinical trial (2) Retrospective study (2) Review (2)		Low
				Clinicians must be aware of the potential for physical, psychological, social and sexual problems after all colorectal surgery, inclding sphincter-saving operations.	Systematic reviews of observational studies (3)		Moderate
NICE	[54]	March 2003	Colorectal cancer	Surgeons should aim to preserve the nerves and plexuses on which sexual potency and bladder function depend, as far as this can be achieved without compromising tumour excision.	Not stated		

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
Marijnen CA 2005	[80]	1,861 rectal cancer patients. Only Dutch patients were evaluated (n=1,530)	Preoperative radiotherapy (PRT) followed by standardized TME surgery or to TME surgery alone in a large, international, multicenter trial. All patients underwent surgery according to the TME principle. Patients assigned to PRT received a total dose of 25 Gy in five fractions over 5 to 7 days. Surgery had to take place within 10 days of the start of PRT.	Health related quality of life (HRQL) based on questionnaires filled out by the patients before treatment and at 3, 6, 12, 18, and 24 months after surgery.	Few differences were found in HRQL between patients treated with or without PRT. Daily activities were significantly less for PRT patients 3 months postoperatively. Irradiated patients recovered slower from defecation problems than TME-only patients (*P* = .006). PRT had a negative effect on sexual functioning in males (*P* = .004) and females (P= .001). Irradiated males had more ejaculation disorders (*P*= .002), and erectile functioning deteriorated over time (*P*= .001). PRT had similar effects in patients who underwent a low anterior resection (LAR) versus an abdominoperineal resection (APR). Patients with an APR scored better on the physical (*P*= .004) and psychologic dimension (P= .007) than LAR patients, but worse on voiding (*P*= .0007).		RCT	Moderate
Pachler J 2004	[140]	1412 patients with respectable	Rectal resection by means of	Quality of life in patients with or without	No firm conclusion can be drawn. Six trials found		Systematic review	Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
		rectal cancer pooled from 11 non-randomized trials	abdominoperineal resection or low anterior resection	permanent colostomy	that patients with permanent colostomy did not have poorer quality of life and 4 studies tend to show the opposite			
Chaudhri S 2006	[319]	25 patients with colorectal cancer	Surgical procedures included 10 colonic resections and 15 rectal resections. Suprapubic catheterization was performed successfully in all 25 patients at surgery. with no complications.	Preoperative and postoperative uroflowmetry and residual urine estimation. All patients were catheterized suprapubically. Uroflowmetry and postvoid residual volumes were recorded postoperatively	Thirty consecutive patients underwent suprapubic catheterization, 25 of whom completed the study. Seventeen (68 percent) patients were able to pass urine within 72 hours of surgery. Recovery of lower urinary tract function was delayed in patients undergoing rectal vs. colonic resections (median, 6 vs. 3 days, P =0.0015). Postvoid residual volumes greater than 200 ml were noted in three (20 percent) patients following rectal resections beyond the tenth postoperative day, with complete emptying achieved by six weeks.		Prospective study	Low
Gosselinck MP 2005	[138]	301 consecutive rectal cancer patients	Low anterior resection with low colo-rectal anastomosis (LRA) or colo-perineal anastomosis (CPA) and abdominoperineal resection (APR) with	To assess quality of life among disease-free survivors after APR, LRA and CPA The quality of life among these patients was assessed using one generic (EQ-5D) and two	The response rate was 82%. The median follow-up was 31 months. Overall, quality of life was good but CPA patients had better quality of life scores than APR and LRA		Retrospective study	Very low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
			total mesorectal excision for cancer in the middle or lower third of the rectum	disease-specific questionnaires (EORTC QLQ-C30 and EORTC QLQ-CR38).	patients. This difference was not only due to the better functional outcome but also to the lower incidence of disturbed micturition and sexual problems in the CPA group. Conclusion The quality of life after colo-anal J-pouch anastomosis is better than after APR and LRA. The quality of life after APR is similar to that after LRA.			
Schmidt CE 2005	[141]	Two hundred forty-nine patients with rectal cancer were included; 46 patients received an APR and 203 an AR. QoL data were available for 212 patients, of which 112 were female and 100 male.	Quality of life in patients undergoing anterior resection *versus* abdominoperineal resection	To assess quality of life, European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 and a tumour-specific module were administered to patients with rectal cancer before surgery, at discharge, and 3, 6, and 12 months after the operation. Comparisons were made between patients receiving an AR and those receiving an APR.	EORTC function scales showed no significant differences, including body image scales, between patients receiving an AR and those receiving an APR. In symptom scores, AR patients had more difficulty with diarrhea and constipation, whereas patients with APR experienced more impaired sexuality and pain in the anoperineal region. At discharge, patients receiving an AR were more confident about their future.	QoL in patients receiving an AR and those receiving an APR is not different. Although patients with APR experience more impaired sexuality, patients receiving an AR experience decreases in QoL because of impaired bowel function.	Prospective study	Low
Kneist W 2004	[136]	42 rectal cancer patients undergoing	One case group of 26 patients with rectal cancer in whom the	Bladder function: residual urine volume pre- and postperatively, measured	Pre-operatively, residual urine volumes differed neither between the pairs	Residual urine volume is an indicator of the completeness of PANP	Prospective case control study	Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
		resection. 26 cases and 26 controls.	pelvic autonomic nerves could not completely be identified and preserved during total mesorectal excision (TME), was compared with 26 patients of a control group in whom, according to standaradized intra-operative documentation, the identification and preservation of the pelvic nerves (superior hypogastric plexus, hypogastric nerve, inferior hypogastric plexus, splanchnic nerves, neurovascular bundles) was established.	by sonography	nor between both groups with and without nerve preservation. In the case group with incomplete PANP there was a difference between preand post-operative (median; quartil: 2.5 ml; 0.0–32.5 ml vs 130 ml; 0.0–317 ml; P=0.001). In the control group there was no difference (median; quartile: 0.0 ml; 0.0–20 ml vs 15.5 ml; 0.0– 62.0 ml; P=0.07). The difference between the postoperatively measured volumes of the case and control group were significant (P ¼ 0.001). With residual urine volume = 100 ml, the risk of incomplete PANP was 14 times higher (odds ratio).	during TME. It should be determined pre- and post-operatively, and besides the recording of the neurogenic bladder, serve as a quality control.		
Borschitz T 2005	[135]	Seventy-five patients with rectal cancer. The tumours were localized in the lower third of the rectum for 31 patients, in the middle for 30, and in the upper	Total mesorectal excision	Postvoid residual urine volume before and after surgical therapy.	An increase in retained urine of more than 100 ml was found in 12 patients (15%), and neurogenic bladder was diagnosed in two (3%). In female patients, urinary bladder malfunctions were significantly less frequent and severe.		Prospective cohort study	Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
		third for 14.						
Grumann MM 2001	[137]	73 patients with rectal cancer	50 patients treated with anterior resection (AR) and 23 patients treated with abdominoperineal excision (APE) were prospectively followed up. All patients were treated in curative attempt and were disease-free throughout the study.	Quality of life (QoL) was assessed before surgery and 6 to 9 and 12 to 15 months after surgery.	Multivariate analysis of variance and subsequent post hoc comparisons revealed a main effect for time (role function, emotional function, body image, future perspective, and micturition-related problems) and group in favor of APE (sleeping problems, constipation, diarrhea), and a time-by-group interaction (role function). No significant results were obtained for the remaining scores, but patients undergoing APE consistently had more favorable QoL scores than those undergoing AR. Multivariate analysis and post hoc comparisons revealed a particularly poor QoL for patients undergoing low AR. They had a significantly lower total QoL, role function, social function, body image, and future perspective, and more gastrointestinal and defecation-related symptoms than patients undergoing high AR.	Patients undergoing APE do not have a poorer QoL than patients undergoing AR. Patients undergoing low AR have a lower QoL than those undergoing APE. Attention should be paid to QoL concerns expressed by patients undergoing low AR.	Prospective cohort study	Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
Jess P 2002	[139]	Fourty patients undergoing surgery for rectal cancer	14 patients underwent abdominoperineal extirpation and 26 anterior resection for rectal cancer	The generic quality of life instrument SF-36 together with a new symptom specific Fecal Incontinence Quality of Life Scale were used. Psychometric analysis of the symptom specific scale was carried out.	The only significant difference between the two groups was found in the total score of the symptom-specific scale in favour of anterior resection (P = 0.02). Psychometric evaluation of the symptom specific fecal incontinence questionnaire proved it reliable and valid.	The present study shows that a stoma influences quality of life only slightly, while a relatively high anterior resection does not. However, a few appropriate newer studies indicate that the cost of spinchter-preserving techniques in the form of incontinence disturbances may influence the quality of life seriously, which should be born in mind when low anterior resection is intended.		Low

Can postoperative morbidity be reduced by preoperative bowel preparation in rectal cancer patients for whom curative surgery is scheduled?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	January 2001	Colorectal cancer	The decision to use bowel preparation must be individualised according to the patient's need and the surgeon's experience.	RCT (2)	Although there is no evidence that bowel preparation confers benefit, the quality of evidence suggesting no effect is too weak (underpowered RCT's) to make a definitve statement that it is not necessary	Moderate
NICE	[54]	March 2003	Colorectal cancer	Each Cancer Network should agree evidence-based guidelines dealing with antibiotic use, prophylaxis for deep vein thrombosis and bowel preparation before surgery. Adherence to these guidelines should be audited.	Expert opinion		Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
Platell C 1998	[143]	Meta-analysis of 3 RCT, 514 patients	Colorectal surgery with and without bowel preparation	Wound infection, anastomotic leak and intra-abdominal infection	Meta-analysis revealed a significantly greater incidence of wound infection in patient who received a mechanical bowel preparation (10.8 *vs.* 7.4 percent; P <0.002; 95 percent confidence interval of the difference, -1.6-8.4 percent). Patients who received mechanical bowel preparation had an incidence of anastomotic leakage that was twice that of control patients. However, this difference was not significant (8.1 *vs.* 4 percent; P < 0.114; 95 percent confidence interval of	Yet, none of these clinical trials are sufficiently reliable to be able to detect possible advantages for bowel preparation.	Meta-analysis	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
					the difference, -0.4-8.4 percent) and raises the possibility of a Type II (false-negative) error.			
Wille-Jorgensen P 2005	[145]	1592 patients (9 RCTs)	789 were allocated to mechanical bowel preparation (Group A) and 803 to no preparation (Group B) before elective colorectal surgery.	Anastomotic leakage and wound infection	Anastomotic leakage developed in 48 (6%) of 772 patients in A compared with 25 (3.2%) of 777 patients in B; Peto OR 2.03, 95% (CI: 1.28–3.26; P ¼ 0.003). Wound infection occurred in 59 (7.4%) of 791 patients in A and in 43 (5.4%) of 803 patients in B; Peto OR 1.46, 95% (CI: 0.97–2.18; P ¼ 0.07);Five (1%) of 509 patients died in group in A compared with 3 (0.61%) of 516 patients in group B; Peto OR 1.72, 95% (CI: 0.43–6.95; nonsignificant)	There is no evidence that patients benefit from mechanical bowel preparation. On the contrary taking colorectal surgery as a whole, pre-operative bowel cleansing leads to a higher rate of anastomotic leakage.	Meta-analysis	High
Slim K 2004	[144]	Eleven trials were retrieved, of which seven, containing 1454 patients	Randomized clinical trials comparing bowel preparation with no preparation in colorectal surgery	anastomotic leakage, wound infection, other septic complications and non-septic complications	Significantly more anastomotic leakage was found aftermechanical bowel preparation (5·6 *versus* 3·2 per cent; odds ratio 1·75 (95 per cent confidence interval 1·05 to 2·90); *P* = 0·032). All other endpoints (wound infection, other septic complications and non-septic complications) also favoured the no-preparation regimen, but the differences were not statistically significant. Sensitivity analysis showed that these results were similar when trials of poor quality were excluded. Subgroup analysis	There is good evidence to suggest that mechanical bowel preparation using PEG should be omitted before elective colorectal surgery. Other bowel preparations should be evaluated by further large randomized trials.	Meta-analysis	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
					showed that anastomotic leakage was significantly greater after bowel preparation with polyethylene glycol (PEG) compared with no preparation, but not after other types of preparation.			
Bucher 2004	[142]	Seven RCTs were retrieved. The total number of patients undergoing colo-rectal surgery for any kind of indication, in these RCTs was 1297	Evaluation of mechanical bowel preparation (MBP) vs no MBP before elective colorectal surgery	Anastomotic leak, intra-abdominal infection, wound infection, reoperation, general morbidity and mortality	Anastomotic leak was significantly more frequent in the MBP group, 5.6% (36/642), compared with the no-MBP group, 2.8% (18/655) (odds ratio, 1.84; *P*=.03) Intra-abdominal infection (3.7% for the MBP group vs 2.0% for the no-MBP group) Wound infection (7.5% for the MBP group vs 5.5% for the no-MBP group), and reoperation (5.2% for the MBP group vs 2.2% for the no-MBP group) rates were nonstatistically significantly higher in the MBP group. General morbidity and mortality rates were slightly higher in the MBP group	There is no evidence to support the use of MBP in patients undergoing elective colorectal surgery. Available data tend to suggest that MBP could be harmful with respect to the incidence of anastomotic leak and does not reduce the incidence of septic complications.	Meta-analysis	High

Can postoperative DVT be reduced by perioperative thromboprophylaxis in rectal cancer patients for whom curative surgery is scheduled?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	January 2001	Colorectal cancer	Patients undergoing surgery for colorectal cancer should have venous thromboembolism prophylaxis	Clinical Practice Guidelines (2)		Low
NICE	[54]	March 2003	Colorectal cancer	Each Cancer Network should agree evidence-based guidelines dealing with antibiotic use, prophylaxis for deep vein thrombosis and bowel preparation before surgery. Adherence to these guidelines should be audited.	Expert opinion		Very Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
Borly L 2004	[146]	19 randomized controlled trials or clinical controlled trials comparing prophylactic interventions and/or placebo.	Comparing prophylactic interventions and/or placebo addressing thrombosis prophylaxis in connection with colorectal surgery.	Outcome was deep venous thrombosis and/or pulmonary embolism diagnosed by various methods	Any kind of heparin is better than no treatment or placebo (11 studies) with a Peto Odds ratio (POR) at 0.32 (95% CI 0.20–0.53). Unfractionated heparin and low molecular weight heparin (4 studies) were equally effective POR 1.01 (95% CI 0.67–1.52). The combination of graduated compression stockings and LMWH is better than LMWH alone (2 studies) with a POR at 4.17 (95% CI 1.37–12.70).	The optimal thromboprophylaxis in colorectal surgery is the combination of graduated compression stockings and low-dose unfractionated heparin or low molecular weight heparin. Study is not specific of rectal surgery.	Meta-analysis	Moderate

Can postoperative septic complications be reduced by antibiotic prophylaxis in rectal cancer patients for whom curative surgery is scheduled?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	January 2001	Colorectal cancer	Patients undergoing surgery for colorectal cancer should have antibiotic prophylaxis consisting of a single dose of antibiotics providing both aerobic and anaerobic cover given within 30 minutes of induction of anesthesia	Meta-analysis (1)		High
NICE	[54]	March 2003	Colorectal cancer	Each Cancer Network should agree evidence-based guidelines dealing with antibiotic use, prophylaxis for deep vein thrombosis and bowel preparation before surgery. Adherence to these guidelines should be audited.	Expert opinion		Very Low

Can preoperative stoma counseling, including stoma sitting, improve postoperative quality of life in rectal cancer patients for whom curative surgery is scheduled?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	January 2001	Colorectal cancer	All patients who may require stoma formation (permenant or temporary) should be referred and assessed by a stoma nurse specialist before admission to hospital	Expert opinion		Very Low
				All patients newly diagnosed or with a suspected diagnosis of colorectal cancer should have access at diagnosis to a clinical nurse specialist (CNS) for support, advice and information	Expert opinion		Very Low
NICE	[54]	March 2003	Colorectal cancer	Patients who may require stomas - whether temporary or permanent - should be counseled before surgery by a CNS (either a colorectal cancer CNS who has expertise in stoma care, or a stoma specialist) on the position and implications of a stoma. After surgery, the same nurse should be available to assist patients in managing the stoma and to advise for as long as required on physical, social, sexual and emotional problems associated with the stoma.	UK national audit (1)	Outcomes were centered on the degree of comprehension of patients. General data about emotional, social and body-image problems are given. Direct impact postoperative hospital stay or morbidity is not discussed.	Very Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
Chaudhri S 2005	[147]	42 patients With ileo- or colostomy either temporary or permanent	Preoperative stoma counselling and marking vs postoperative counselling	Patient well-being assessed on anxiety/depression scale preoperatively and 6 weeks postop. Secondary outcome were incidence of anxiety and patient's satisfaction with the stoma support service, time to stoma proficiency and hospital stay.	Median time to stoma proficiency 5,5 days vs 9 (p=0.0005), median postoperative hospital stay 8 vs 10 days (p=0,029), no significant differences were found concerning degree and incidence of anxiety	Stoma education is more effective if undertaken preoperatively and I enables patients to attain proficiency in managing their stoma earlier and reduces postoperative hospital stay.	RCT	High

What is (are) the standard surgical procedure(s) for resection of rectal cancer? What is the impact of high versus low ligation of the inferior mesenteric artery on outcome in rectal cancer patients for whom curative surgery is scheduled?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
DGVS	[52]	Unsure	Colorectal cancer	Ligation of the IMA at its origin does not have a major prognostic impact; nevertheless, this step is necessary to ensure enough mobility of the left colon in order to allow an easy reconstruction	Retrospective studies (3)		Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
Kanemitsu Y	[155]	1188 consecutive patients with sigmoid colon or rectal cancer	resection of sigmoid or rectum for cancer, with high ligation of the inferior mesenteric artery (IMA)	Survival of patients with involvement of nodes along the IMA proximal to the origin of the left colic artery through the bifurcation of the superior rectal artery, curability of resection and survival	Twenty patients (1·7 per cent) had metastatic involvement of station 253 (origin of IMA) lymph nodes and 99 (8·3 per cent) had metastases to station 252 (proximal to the origin of the left colic artery). The 5- and 10-year survival rates of patients with metastases to station 253 were 40 and 21 per cent, and those for patients with metastases to station 252 were 50 and 35 per cent, respectively	High ligation of the IMA can be performed safely and allows curative resection and long-term survival in patients withncancer of the sigmoid colon or rectum and nodal metastases at the origin of the IMA	Non randomized, non controlled prospective clinical serie	Low
Kim JC	[156]	Seventy-three patients with Inferior mesenteric lymph node metastasis (IMLN +) were identified among 2040 patients with sigmoid colon and rectal cancers over six years (1993–1999) This study was confined to 63 patients undergoing curative surgery among the 73 IMLN + patients. The control group without IMLN metastasis (IMLN -) was consecutively recruited from 108 rectal and sigmoid cancer patients of stage III and IV during the same period	Curative surgery with inferior mesenteric lymph node sampling routinely performed prior to inferior mesenteric artery ligation	Survival, recurrence pattern and treatment protocols were compared between 63 IMLN + patients and 108 IMLN -	5-year disease-free survival rates were 50% in IMLN - and 31% in IMLN + patients (P = 0,004), Cox regression analysis showed IMLN + , lymphovascular tumour invasion, T4, M1, and pre-operative serum CEA level over 6 ng/ml were independently associated with unfavorable disease-free survival The prognostic significance of M category was greater when the IMLN + was included in the M1. Post-operative recurrence rates were 34% for IMLN 2 and 57% for IMLN þ patients (P ¼ 0:009; OR, 2.611; 95% CI, 1.313–5.194)	IMLN + is an independent survival factor enhancing the prognostic significance of the M category in the AJCC staging. Curative radical surgery and postoperative chemoradiotherapy appears to be warranted for IMLN + colorectal cancer	Retrospective case control study	Very low

What is the impact of lateral lymphatic dissection (iliac nodes) on outcome in rectal cancer patients for whom curative surgery is scheduled?

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
Nagawa H 2001	[157]	51 patients with respectable lower rectum cancer	Randomly allocated to complete autonomic nerve-preserving surgery without lateral node dissection (D1), or surgery with dissection of the lateral lymph nodes including autonomic nerves (D2) after preoperative radiation therapy	Function of pelvic organs, local recurrences	No difference was observed in either survival, disease-free survival or recurrence rate between D1 and D2 groups. Sexual and urinary functions were significantly worse in the D2 group one year after surgery.	This study suggests that lateral node dissection is not necessary in terms of curability for patients with advanced carcinoma of the lower rectum who undergo preoperative radiotherapy.	RCT	High

Can sphincter saving operation be performed for rectal cancer of the lower third of the rectum without compromising the (oncological and functional) outcome in patients for whom curative surgery is scheduled?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	January 2001	Colorectal cancer	Mesorectal excision is recommended for most rectal cancers where the patient is fit for radical surgery. The mesorectal excision should be total for tumours of the middle and lower thirds of the rectum, and care should be taken to preserve the pelvic autonomic nerves wherever this is possible without compromising tumour clearance.	Prospective clinical trial (2) Retrospective study (2) Review (2)		Low
				Surgery for colorectal cancer should only be carried out by appropriately trained surgeons whose work is audited. Low rectal cancer should only be performed by those trained to carry out TME.	Systematic review (2) Retrospective study (1)		Moderate

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE	[54]	March 2003	Colorectal cancer	Since TME is the technique most likely to achieve clear surgical margins of cancers of the middle and lower third of the rectum, it should be available for all patients with rectal cancer for whom it is appropriate	Prospective studies (6) Retrospective study (12)	All studies except one comparing different tumour location concludes in favour of TME vs blunt dissection with very significant decrease in local recurrence	Moderate
				Surgery should be undertaken by specialist colorectal cancer surgeons who are members of colorectal cancer multi-disciplinary teams (MDTs) […]Every MDT which treats patients with rectal cancer should undergo training in total mesorectal excision (TME) […]	Retrospective study (1)		Very low
				Surgeons should aim, wherever possible and desirable, to conserve the anal sphincter.	Not stated		
				The histopathologist should search for as many lymph nodes as possible in the excised specimen (particularly when the tumour appears to be Dukes' stage B), and the number found should be audited. In patients with colon cancer who are treated with curative intent, 12 or more nodes should normally be examined; if the median number is consistently below 12, the surgeon and the histopathologist should discuss their techniques.	Retrospective study (26)	Almost all the studies do not consider the difference between colon and rectal cancer, thus conclusions about rectal cancer cannot be drawn	Moderate
DGVS	[52]	Unsure	Colorectal cancer	For middle and low rectal cancer, patient should undergo proctectomy with total mesorectal excision.	Retrospective studies (8) Review (3)		Low
				In case of upper rectal cancer, partial mesorectal excision can be performed;	Retrospective studies (6)		Low

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				the mesorectum should be excised with 5 cm surgical margin below the inferior pole of the tumour (no coning)			
				In case of low-grade carcinoma of the lower third of the rectum, a distal safety margin of 2 cm (in situ) and 1 cm (on the specimen) should be respected; in case of high-grade tumour this margin should be greater.	Retrospective study (5)		Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
Matthiessen 2006	[180]	6833 patients underwent elective anterior resection of the rectum in Sweden	Anterior resection for RC	30 day death risk factors	Mortality rate after elective anterior resection was 2.1%. On multivariate regression analysis clinical anastomotic leakage was major cause of postoperative death		Case-control study	Low
Martling 2004	[152]	1707 patients with resected rectal neoplasm,157 stage IV excluded1550	Rectal cancer resection; determining completness of resection by surgeon and pathologist	Reports from surgeons / pathologists whether surgery was complete, uncertain or incomplete related to recurrence and survival	surgeon's and pathologist's assessment of the completeness of the clearance are powerful prognostic factors with regard to recurrence and survival	completeness of resection confirmed as a major prognostic factor If surgeon and patho. Disagree about clearance, prognosis is almost as bad as in incomplete resection Population study is a mix of TME and classical blunt dissection resection!	RCT	High
Kapiteijn 2002	[150]	269 and 661 radomized patients extracted from the CRAB (randomized to	introduction and training of TME on outcome of rectal cancer	Short-term outcomes: operating time, blood loss during operation, hospital stay, anastomotic leakage, wound infection and 30-day mortality, long-term	In the univariate analysis, a higher clinical anastomotic leak rate was found in patients following low anterior resection in the TME trial (P = 0,046), but this association was not significant in the multivariate analysis. The local	This study is a comparaison of patients extracted from two RCTs that weren't designed initially to answer the question addressed in this paper. Nevertheless,	Subgroup analysis of 2 RCTs	Moderate

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
		transfusion of leucocyte-depleted or buffy coat-depleted blood and received blood transfusion upon indication and standard surgery) and the TME (phase III trial `Total mesorectal excision with or without short-term preoperative radiotherapy) trials respectively		outcomes: local and distant recurrence and overall survival.	recurrence rate decreased from 16 per cent in the CRAB trial to 9 per cent in the TME trial, and type of operation (conventional (CRAB trial) versus TME (TME trial)) was an independent predictor of local recurrence (P = 0,002). Type of operation was also an independent predictor of overall survival (P = 0,019); there was a higher survival rate in the TME trial.	the study is well conducted and no RCTs comparing TME with standard surgery are available.		
Nagtegaal 2005	[153]	1219 patients underwent TME +- RT (5X5Gy) for RC	abdominoperineal resection (APR) and anterior resection (AR) for RC	Survival, circumferential margin involvement, plane of resection on the sphincteric muscle level	Survival worse in APR vs AR (38.5% *v* 57.6%, *P*=0.008). Low rectal carcinomas have a higher frequency of circumferential margin involvement (26.5% *v* 12.6%, *P*= 0.001). More positive margins in APR (30.4%) vs AR (10.7%, *P* = 0.002). More perforations in APR vs AR (13.7% *v* 2.5%, *P*= 0.001). Plane of resection lies within the sphincteric muscle, the submucosa or lumen in more than 1/3 of the APR		RCT	High
Peeters KC 2004	[154]	Dutch patients with operable rectal cancer who (924	Total mesorectal excision (TME) with or without neoadjuvant short course	Symptomatic anastomotic leakage, the endpoint of this analysis, was defined as clinically apparent leakage	In multiple regression analysis, absence of a defunctioning stoma and lack of pelvic drainage remained the only two significant risk factors. The absence of a	Subgroup analysis of the Dutch TME trial	Retrospective study based on the Dutch	Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
		patients)	radiotherapy	(gas, pus or faecal discharge from the pelvic drain, or peritonitis) or extravasation of endoluminally administered water-soluble contrast on radiography or computed tomography. An abscess around the anastomosis was also recorded as a leakage.	protective stoma was significantly associated with increased anastomotic dehiscence rates in both men and women. Moreover, this association was also observed in patients with low or high rectal tumours		TME trial	
Mynster T 2004	[148]	Two different multicentre-studies including 246 patients were operated in the period 1991–93 with a conventional technique and 311 patients were operated with TME technique in the period 1996–98.	Conventional surgery *versus* total mesorectal excision	Comparison of transfusion history in rectal cancer resections. Peri-operative data, including blood transfusion from one month before until one month after the operation, was recorded prospectively.	The median intra-operative blood loss was 1000 ml, range 50–6000 ml, before, and 550 ml, range 10–6000 ml (P < 0.001) after introduction of TME. The overall peri-operative transfusion rate was reduced from 73% to 43% (P < 0.001). When adjusted for blood loss, age, gender, weight, and type of resection, TME signi- ficantly reduced the risk of receiving intra or postoperative blood transfusion by 0.4 (CI: 0.3–0.6). The variability in blood loss among 12 TME-centres was more than 400% and not correlated with transfusion requirements within the centres.	TME results in a reduced blood loss and a reduction of blood transfusion, but additional factors others than blood loss seems to influence the decision of transfusion. Study of secondary end-points in the Danish TME Study.	RCT, secondary end-point	Moderate
Bulow S 2003	[149]	311 patients with a mobile rectal cancer.	Total mesorectal excision with curative intent performed by certified surgeons. A series of patients who had conventional operations for rectal cancer served as a control group	Demographic, perioperative and follow-up data were recorded prospectively for 3 years.	Cumulative 3-year local recurrence rate was 11 per cent after mesorectal excision compared with 30 per cent after conventional surgery (hazard ratio (HR) 0·33 (95 per cent confidence interval (c.i.) 0·21 to 0·52); *P* < 0·001). Multivariate regression analysis showed that only advanced age (HR 0·97 (95 per cent c.i. 0·94 to 1·00); *P* = 0·048)		Controlled clinical trial	Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
					and tumour in the lower third of the rectum (HR 0·21 (95 per cent c.i. 0·04 to 1·97); *P* = 0·075) were marginal independent predictors of local recurrence after mesorectal excision. Cumulative crude 3-year survival rate was 77 per cent after mesorectal excision and 62 per cent after conventional surgery (HR 0·58 (95 per cent c.i. 0·43 to 0·77); *P* < 0·001). Age was the only independent predictor of death after mesorectal excision (HR 1·04 (95 per cent c.i. 1·02 to 1·07); *P* = 0·001).			
Nowacki M 2005	[320]	229 rectal cancer patients	Tumours were resected using a TME technique after randomization into two groups: GRM(+), in which a gentamycin collagen sponge was used, and GRM(-), without the sponge. In the GRM(+) group, the sponge was placed into the tumour bed	To evaluate the efficacy of the gentamycin collagen sponge placed in the pelvic cavity after excision of rectal cancer in view of postoperative complications and the risk of cancer recurrence	There were fewer early postoperative complications in the GRM(+) group: 20.7 vs. 37.5%; p=0.044. This effect was found mainly in patients with surgery lasting longer than 3 h. After 36 months' follow-up, the overall survival after R0 resection for the GRM(+) and GRM(-) groups was: 88.66 vs. 73.96%. There was significant reduction in the distant metastasis rate in favor of the GRM(+) group		RCT	High
Maeda K 2004	[151]	Twenty consecutive patients	Laparotomy with surgery of the lower rectum for rectal cancer	To study whether (and if so to what extent) different positions of the patient on the operating table might improve accessibility to the pelvis. Four positions were studied: position I (lithotomy position), position II (thighs-flat position), position I with	Position II caused significant extension movement of the lumbosacral joint. Augmentation of the lumbar lordosis widened the pelvic view and enabled a more vertical view of the lower rectum (27.5 degrees in lithotomy position, 13.0 degrees in the thighs-flat position). Insertion of a "lumbar pad" contributed further to the augmentation (7	Interesting study of a technical issue crucial for the patients because on-table position certainly co-determines the quality of surgery. Study outcome only comprised radiological measures and no patient related outcome.	RCT	Moderate

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
				a sacral pad, and position II with a lumbar pad. The geometric configuration of the pelvis was studied and compared on lateral radiographs obtained at the operating table in each of four positions.	degrees). When compared on radiographic studies, the thighs-flat position is preferable to the conventional lithotomy position in terms of facilitating low rectal surgery by improving both visibility and accessibility to the pelvic cavity			
Amin Al 2003	[179]	Between September 1996 and April 2001, 118 consecutive patients underwent total mesorectal excision with anterior resection for distal rectal cancer. A short colonic J pouch neorectum was created and reconstruction was by the triple stapling technique.	Proximal defunctioning loop stoma (LS) *versus* a novel transanal stent (TAS)	The primary endpoint was anastomotic leakage, although total length of stay, and morbidity and mortality rates were also assessed.	The anastomotic leakage rate was three of 41 in the TAS group compared with two of 35 in the LS group. There was no difference in the complication rate directly related to surgery (23 per cent in the LS group compared with 22 per cent in the TAS group). The median (interquartile range) hospital stay was 13 (12–17) days for the TAS group and 23 (20–34) days for the LS group ($P <$ 0·001).	A criticism of this study is the absence of a control group with neither a stent nor a stoma. However, the authors experience, and that of others, has shown unacceptably high leak rates with associated morbidity and mortality in patients who have not been defunctioned.	RCT	High
Brown S 2001	[182]	All patients attending one specialist unit over an 8-month period for elective rectal cancer resection with an infra-	Patients were randomised to drainage or no drainage to assess the effect of prophylactic drainage after anastomosis below the peritoneal reflection.	The incidence of anastomotic leak and complications specific to the drain as well as other complications were compared.	Fifty-nine patients were analysed (31 with drain). Twenty-five of the drained and 16 of the no drain patients had a defunctioning stoma (p=ns). The groups were comparable for demographic data, operation and anastomotic height from the anal verge. There were three leaks (10%) in the drain group and five leaks	This study supports the contention that there is no difference in morbidity with or without the use of a drain for infra-peritoneal anastomoses.	RCT	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of evidence
		peritoneal anastomosis.			(18%) in the no drain group (*p*=ns). There were 2 (7%) patients in each group with a clinical leak. There were no specific drain complications and the incidence of other complications was similar in both groups.			

Can laparoscopic resection be performed without compromising the outcome in rectal cancer patients for whom curative surgery is scheduled?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	January 2001	Colorectal cancer	Laparoscopic surgery can be considered for colorectal surgery	Systematic review (1)	Outdated data, no difference is made between rectal and colonic surgery	High
DGVS	[52]	Unsure	Colorectal cancer	Due to a lack of long-term oncological results, laparoscopic rectal resection should not be performed outside a study setting	RCT (2) Retrospective study (3)		Moderate

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
Aziz O 2006	[159]	2071 subjects (20 studies) of whom 909 (44%) underwent laparoscopic and 1162 (56%) underwent open surgery for rectal cancer	Laparoscopic vs open rectal resection. Subgroup analysis was performed on patients undergoing abdominoperineal excision of the rectum	operative outcomes, postoperative recovery, and early and late adverse events	Laparoscopic rectal cancer surgery results in an earlier postoperative recovery and a resected specimen that is oncologically comparable to open surgery.	No long-term outcomes such as cancer recurrence (local and metastatic) and 5-year survival are analysed but are of foremost importance to validate laparoscopic approach in colo-rectal cancer	Meta-analysis	High
Jayne 2005	[161]	247 patients out of 347 participated by sending in the questionnaire	Open *vs* laparoscopic rectal resection for cancer	The primary endpoints were overall symptom score for bladder function and overall function scores for sexual function. Secondary endpoints were the individual I-PSS item scores for bladder function and the domain-specific scores for sexual function	Laparoscopic rectal resection did not adversely affect bladder function, but there was a trend towards worse male sexual function. This may be explained by the higher rate of TME observed in the laparoscopic rectal resection group. Although no differences were detected between any of the groups, the response rates were low and there were a large number of missing data	Bladder and sexual function were not primary outcomes of the study (originally CLASICC study comparing conventional *vs* laparoscopic assisted surgery in colorectal cancer	RCT	High
Araujo SE 2003	[158]	28 patients with distal rectal adenocarcinoma	Laparoscopic (13 patients) vs open abdominoperineal resection (15 patients) for surgical treatment of patients with distal rectal cancer presenting incomplete response after chemoradiation	Intra and post operative complications, blood transfusion, hospital stay length of resected segment, pathological staging, mean operation time, conversion rate, local recurrences	Intra and post operative complications, need for blood transfusion, hospital stay after surgery, length of resected segment and pathological staging were similar in both groups. Mean operation time was significantly shorter for the laparoscopic than the conventional approach. There was no need for conversion to open approach in this series. At mean follow-up of 47.2	Laparoscopic APR is feasible, similar to C-APR concerning surgery duration, intra operative morbidity, blood requirements and post operative morbidity. Larger number of cases and an extended follow-up are required to adequate evaluation of oncological results for patients undergoing L-APR after chemoradiation for radical treatment of distal rectal cancer.	RCT	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
					months (2 patients excluded of the conventional group because of unsuspected synchronic metastasis) there were two local recurrences in the conventional group and in none in the laparoscopic group.			
Zhou ZG 2004	[164]	171 patients with low rectal cancer	Laparoscopic vs open total mesorectal excision (TME) with anal sphincter preservation (ASP)	Short-term oncological follow-up, operative procedure, location of the cancer, and final pathologic diagnosis. Morbidity and mortality, tumour and anastomotic heights from dentate line, duration of surgery, length of specimen removed, duration of parenteral analgesia, onset of borborygmus, time to give off flatus, time to intake liquid and solid food, hospital stay, frequency and amount of defecation daily. A pain score criteria was introduced for evaluating postoperative pain	TME and ASP were accomplished on all patients. In the laparoscopic group, the level of the anastomosis was below peritoneal reflection and above 1.5 cm from the dentate line in 30 patients, the anastomotic height was within 2 cm of the dentate line in 27 patients, level of the anastomosis was at or below the dentate line in 25 patients. In the open group, the numbers were 35, 27, and 27, respectively. Mean operating times and mean operative blood loss for the laparoscopic was significantly lower as in open procedures. The average operation time, analgesics and start of food intake were not statistically different between the two groups. Results of operation showed that the advantages of minimally invasive surgery, including early return of bowel function, reduction in pain, earlier resumption of preoperative activity, shorter hospitalization. Morbidity was lower in the laparoscopic group ($p < 0.05$). In both groups, most of the patients with low or ultralow anastomosis	No satisfying oncological issues which are crucial for the validity of the approach.	RCT	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
					experienced a quick recovery of their anal sphincter's function			
Quah HM 2002	[162]	170 patients with rectal cancer	Laparoscopic vs open total mesorectal excision	Bladder and sexual dysfunction	No significant deterioration in bladder function was observed. In men, significant increase of sexual impairement in the laparoscopic group (p=0,004)	All the patients with either sexual or bladder dysfunction in the laparoscopic group had resection of either bulky or low rectal cancer. The results of this study are to be considered very cautiously as the results are based on postal questionnaire and phone interviews.	Retrospective study based on previous RCT	Low
Breukink S 2006	[160]	80 studies were identified of which 48 studies, representing 4224 rectal cancer patients	Elective laparoscopic total mesorectal excision (LTME)	disease-free survival rate, local recurrence rate, mortality, morbidity, anastomotic leakage, resection margins, number of retrieved lymph nodes, blood loss, time to return to normal diet, pain, immune response operative time costs, and quality of life	No significant differences in terms of disease-free survival rate, local recurrence rate, mortality, morbidity, anastomotic leakage, resection margins, or recovered lymph nodes were found. There is evidence that LTME results in less blood loss, quicker return to normal diet, less pain, less narcotic use and less immune response. It seems likely that LTME is associated with longer operative time and higher costs. No results of quality of life were reported.	Based on evidence mainly from non-randomized studies, LTME appears to have clinically measurable short-term advantages in patients with primary resectable rectal cancer. The long-term impact on oncological endpoints awaits the findings from large on-going randomized trials.	Systematic review	High
Schwenk W 2005	[163]	25 RCT including patients undergoing colorectal resection regardless of disease	Laparoscopic versus conventional colorectal resection	benefits of the laparoscopic method in the short-term postoperative period (up to 3 months post surgery)	Operative time was longer in laparscopic surgery, but intraoperative blood was less than in conventional surgery. Intensity of postoperative pain and duration of postoperative ileus was shorter after laparoscopic colorectal resection and pulmonary function was improved after a laparoscopic approach. Total	Under traditional perioperative treatment, lapararoscopic colonic resections show clinically relevant advantages in selected patients. This review is neither specific to rectal resection nor to rectal cancer, thus conclusion might not be applicable to the present guidelines	Systematic review	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
					morbidity and local (surgical) morbidity was decreased in the laparoscopic groups. General morbidity and mortality was not different between both groups. Until the 30th postoperative day, quality of life was better in laparoscopic patients. Postoperative hospital stay was less in laparoscopic patients.			

Does inadvertent perforation of the rectum during surgery influence oncological outcome in rectal cancer patients for whom curative surgery is scheduled?

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
Chapuis PH 2006	[165]	1613 patients undergoing surgical resection for rectal cancer	resections for rectal cancer performed only by specialist colorectal surgeons following a standardized procedure along anatomical planes	Tumour in circumferential line of resection regarding age (years), metachronous cancer, fungating tumour, plaque tumour, free serosal surface, sex, urgent resection, tumour size (cm), tumour level (cm), polypoid tumour, ulcerating tumour, stenosing tumour, adherent to other organ, tumour perforation, preoperative radiotherapy,	The following variables were independently associated with transected tumour: tumour perforation, a non-restorative operation, tumour adherence, non-standardized operative technique, preoperative radiotherapy, male sex, histological involvement of an adjacent organ or tissue, high-grade tumour and venous invasion	In this serie a strong association was shown between tumour perforation and circumferential margin involvement which in turn is one of the strongest predictor of local recurrence.	Retrospective study	Very low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
				restorative operation, standardized surgical, technique, lymph node metastasis, apical node metastasis, distant metastasis, tumour grade, venous invasion, adjacent structure involved (histological)				
Eriksen MT 2004	[166]	2873 patients undergoing major resection of rectal carcinoma at 54 Norwegian hospitals from November 1993 to December 1999	To examine the influence of intraoperative perforation following the introduction of mesorectal excision as a standard surgical technique in Norway	Data on local recurrence, metastasis and death	234 patients (8,1%) with reported perforation. Intraoperative perforation has an independent negative effect on the local recurrence and survival rates of patients undergoing resection of rectal cancer.		Prospective cohort study	Low
Wibe A. 2004	[167]	2,136 patients undergoing total mesorectal excision in 47 hospitals during the period November 1993 to December 1999.	1,315 (62 percent) anterior resections and 821 (38 percent) abdominoperineal resections, uni	Rates of local recurrence and survival, , uni- and multivariate analysis on following variables: age, sexe, T status, N status, TNM stage, differentiation, preoperative perforation, involved CRM, adjuvant therapy	T4 tumours, R1 resections, and/or intraoperative perforation of the tumour or bowel wall are main features of low rectal cancers, causing inferior oncologic outcomes for tumours in this area		Prospective cohort study	Low
Nagtegaal ID	[153]	1,219 patients	evaluated TME surgery	Survival,	Survival differed greatly between	APR has a high perforation	RCT, secondary	Moderate

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
2005		selected from the RT _ TME trial, a large multicenter trial in the Netherlands, in which 1,530 patients were included from January 1996 until December 1999.	with or without preoperative radiotherapy (5 _ 5 Gy), patient undergoing anterior resection (AR) and abdominoperineal resection (APR) were compared	circumferential margin involvement, preoperative perforations	abdominoperineal resection (APR) and anterior resection (AR; 38.5% *v* 57.6%, *P* = .008). Low rectal carcinomas have a higher frequency of circumferential margin involvement (26.5% *v* 12.6%, *P* = .001). More positive margins were present in the patients operated with APR (30.4%) compared to AR (10.7%, *P* = .002). Furthermore, more perforations were present in these specimens (13.7% *v* 2.5%, *P* = .001). The plane of resection lies within the sphincteric muscle, the submucosa or lumen in more than 1/3 of the APR cases, and in the remainder lay on the sphincteric muscles.	rate (13.7%). This usually occurs in the low rectum either where the mesorectum thins or where it joins the sphincters or in the sphincters themselves. It could be argued that a wider surgical approach equivalent to total mesorectal excision in the upper- and mid-rectum, and aiming to remove the entire rectum as a cylinder following the mesorectal plane from above and encompassing the levator plane from below should be used	endpoint	

Does rectal stump wash-out prior to anastomosis decrease local recurrence in rectal cancer patients for whom curative surgery is scheduled?

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
Terzi C 2006	[169]	96 patients with carcinoma of the rectum and distal sigmoid colon undergoing anterior resection	38 patients had rectal washout with 5% povidone-iodine before mechanical anastomosis, 58 patients did not. A circular stapler was used for anastomosis, and the stapler was immediately rinsed in 100 ml of saline. The fluid was then classified as "acellular," "malignant cells identified," or "benign cells identified" by pathologists	Assess whether malignant cells are likely to be collected by a circular stapler introduced transanally to perform an anastomosis, local recurrences during follow-up, with special attention to the washout status of patients	Malignant cells were collected from the circular stapler after use in 3 patients (8%) on whom rectal washout was performed and in 2 (3%) patients who did not have rectal washout performed (P = 0.631). Three patients (8%) in the washout group developed local recurrence, and 2 patients (3.4%) in the no-washout group had local recurrence (one was anastomotic recurrence) (P = 0.338). The median follow-up time was 23 (range: 9–70) months.	This non randomized study does not offer rational arguments in support of intraoperative rectal washout when a circular stapler is used after low anterior resection for carcinoma.	Retrospectiv e study	Very low
Maeda K 2004	[168]	30 consecutive patients operated on by anterior resection for rectal cancer	After cross-clamping the rectum below the tumour, a washout sample was collected for examination after every incremental 500 ml of saline irrigation up to 2 liters.	The presence of shed cancer cells was investigated and correlated with the washout volume and tumour characteristics	Cancer cells were found in 29 of 30 patients (97 percent) in the first sample of irrigation fluid and decreased gradually in frequency and number with increasing irrigation volumes. No cancer cells were demonstrated after 1.5 liters of irrigation in patients with tumour below the peritoneal reflection, whereas cancer cells were still present in one-fourth of the patients with tumour located above the peritoneal reflection. Finally, only a small number of cancer cells was confirmed in one patient after 2 liters of irrigation.	Although rectal washout is still a sound surgical principle in an attempt to prevent development of anastomotic recurrence, no evidence in this occurrence is given here.	Prospective non controlled, non randomized study	Low

Should a colonic pouch, a coloplasty or a straight coloanal anastomosis be performed for optimal functional outcome in rectal cancer patients for whom curative surgery is scheduled?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	January 2001	Colorectal cancer	With low rectal anastomosis after TME, consider a colopouch	RCT (2) Systematic review (1)		High
DGVS	[52]	Unsure	Colorectal cancer	After low rectal anastomosis after TME colopouch should be constructed	RCT (5) Prospective study (1) Review (2) Retrospective study (2)		High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
Jiang 2006	[174]	56 mid- to low RC	TME + J-pouch vs side-to-end anastomosis	Surgical outcomes, functional evaluation, including anorectal manometry and functional assessment, preoperatively and then 3 months, 6 months, 1 year, and 2 years postoperatively	Anastomosis could be performed safely from the abdomen whilst minimizing sphincter injury and showed good continence preservation. Surgical outcomes and long-term functional results of side-to-end anastomosis were comparable with colonic Jpouch. Side-to-end anastomosis provides an easier, alternative way for		RCT	High
Ulrich A 2005	[178]	106 rectal cancer patients	Total mesorectal excision (TME) and colo-anal anastomosis with colon J-pouch (CJP) versus transverse coloplasty pouch (TCP)	Compare the two pouch reconstruction techniques in terms of morbidity, mortality and functional results	Functional results after TCP and CJP anastomosis are similar. Evacuation problems after TCP have not been reported like in CJP.		RCT	High
Park 2005	[171]	50 patients with low rectal cancer (up to 5 cm of anal verge)	Straight CAA *vs* colonic J-pouch anal anastomosis after ultra low anterior (ULAR) resection and partial intersphincteric dissection	Functional outcome in terms of fecal incontinence and quality of life	Colonic J-pouch anal anastomosis decreases the severity of fecal incontinence and improves the quality of life for 10 mo after ileostomy takedown in patients undergoing ULAR low-lying rectal cancer	Differences between 2 groups dissappear after 10 months	RCT	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
Laurent 2005	[170]	37 patients with low rectal cancer	Low anterior resection with either stapled or handsewn colonic J-pouch anal anastomosis	Operating time, morbidity and functional outcome	Stapled coloanal anastomosis is significantly faster than handsewn CAA and has similar functional results		RCT	High
Furst A 2003	[173]	40 consecutive patientswith distal rectal cancer (<12 cm from the anal verge)	Randomized into the J-pouch or coloplasty group. A low rectal resection and coloanal anastomosis was performed in all patients.	Functional data were collected by a standardized questionnaire and anorectal manometry, preoperatively and six months postoperatively. Primary end points of the study were potentially differences of both groups regarding technical feasibility, stool frequency, and anorectal manometry	The construction of a coloplasty pouch was feasible in all cases of the coloplasty group, but not in 5 of 20 (25 percent) patients of the J-pouch group, because of colonic adipose tissue. Six months after operation or stoma closure, respectively, stool frequency was comparable in both groups, as were resting and squeeze pressure as well as neorectal volume. Neorectal sensitivity was increased in the coloplasty group	In this study, functional results were nearly identical in the coloplasty group compared with the J-pouch group. Construction of a coloplasty pouch was feasible in all patients, but not in all patients randomized to colonic J-pouch. Therefore, the colonic coloplasty is an attractive pouch design because of its feasibility, simplicity, and effectiveness	RCT	High
Pimentel JM 2003	[175]	30 patients with mid and low rectal cancer	Total mesorectal excision with either a transverse coloplasty pouch (TCP) or a colonic J-pouch (CJP)	Clinical defaecatory function was assessed and anorectal physiological assessment was carried out, pre-operatively and at 3, 6 and 12 months postoperatively, by means of a standard clinical questionnaire and by anorectal manometry	No statistically significant differences were found between the two groups regarding bowel function. The postoperative frequency of daily bowel movements was lower in the TCP group in all the phases of the study, the same occurring with fragmentation. Less urgency was also seen in the TCP group during the first 6 months. No significant differences were found concerning incontinence grading and scoring. The anorectal manometry data was similar in both types of pouches. The local complication rates were also identical in the two groups	The data of this ongoing trial shows that the transverse coloplasty pouch has similar functional results	RCT	High
Machado	[176]	One-hundred	Total mesorectal excision	Surgical results and	There was no significant difference	The data from this study show	RCT	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
M 2003		patients with rectal cancer	and colo-anal anastomosis were randomized to receive either a colonic pouch or a side-to-end anastomosis using the descending colon	complications were recorded. Patients were followed with a functional evaluation at 6 and 12 months postoperatively	in surgical outcome between the 2 techniques with respect to anastomotic height (4 cm), perioperative blood loss (500 ml), hospital stay (11 days), postoperative complications, reoperations or pelvic sepsis rates. Comparing functional results in the 2 study groups, only the ability to evacuate the bowel in <15 minutes at 6 months reached a significant difference in favor of the pouch procedure.	that either a colonic J-pouch or a side-to-end anastomosis performed on the descending colon in low-anterior resection with total mesorectal excision are methods that can be used with similar expected functional and surgical results.		
Machado M 2005	[177]	The patients in this study (n = 71) were part of a prospective, randomized trial on 100 operated patients, comparing a range of variables in the postoperative period.	Total mesorectal excision and colo-anal anastomosis were randomized to receive either a colonic pouch or a side-to-end anastomosis using the descending colon	Anal manometry was performed before preoperative radiotherapy was given. Rectal evaluation was not performed before the operation, because bulky tumours likely would influence volume and compliance. Postoperative investigations were performed at six months and one and two years. Anal sphincter pressures were evaluated with anal manometry (vectorvolume) and neorectal characteristics with manovolumetry (barostat).	There was no statistical difference in functional outcome between groups at two years. Maximum neorectal volume increased in both groups but was approximately 40 percent greater at two years in pouches compared with the side-to-end anastomosis. Anal sphincter pressures volumes were halved postoperatively and did not recover during follow-up of two years. Male gender, low anastomotic level, pelvic sepsis, and the postoperative decrease of sphincter pressures were independent factors for more incontinence symptoms.	both J-pouch and side-toend anastomosis can be used with similar functional results at two-year follow-up. Although neorectal volume was larger in the J-pouch compared with the side-to-end anastomosis, this seems to have limited if any influence on postoperative function.	RCT	High
Sailer M 2002	[172]	Sixty-four patients were randomized to either straight (n = 32) or coloanal J pouch	Patients were studied before operation, at the time of stoma reversal and at 3-month intervals for 1 year thereafter.	Quality of life was measured using two generic (Gastrointestinal Quality of Life Index and European Organization for Research and Treatment of Cancer (EORTC)	Thirty-nine patients (19 with a pouch and 20 with a straight anastomosis) completed the trial. There was a marked difference between the two groups with regard to quality of life profile.	patients undergoing low anterior rectal resection and coloanal J pouch reconstruction may not only expect better functional results but also an improved quality of	RCT	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
		(n = 32) anastomosis after total proctectomy with TME		QLQ-C30) and one disease-specific (EORTC QLQ-CR38) instruments. Functional results using a standardized score as well as manometric variables were recorded.	Patients with a pouch reconstruction had a significantly better quality of life, particularly in the early postoperative period.	life in the early months after surgery compared with patients who receive a straight coloanal anastomosis.		

Should a temporary defunctioning stoma routinely or selectively be constructed at restorative proctectomy in order to reduce clinical leak rate in rectal cancer patients for whom curative surgery is scheduled?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	January 2001	Colorectal cancer	With low rectal anastomosis, consider giving a defunctioning stoma	Retrospective study (1)		Low
DGVS	[52]	Unsure	Colorectal cancer	After total mesorectal excision, a temporary defunctioning stoma should be constructed; ileostoma and colostoma have the same efficiency.	RCT (2) Retrospective study (2)		High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
Law WL 2002	[184]	80 patients undergoing low anterior resection for rectal cancer	Patients randomized for construction of loop ileostomy (42) versus loop transverse colostomy (38)	Postoperative morbidity, stoma-related problems and morbidity after closure	Postoperative intestinal obstruction and prolonged ileus occurred more frequently after ileostomy (p=0,037), no difference was found in time to resumption, length of hospital stay following closure and incidence of stoma-related complication after discharge, there were significantly more bowel obstruction in the ileostomy group from the time of stoma creation to the time of		RCT	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
					stoma closure			
Poon JT 2004	[181]	214 consecutive patients who had undergone low anterior resection for rectal cancer from August 1993 to March 1999	Patients with unplanned admissions, with the diagnosis of small bowel obstruction, were reviewed	Incidence, aetiologies and outcomes of small bowel obstruction in patients after low anterior resection for rectal cancer. The factors that might affect the incidences of small bowel obstruction were analysed.	22 patients presented with 30 episodes of small bowel obstruction, operations were necessary in nine patients (40.9%). Malignant obstruction occurred in two patients (10.3%). Obstruction within 6 weeks of surgery (including closure of stoma) occurred in 13 patients (6.1%). Early obstruction occurred at a higher incidence in those patients who had had an ileostomy than in those who did not (9.1% vs 2.9%, P=0.048).		Retrospective study	Very low
Peeters KC 2005	[154]	924 patients with operable rectal cancer between 1996 and 1999	Patients were randomized to receive short-term radiotherapy followed by TME or to undergo TME alone	risk factors associated with symptomatic anastomotic leakage after total mesorectal excision (TME)	Symptomatic anastomotic leakage occurred in 107 patients (11,6 per cent). Pelvic drainage and the use of a defunctioning stoma were significantly associated with a lower anastomotic failure rate. A significant correlation between the absence of a stoma and anastomotic dehiscence was observed in both men and women, for both distal and proximal rectal tumours. In patients with anastomotic failure, the presence of pelvic drains and a covering stoma were both related to a lower requirement for surgical reintervention.	Placement of one or more pelvic drains after TME may limit the consequences of anastomotic failure. The clinical decision to construct a defunctioning stoma is supported by this study.	Retrospective study	Very low

Can a local resection or transanal endoscopic microsurgical resection be performed instead of a radical resection without compromising the outcome in rectal cancer patients for whom curative surgery is scheduled?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	January 2001	Colorectal cancer	The relative risk of operative morbidity and recurrence must be carefully weighed and explained fully to the patient so that an informed decision can be made regarding local excision and rectal cancer	RCT (1) Retrospective study (2)		Moderate
DGVS	[52]	Unsure	Colorectal cancer	Local excision / TEMS is an alternative to TME for pT1 carcinomas up to 3 cm in diameter, showing a good histologic differenciation, without lymphatic invasion and R0 resection	RCT (1) Retrospective study (2) Review (1)		Moderate

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
Winde G 1997		241 patients, 188 with rectal adenoma and 53 with rectal carcinoma	Four-arm RCT stratified by diagnosis. 25 patients with carcinoma, were assigned to transanal endoscopocic microsurgery (TEM) and 28 to anterior resection(AR). 98 adenoma patients were assigned to TEM and 90 to perianal submucosal excision (PSE)	Operating time, morbidity and mortality according to each sub-group, local recurrence and overall survival	No perioperative deaths, survival not given for the adenoma patients. Significantly higher rate of local recurrence in the PSE group than in the TEM group and operating time significantly longer for TEM than PSE. At follow-up of 45.8 months for AR and 40.9 months for TEM, there was one death in each group (1/28 in the AR group and 1/25 in the TEM group. No differences between TEM	Patients were followed up for just under four years, lack of power TEM should be regarded as a niche procedure suitable for treating only a small percentage of rectal tumours.	RCT	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
					and AR for the overall early complication rate. Survival graphs for TEM *vs.* AR showed no differences at follow-up of nearly four years. Two of the 25 TEM patients showed local recurrence at follow-up. Operating time was significantly less for TEM patients than for AR			
Lezoche E 2005	[186]	40 patients with T2N0 rectal cancer	transanal endoscopic microsurgery (TEM) with neoadjuvant radiochemotherapy and laparoscopic resection (LR), also with neoadjuvant radiochemotherapy	oncological outcomes: local recurrence and distant metastasis	At a median follow-up period of 56 months (range, 44–67 months) in both arms, one local failure (5%) occurred after 6 months in arm A and one (5%) after 48 months in arm B. Distant metastases occurred in one arm A patient (5%) after 26 months of follow-up evaluation and in one arm B patient (5%) at 31 months. The probability of local or distant failure was 10% for TEM and 12% for laparoscopic resection, whereas the probability of survival was 95% for TEM and 83% for laparoscopic resection	The findings show comparative results between the two study arms in terms of probability of failure and survival. Nevertheless, care should be taken in concluding on oncological results as this study does compare local resection with the laparoscopic approach which is not fully validated at this time	RCT	High

Can a local resection or transanal endoscopic microsurgical resection be performed instead of a radical resection without compromising the outcome in rectal cancer patients for whom curative surgery is scheduled?

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
Mellgren A 2000	[62]	261 T1 and T2 rectal cancer patients	108 T1 and T2 rectal cancer treated by local excision compared with 153 T1N0 and T2N0 rectal cancer treated by radical surgery. Neither group received adjuvant chemoradiation	five-year local recurrence rate, overall recurrence, five-year overall survival rate	The estimated five-year local recurrence rate was 28 percent (18 percent for T1 tumours and 47 percent for T2 tumours) after local excision and 4 percent (none for T1 tumours and 6 percent for T2 tumours) after radical surgery. Overall recurrence was also higher after local excision (21 percent for T1 tumours and 47 percent for T2 tumours) than after radical surgery (9 percent for T1 tumours and 16 percent for T2 tumours). Twenty-four of 27 patients with recurrence after local excision underwent salvage surgery. The estimated five-year overall survival rate was 69 percent after local excision (72 percent for T1 tumours and 65 percent after T2 tumours) and 82 percent after radical surgery (80 percent for T1 tumours and 81 percent for T2 tumours).		Retrospective study	Very low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
					Differences in survival rate between local excision and radical surgery were statistically significant in patients with T2 tumours.			
Nascimbeni R 2004	[63]	144 patients with T1 sessile adenocarcinoma in the lower third or middle third of the rectum.	70 patients underwent local excision compared with 74 patients who underwent radical resection	five-year and ten-year cumulative probabilities of local recurrence, distant metastasis, overall survival, and cancer-free survival	Among patients with lesions in the middle or lower third of the rectum, 1) the five-year and ten-year outcomes were significantly better for overall survival and cancer-free survival in the radical resection group, but there were no significant differences in local recurrence or distant metastasis; 2) the multivariate risk factors for long-term, cancer-free survival were invasion into the lower third of the submucosa, local excision, and older than aged 68 years; and 3) for lesions with invasion into the lower third of the submucosa, the radical resection group had lower rates of distant metastasis and better survival. Among patients with lesions in the lower third of the rectum, 1) the five-year and ten-year outcomes showed no		Retrospective study	Very low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
					significant differences in survival, local recurrence, or distant metastasis between the two groups; and 2) for lesions with invasion into the lower third of the submucosa, the radical resection group showed a trend of improved survival, which was not statistically significant, possibly because of low statistical power from the small sample size.			
Bentrem DJ 2005	[61]	319 consecutive T1 rectal cancer patients	Transanal excision compared with radical TME surgery	Local and distant reccurence, overall and disease-specific survival	Patients who underwent radical surgery had fewer local recurrences, fewer distant recurrences, and significantly better recurrence-free survival (*P* 0.0001). Overall and disease-specific survival was similar for RAD and TAE groups.		Retrospective study	Very low
You YN 2005	[64]	2124 stage I rectal cancer patients	765 T1 and T2 rectal cancer treated by local excision LE compared to 1359 T1 and T2 rectal cancer treated by standard resection SR	30-day morbidity, 5-year local recurrence, 5-year overall survival	LE provided a significantly lower 30-day morbidity versus SR (5.6% vs. 14.6%; P < 0.001). After adjusting for patient and tumour characteristics, the 5-year local recurrence after LE versus SR was 12.5 versus 6.9% (P = 0.003; hazard ratio = 0.38; 95% CI, 0.23-		Retrospective study	Very low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
					0.62) for T1 tumours, and 22.1 versus 15.1% (P = 0.01; hazard ratio = 0.69; 95% CI, 0.44-1.07) for T2 tumours. The 5-year overall survival (T1, 77.4% vs. 81.7%, P = 0.09; T2, 67.6% vs. 76.5%, P = 0.01) was influenced by age and comorbidities but not the type of surgery.			
Nascimbeni R 2002	[187]	353 patients with sessile T1 lesions of the colon and rectum	Colorectal resection	carcinoma-related variables were assessed: size, mucinous subtype, carcinomatous component, grade, site in colon and rectum, lymphovascular invasion, and depth of submucosal invasion. For the depth, the submucosa was divided into upper third (sm1), middle third (sm2), and lower third (sm3)	The incidence of T1 lesions was 8.6 percent. In the analysis cohort, the lymph node metastasis rate was 13 percent. Significant predictors of lymph node metastasis both univariately and multivariately were sm3 (P = 0.001), lymphovascular invasion (P = 0.005), and lesions in the lower third of the rectum (P = 0.007). Poorly differentiated carcinoma was significant univariately (P = 0.001) but not in the multivariate model. No other parameter was associated with a significant risk.		Retrospective study	Very low

Is stenting a valid alternative for stoma construction in a palliative setting?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	January 2001	Colorectal cancer	Where facilities and expertise are available, colonic stenting should be considered.	Retrospective study (2)	Studies only include colonic obstruction, no rectal tumours	Low
NICE	[54]	March 2003	Colorectal cancer	Facilities and services should be established to provide stenting for patients with intestinal obstruction, particularly those with serious comorbidity, so that emergency surgery may be avoided. […] Decision-making on use of stents should be the responsibility of colorectal cancer MDTs. Stents should be inserted within 48 hours of admission, by appropriately trained individuals (usually interventional radiologists, ideally working with endoscopists).	Systematic review (1) Prospective observational studies (6) Retrospective case series (12)		Moderate
DGVS	[52]	Unsure	Colorectal cancer	In case of obstructive rectal carcinoma, and in appropriate patients, stenting may be considered as an alternative to right transverse colostomy.	Systematic review (1)		Moderate

Radiotherapy vs. observation in resected rectal cancer

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[206]	December 2001	Patients with resected stage II or III rectal cancer	If the goal of adjuvant therapy is to improve survival, there is no evidence to support the use of radiotherapy alone	8 RCT: odds ratio [for local failure], 0.73; 95% confidence interval, 0.55 to 0.96; p=0.022 odds ratio [for death], 0.92; 95% confidence interval, 0.77 to 1.11; p=0.40		High
SIGN	[55]	January 2001	Colorectal cancer	When postoperative radiotherapy is indicated, a schedule of 45 Gy in 25 fractions over five weeks is recommended. Patients should not be treated with parallel opposed fields, a planned technique with tree or four fields should be used	27 RCT + 2 meta-analysis: reduction in risk of loss of local control 9% (NNT 11), no benefit in OS in meta-analysis, bowel function significantly worse with RT		High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
James 2003	[212]	3583 pt with CRC randomised to PoVI or not (7d 1g 5-FU/d), 761 RC pt randomised	CRC: PoVI (postoperative portal venous infusion with 1 g 5-FU/d 7d) or not, RC: RT (either preop or postop) or not	OS DFS LR Median FU 70 months	Only DFS benefit for PoVI for pt with colonic cancer, no survival benefit for RT	No survival benefit was seen in the 761 patients randomized with respect to radiotherapy; although not statistically significant, the impact on local recurrence rates was similar to that reported in the literature	RCT	High
Bosset 2001	[214]	484 pt with curative resected st B2-3C1-3 rectal cancer	Pelvic RT (50 Gy) vs Pelvic RT + RT on para-aortic nodes and liver (25 Gy)	OS toxicity	No difference in OS, more toxic (haematological, hepatological, intestinal)		RCT	High

Chemotherapy versus observation in resected rectal cancer without preoperative RT

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[206]	December 2001	Patients with resected stage II or III rectal cancer	Patients with resected stage II or III rectal cancer should be offered adjuvant therapy with the combination of radiotherapy and chemotherapy.	Pooled results of three RCTs comparing chemotherapy with observation.		High
SIGN	[55]	January 2001	Colorectal cancer	Patients with Dukes' C tumours of the colon or rectum should be considered for adjuvant chemotherapy	Absolute survival benefit at 5 years of 4-13% in colon cancer (strong evidence) Somewhat weaker evidence for benefit in overall survival in rectal cancer Evidence of no benefit for adjuvant therapy in Dukes B tumours		High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
Akasu 2006	[216]	276 pt with st III resected (TME) rectal cancer	1 yr oral uracil tegafur (400 mg/m2/d) vs observation	3 yr OS 3 yr RFS LR toxicity	- Primary endpoint: RFS, better with CT (78 vs 60%, p=0,001) - Secondary endpoint: OS : better with CT (91 vs 81%, p 0,005) - no difference in LR	- Standardised mesorectal excision with selective lateral pelvic lymphadenectomy - 17% grade III events in CT group	RCT	High
Taal 2001	[217]	299 rectal ca, 730 colonic ca stage II/III	1 yr 5-FU+ levamisole vs observation	OS	4,75 yr FU, significant difference for colonic ca: Overall: 25% reduction in odds of death (p 0,007)	- type of surgery not mentioned - caution with subgroup analysis: stage III 27% reduction in odds of death, stage II 19%, pt with rectal ca: too few to draw firm conclusions	RCT	High
Glimelius 2005	[218]	2224 pt with colorectal ca st II/III (691 rectal ca)	Adjuvant CT (meta-analysis of various regimens) vs observation	OS	Only for colonic stage III a small but clinically meaningfull difference (7%, p0,15)		SR	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
Kato 2002	[219]	320 pt st B/C colorectal cancer	2 yr UFT 400 mg/d vs observation	5 yr OS 5 yr DFS LR, toxicity	Better 5 yr DFS with CT (75,7 vs 60%, p=0,0081) no difference in OS (80,4% (CT) vs 76,5% (obs))	Type of surgery not mentioned. Subanalysis: 5yr DFS in rectal ca 73,6 (CT) vs 42,4 (obs) (p=0,0016) but with only 66 (CT) vs 63 (obs) pt having rectal ca of which 25 (CT) and 21 (obs) "rectosigmoidal"	RCT	High
Sakamoto 2004	[220]	5223 pt, meta-analysis of 3 trials, colon + rectal cancer (2385 pt) st I-III	CT with oral 5-FU vs observation	OS, DFS	overall hazard ratio in favor of oral therapy 0.89 for survival (95% CI, 0.80 to 0.99; P=0.04), and 0.85 for disease-free survival (95% CI, 0.77 to 0.93; P<0 .001)	Type of surgery not known	RCT	High

Chemotherapy versus radiotherapy in resected rectal cancer

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[206]	December 2001	Patients with resected stage II or III rectal cancer	Patients with resected stage II or III rectal cancer should be offered adjuvant therapy with the combination of radiotherapy and chemotherapy.	None of the three randomized controlled trials of chemotherapy versus radiotherapy found a benefit for overall survival or disease-free survival. The pooled results of the three randomized controlled trials confirmed no survival benefit (odds ratio [for death], 0.80; 95% confidence interval, 0.58 to 1.10; p=0.17).		High

Which combination of chemotherapy is superior?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[206]	December 2001	Patients with resected stage II or III rectal cancer	There is evidence that chemotherapy should include 5-fluorouracil (5-FU), but not semustine.	RCTs		High
SIGN	[55]	January 2001	Colorectal cancer	- The addition of levamisole or interferon alpha to fluorouracil and folinic acid (FUFA) chemotherapy as adjuvant treatment is ineffective in colorectal cancer and should not be considered - The recommended adjuvant regimen in patients with Dukes' C tumours is bolus FUFA, administered over five days every four weeks. The duration of treatment should be six months - The schedule of FUFA given once weekly for 30 weeks used in the QUASAR (QUick And Simple And Reliable) trial may be an acceptable option for certain patients.	RCTs		High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
Tsavaris 2004	[208]	150 pt with resected st B2/C rectal cancer	6 m LV (20 mg/m2) + 5-FU 450 mg/m2/d 5d x6 versus 12 m 5-FU 450 mg/m2/w + levamisole 5O mg tid d1-3	FU 7,4 yr LR, DFS	No diff in DFS (□2: 0,051, p=0,821) or OS (□2: 0,202, p=0,654) 5-FU/LV less toxic (leucopenia gr III 4 vs 12%, p<0,04)	Inclusion only if inferior margin within peritoneal flection, all patients radiotherapy (25*1.8 Gy + 5 Gy), endpoints OS and DFS	RCT	High
De placido 2005	[207]	1327 pt with colorectal ca st II/III	5-FU alone vs 5-FU/Lev vs 5-FU/FA vs 5-FU/lev/FA	OS, DFS, toxicity	No difference in OS, DFS, FA more toxic	No differentiation between colonic and rectal cancer	RCT	High
Kotake 2005	[209]	429 st II/III colorectal cancer	14 d 5-FU continuous infusion (320 mg/m2/d) + 1 year HCFU vs 5-FU 14d alone	OS, DFS	Only better 5 yr DFS in colon cancer, not in rectal cancer, no difference in OS	- Type of surgery not mentioned - number of rectal ca not mentioned - Endpoints: OS, DFS, adverse reactions, patterns of recurrence (ITT) - 5-yr OS 83.5% study group, 83.8% control group (HR, 0.96; 95%CI, 0.59-1.57; p=0.866) - 5 yr DFS: 1.2 (95%CI: 0.79-1.84, p=0,383) - 5 yr DFS colon ca: hazard ratio = 1.87; 95% confidence interval 1.03-3.38; p=0.037. - Recurrence rate and pattern did not differ between the 2 groups in rectal ca - Adverse reactions 22 vs 13%, p=0,016	RCT	High
Iwagaki 2001	[210]	321 pr st IIIa/IIIb colorectal cancer	High dose induction 5-FU + 1 yr HCFU versus low dose induction 5-FU + 1 yr HCFU	OS, DFS	No difference, only retrospective analysis: better DFS for rectal ca with low dose induction 5-FU		RCT	Moderate
Watanabe 2004	[211]	760 pt colonic cancer , 669 pt rectal cancer, Dukes B&C	Immunochemotherapy (MMC+5-FU+HCFU+OK432) vs chemotherapy (MMC+5-FU+HCFU) vs observation	5 yr OS 5 yr DFS toxicity	No difference in OS, DFS, no severe adverse events	5 yr OS 73.5% (immunochemo), 71.8 (chemo) and 72.6% (control), p=0.933 5 yr DFS 67.8 (immunochemo), 65.4 (chemo) and 64.8% (control), p=0.785 Significant differences in toxicity between immunochemo/chemo and control: hematologic, anorexia, nausea, vomiting, diarrhea and respiratory disorders	RCT	High

Chemotherapy by portal venous infusion versus observation in resected rectal cancer

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[206]	December 2001	Patients with resected stage II or III rectal cancer	No recommendation stated	-	-	-
SIGN	[55]	January 2001	Colorectal cancer	Portal vein chemotherapy should not be used as the sole regimen in postoperative adjuvant treatment	Some studies suggest a modest effect with a 4.7% absolute increase in 5-yr survival (NNT=20)		Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
James 2003 (AXIS)	[212]	3583 pt with CRC randomised to PoVI or not (7d 1g 5-FU/d), 761 RC pt randomised	CRC: PoVI (postoperative portal venous infusion with 1 g 5-FU/d 7d) or not, RC: RT (either preop or postop) or not	OS DFS LR Median FU 70 months	No benefit in ITT analyses, in subanalyses only trend for DFS benefit for PoVI for pt with colonic cancer	- no TME - relatively low - Survival: all patients (ITT) HR 1 (95%CI: 0.92-1.11, p=0.895), patients without residual disease HR 0.94 (95%CI: 0.86-1.06, p=0.329) - DFS: all patients HR 1 (95%CI 0.9-1.11, p=0.994), curatively resected patients HR 0.9 (95%CI 0.78-1.04, p=0.157) - only trend for treatment benefit for DFS in curatively operated patients (p=0.067) - updated meta-analysis: HR for colonic ca 0.82 (95%CI 0.74-0.91), HR for rectal ca HR 1 (95%CI 0.87-1.15)	RCT	High

Chemotherapy and radiotherapy versus observation in resected rectal cancer

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[206]	December 2001	Patients with resected stage II or III rectal cancer	Patients with resected stage II or III rectal cancer should be offered adjuvant therapy with the combination of radiotherapy and chemotherapy.	RCTs	A covariate-adjusted comparison of chemotherapy plus radiotherapy compared with observation revealed significantly improved time to recurrence with chemotherapy plus radiotherapy in one trial (p=0.005). A second randomized controlled trial found a significant decrease in local recurrence rates (12% versus 30%; p=0.01) as well as improvement in 5-year overall survival (64% versus 50%; p=0.05) and 5-year recurrence-free survival rates (64% versus 46%; p=0.01) favouring chemotherapy plus radiotherapy.	High

Chemotherapy and radiotherapy versus radiotherapy in resected rectal cancer

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[206]	December 2001	Patients with resected stage II or III rectal cancer	Patients with resected stage II or III rectal cancer should be offered adjuvant therapy with the combination of radiotherapy and chemotherapy	RCT	Pooled analysis of three trials of chemotherapy plus radiotherapy versus radiotherapy revealed a benefit for chemotherapy plus radiotherapy for both survival (odds ratio, 0.58; 95% confidence interval, 0.37 to 0.92; p=0.019) and local control (odds ratio, 0.50; 95% confidence interval, 0.27 to 0.92; p=0.025).	High
SIGN	[55]	January 2001	Colorectal cancer	Chemotherapy should be given synchronously with the radiotherapy using one of the following three regimens: -Intermittently infused FUFA (Bosset) - Continuous fluorouracil (Lokich) - Bolus FUFA	Observational studies	No results from studies comparing short course (5 fractions) RT +/- CT. Only 3 trials have randomised patients with rectal cancer to long course RT as apposed to CRT. All were of low quality and reporting is incomplete. Prospective cohort studies: addition of CT to RT improves complete response rate and the respectability rate in more advanced tumours. The design of the studies does not allow an assessment of survival. The regimens using intermittently infused FUFA or continuous FU have been widely and safely used.	Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
Cafiero 2003	[215]	218 pt st II-III respectable rectal cancer	Postop RT (50 Gy, 2 Gy 5*/wk, 5 wks) vs Postop RT + CT (5-FU bolus 450 mg/m2/d 5d/28d 6x, levamisole 150 mg/d 3d/14), RT week 2 of 1° cycle)	1°: OS 2°: DFS, LR, toxicity	No difference in OS, DFS or LR	- Low adherence to CT (59%), RT and CT sequential, not concurrent - node-negative patients: 5 yr OS 72% (RT) vs 47% (RT+CT), p-value not given, relative risk of death with RT+CT 33% higher (p=0.18) - node-positive patients: 5 yr OS 46% (RT) vs 38% (RT+CT) p-value not given - unbalance of stageII-III disease in the two groups (more stage III in RT+CT, exact numbers not given)	RCT	Moderate

Chemotherapy and radiotherapy versus chemotherapy in resected rectal cancer

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[206]	December 2001	Patients with resected stage II or III rectal cancer	Patients with resected stage II or III rectal cancer should be offered adjuvant therapy with the combination of radiotherapy and chemotherapy	RCT	Pooled results from two trials showed no significant survival benefit for chemotherapy plus radiotherapy versus chemotherapy (OR 0.80; 95%CI 0.48 to 1.32; p=0.37). In a third trial, the addition of radiotherapy to chemotherapy did not significantly improve disease-free survival (HR, 0.99; 95%CI 0.80 to 1.22; p=0.90) or overall survival (HR 0.98; 95%CI 0.78 to 1.24; p=0.89).	High

Comparison of chemotherapy and radiotherapy regimens

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[206]	December 2001	Patients with resected stage II or III rectal cancer	During the concurrent component of combination therapy, intravenous infusion with 5-FU is more effective than bolus injection	RCT	When CT with 5-fluorouracil was given concurrently with RT, continuous intravenous infusion was more effective than the drug administered by bolus. The addition of semustine to 5-fluorouracil was ineffective. Two trials found no improvement in survival when levamisole or leucovorin was added to 5-fluorouracil. Preliminary results of two RCTs have been published in abstract form. In the first, the addition of interferon alfa-2b to adjuvant 5-fluorouracil, leucovorin and RT was not associated with significant improvements in recurrence or survival rates. The second trial failed to show a significant difference between six and 12 months of 5-fluorouracil plus medium-dose folinic acid in terms of relapse rates, disease-free survival and overall survival.	High
SIGN	[55]	January 2001	Colorectal cancer	Chemotherapy should be given synchronously with the radiotherapy using one of the following three regimens: Intermittently infused FUFA (Bosset) Continuous fluorouracil (Lokich) or Bolus FUFA	Observational studies	The more useful evidence comes from several prospective cohort studies. The addition of CT to RT improves complete response rate and the respectability rate in more advanced tumours. The design of the studies does not allow an assessment of survival. The regimens using intermittently infused FUFA or continuous fluorouracil have been widely and safely used.	Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
Smalley 2006	[221]	1917 pt after resection of T3-4NOMO or T1-4N1-2M0 rectal adenocarcinoma	Randomly assigned to bolus FU (500 mg/m2/d 5d q4w *2 before, 425 mg/m2 after) before and after RT (25*1.8 Gy + boost 5.4 Gy), PVI (225 mg/m2/d) during RT (1), PVI only with PVI before, during and after RT (2), bolus only with bolus before (425 mg/m2/d + LV 20 mg/m2 + levamisole 50 mg tid 3d/14d), during and after RT (3)	3yr OS 3yr DFS LRF toxicity	Similar OS and DFS and LRF, less toxicity if PVI	- Sandwich therapy not currently used in Europe - gr 3-4 hematological toxicity 49% arm I, 55% arm III (bolus-arms) vs 4% in PVI arm - 5 yr OS 68% (arm I), 71% (arm II), 68% (arm III), p=0.5 - 5 yr DFS 62% (arm I), 62% (arm II), 57% (arm III), p=0.25 - arm II opposed to arm I : HR for OS 0.91 (95%CI 0.75-1.11), DFS HR 0.95 (95% CI 0.8-1.13) - LRF 8% (arm I), 4.6% (arm II), 7% (arm III)	RCT	High

Chemotherapy versus observation after resected rectal cancer with preoperative RT

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[206]	December 2001	Patients with resected stage II or III rectal cancer	Patients with resected stage II or III rectal cancer should be offered adjuvant therapy with the combination of radiotherapy and chemotherapy	-	No specific search on this topic. In fact, in the interpretative summary after reviewing the evidence, authors conclude: "The duration of chemotherapy can be as short as seven days for portal vein infusion and six months or less for systemic administration"	Very low
SIGN	[55]	January 2001	Colorectal cancer	The recommended adjuvant regimen in patients with Dukes' C tumours is bolus FUFA, administered over five days every four weeks. The duration of treatment should be six months		FUFA given by IV injection for 5 days every 4 weeks for 6 cycles is the regimen for which the most evidence is available and it is clearly effective in prolonging survival in patients with Dukes C. One study has shown no benefit from higher (175 mg) as apposed to lower (25 mg) doses of L-folinic acid. Low dose FUFA has not been shown to be superior to 12 months of fluorouracil with levamisole.	Low

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
Bosset 2006	[75]	cT3-T4 rectal cancer 1011 patients	Random allocation to preop RT (1) preop CRT (2), preop RT + postop CT (3), preop RCT + postop CT (4)	OS(5 yr) and local control	No difference in OS but significant benefit on local control with CT either preop or postop	- No optimal chemotherapy (old fashioned regime) - 26.9% never started adjuvant CT (complications, progression, refusal, no surgery) - acute toxic effects in 57.8% (no deaths) - late effects: ≥ gr 2 diarrhea 9.7%, fecal incontinence in pts with sphinterserving operation 9% (2/522 pt colostomy), stenosis of anastomosis in 31/522 pts (colostomy in 11) - 5 yr OS 63.2% without CT, 67.2% with CT (p=0.12), HR for death with CT 0.85 (95%CI 0.68-1.04) - 5 yr DFS 52.2% without CT, 58.2% with CT (p=0.13), HR for adjuvant CT 0.87 (95%CI 0.72-1.04) - LR 17.1% (RT alone), 8.7% (preop CRT), 9.6% (preop RT, postop CT), 7.6% (preop CRT-postop CT). p=0.002 between 1° group and other 3, independent of location of tumour (</> 5 cm from anal verge)	RCT	High

Adverse effects

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[206]	December 2001	Patients with resected stage II or III rectal cancer	-	-	-	-
SIGN	[55]	January 2001	Colorectal cancer	-	-	-	-

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
Lundby 2005	[222]	15 pt with postop RT vs 12 pt without	Postop radiotherapy vs no adjuvant treatment	Anorectal function	Severe long-term anorectal dysfunction as result of a	- Small study - fecal incontinence: 60% (RT) vs 8%, p=0.004 - loose or liquid stool: 60% (RT) vs 23%, p=0.05	RCT	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
		Dukes B/C rectal ca			weakened, less sensitive anal sphincter and undistensible rectum	- reduced rectal capacity: 146 vs 215 ml (p=0.03) - maximum squeeze pressure: 59 vs 93 mmHg (p=0.003)		
Dencausse 2001	[223]	28 pt with resected st II/III rectal cancer	Postoperative RT + concomitant high dose 5-FU (2600 mg/m2/week, with FA 500mg/m2/week)	toxicity	Too toxic: gr III/IV in 5 out of 21 evaluable pt	Small study (preliminary results)	RCT	Low
Miller 2002	[224]	656 pt with resected, T3-4N0-2M0 and T1-2N1-2M0	- 45 Gy in 25 fractions, additional boost of 5.4-9 Gy - group 1: 5-FU 500 mg/m2 bolus d1-3, wk 1 & 5 of RT - group 2: 5-FU 225 mg/m2/d PVI	toxicity	The rate of diarrhea was significantly greater in the PVI group	- detailed analysis of toxicity of a previous reported trial by the North Central Cancer Treatment Group (O'Connell et al, NEJM 2004) - ≥ gr 3 diarrhea: 21% (PVI) vs 13% (bolus) p =0.007 - if anterior resection: ≥ gr 3 diarrhea: 31% (PVI) vs 12% (bolus), p< 0.001	RCT	High

How to precise the resectability of a metastatic disease? What are the resectability criteria?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Garden 2006	[228]	October 2000	Metastatic colorectal cancer	Patients with primary colorectal cancer should have a CT scan of the abdomen and pelvis performed with intravenous contrast and ideally a maximum collimation of 5 mm.	MA		High
				A chest CT is ideal to assess the presence of pulmonary metastases but a chest x-ray is considered satisfactory.			Very low
				The whole colon should be visualised to ensure a "clean colon".	Cochrane review on follow-up 2002		High
				A baseline measurement of CEA should be performed.			Very low
				For a patient discovered to have isolated liver metastases, CT of the chest, abdomen, and pelvis should be performed by the liver surgery unit or using protocols agreed with that unit.			Very low
				Biopsy of hepatic lesions should not be performed without discussion with the regional hepatobiliary unit.			Very low
				Patients with "high risk" primary disease (T4, C2) should have careful preoperative investigations that might include PET scan and laparoscopy.	No MA nor SR nor RCT (8 papers)		Very low
NICE	[54]	March 2003	Colorectal cancer	Patients with metastases confined to limited areas of the liver or lung and who are sufficiently fit to undergo further treatment after resection of the primary tumour, should be referred to a specialist MDT for an opinion on their management.			Very low
				Patients should undergo preoperative abdomino-pelvic CT scanning to assess cancer stage and metastatic spread, unless this information would have no influence on the management-for example, if the patient is receiving palliative treatment only. CT or MR imaging of the liver is especially important for patients who appear to have Duke's stage B or C cancers and are fit enough for local treatment of liver metastases; when a patients appears to have limited liver metastases, his or her management should be discussed with the liver resection MDT.			Very low

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				Positron emission tomography (PET) scanning is an emerging technology, capable of identifying local recurrence, liver metastases and distant metastases in colorectal cancer. In conjunction with other imaging modalities, it may be helpful in assessing the extent of metastatic disease, and hence influencing decisions on patient management. The optimum role of PET scanning in relation to more established imaging methods is not yet clear.			Very low
CCO	[68]	September 2004	Metastatic colorectal cancer	CT and MRI are superior to ultrasound to detect liver metastases and are equivalent in their ability to detect disease recurrence.	47 references		High
Lazorthes 2003	[59]	Unsure	Metastatic colorectal cancer	Clinical examination and evaluation of the general status of the patient conditions further staging.	Prospective studies		Very low
				CT scan with contrast injection. If not possible (contra-indication to contrast injection): MRI liver.			Low
				CT chest better than RX.			Low
				Dosage of CEA is useful to monitor the clinical response.			Very low
				MRI is useful to characterize lesions and to evaluate the volume of liver in case of bread resection.			Low
				PET is useful before resection of metastases to evaluate de extra-hepatic dissemination of disease. Indicated if high risk of extra-hepatic dissemination.			Low
DGVS	[52]	Unsure	Colorectal cancer	CT is recommended for the detection of lung, liver metastases and local recurrence			Low

Resectability criteria

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Garden 2006	[228]	October 2000	Metastatic colorectal cancer	The ability to achieve clear margins (R0 resection) should be determined by the radiologist and surgeon in the regional hepatobiliary unit.	92 ref (RCT, review, prospective studies, MA)		Very low
				The surgeon should define the acceptable residual functioning volume, approximately one third of the standard liver volume, of the equivalent of a minimum of two segments.			
				Patients with extrahepatic disease that should be considered for liver resection include resectable/ablatable pulmonary metastases, resectable/ablatable extrahepatic sites and local direct extension of liver metastases.			
				Contraindications to liver resection would include incontrollable extrahepatic disease.			
				Those patients with tumours though to be borderline for resection may have resectable or ablatable disease and should be referred for discussion with the regional hepatobiliary unit before CT.			
				Resectability may be achieved by portal vein embolisation or two stage hepatectomy to increase hepatic functional reserve and also by the combinations of surgery and ablation.			
Lazorthes 2003	[59]	Unsure	Metastatic colorectal cancer	Contraindications to hepatic resection: Impossibility to obtain free resection margins. Impossibility to resecate all tumoral tissue in or out the liver. Impossibility to let enough liver tissue to avoid post-operative liver insufficiency.			

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study Type	Level of Evidence
Wiering 2005	[236]	Patients with CRC liver metatases	PET scan		Added value in the diagnostic work-up of patients with colorectal liver metastases	Only observational studies found	SR	Low
Rau 2005	[235]	Patients with GI cancer, gynaecological cancers	Laparoscopy		Further studies required, only prospective and retrospective observational studies in GI cancers	Only observational studies found	SR	Low

Should induction treatment be applied in resectable metastatic rectal cancer?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
SIGN	[55]	January 2001	Colorectal cancer	Preoperative RT, planned with three or four fields, should be considered in patients with operable rectal cancer.	27 RCT-2MA		High
				RT to convert inoperable rectal cancer into operable disease should be combined with CT. Suitable regimens include intermittent infusional 5-FU/FA, continuously infused 5-FU or bolus 5-FU/FA.	5 reviews		Very low
				For patients with totally inoperable rectal cancer, and who are fit for an aggressive approach to treatment, CT-RT should be offered as for potentially resectable disease.	Expert opinion		-
CCO	[282]	January 2004	Adult pts with clinically resectable rectal cancer	Both preoperative and postoperative RT decrease local recurrence but neither improves survival as much as postoperative RT combined with chemotherapy (CT). Therefore, if preoperative RT is used, CT should be added postoperatively, at least for patients with stage III disease.	11 RCT		High

Study ID	Ref	Population	Intervention	Ouctomes	Results	Comments	Study type	Level of evidence
Bosset 2006	[75]	T3-T4 resectable rectal cancers 1011 pts	Random 4 arms with pre- or postoperative treatments	Overall survival and local control	Benefit of the chemotherapy on the local control but not on survival		RCT	High

Sequential or synchronous surgery? Neoadjuvant or adjuvant chemotherapy?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Garden 2006	[228]	October 2000	Metastatic colorectal cancer	Normally, colorectal cancer resection and liver resection would not be performed synchronously but management of accessible small metastases detected perioperatively may be considered for combined resection. Simultaneous colon en liver resection has been shown to be safe and efficient in the treatment of patients with colorectal cancer and synchronous liver metastases when undertaken in high volume centres with appropriate experience in liver resectional surgery.	92 ref (RCT, review, prospective studies, MA)		Very low
				Patients should be referred for consideration of liver resection after recovery from primary surgery and it seems appropriate to allow the patient to recover from colorectal surgery before consideration is giver to a further elective operative procedure.			
				Patients with potentially resectable liver disease and who have undergone radical resection of the primary tumour should be considered for liver resection before consideration of chemotherapy.			
				Patients with unfavourable primary pathology such as perforated primary tumour or extensive nodal involvement should be considered for adjuvant chemotherapy prior to liver resection and be restaged at 3 months.			
NICE	[54]	March 2003	Colorectal cancer	Participation in clinical trials evaluating the role of adjuvant chemotherapy in addition to liver resection should be			

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				encouraged.			
				Preoperative chemotherapy may be appropriate to shrink liver metastases. NICE recommends that the combination of oxaliplatin en FUFA should be considered for patients with metastases confined to the liver, whose disease might become resectable after chemotherapy.			
Lazorthes 2003	[59]	Unsure	Metastatic colorectal cancer	After Ro resection of colorectal metastases, inclusion of patients in trials, chemotherapy is an option using systemic 5-FU/folinic acid.			Low
				Interest of intraarterial chemotherapy in combination with systemic CT is limited and non applicable outside clinical trials.			High
				No recommandation to perform neoadjuvant chemotherapy before the resection of resectable metastases.			
				If the metastases are not resectable, chemotherapy is indicated for the patients in good condition because it increases QOL and improves OS.			High
DGVS	[52]	Unsure	Colorectal cancer	Synchronous or metachronous resection of metastases			Very low
				If resectable metastases: indication of primary resection. No arguments for neoadjuvant or adjuvant therapy.			High
				If non resectable metastase: palliative chemotherapy.			High

Study ID	Ref	Population	Intervention	Ouctomes	Results	Comments	Study type	Level of evidence
Delaunoit 2005	[240]	Previouly untreated MCRC, 795 pts 24 pts resected	(A) irinotecan/5-FU/leucovorin (LV) (IFL, n = 264), (F) oxaliplatin/5-FU/LV (FOLFOX4, n = 267) and (G) oxaliplatin/irinotecan (IROX, n = 265)	TTP Median OS	TTP 18.4 mo mOS 42.4 mo majority of patients resected had oxali-based regimen (92%)		RCT	Low
Portier 2006	[243]	173 hepatic resected mCRC	Surgery alone and observation (87 patients) vs. surgery followed by 6 months of systemic adjuvant chemotherapy with a fluorouracil and folinic acid monthly regimen (86 patients)	DFS, OS, treatment related toxicity	DFS with adjuvant treatment but not OS		RCT	Low

Is local treatment of the primary tumour useful in case of non resectable metastases?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Garden 2006	[228]	October 2000	Metastatic colorectal cancer	Patients with advanced disease unsuitable for liver resection or ablative therapy should be referred to the clinical or medical oncologist with a special interest in CRC for further management			Very low
NICE	[54]	March 2003	Colorectal cancer	Radiotherapy can provide valuable palliation. RT should also be offered to those patients with locally recurrent or advanced rectal cancer and pelvic pain, who have not previously undergone RT. External radiotherapy used aloes eases pain in a high proportion of patients with locally advanced rectal cancer.			High
Lazorthes 2003	[59]	Unsure	Metastatic colorectal cancer	In the case of synchronous not resectable metastases, and without any hope of future resection, and in absence of sign of local complication, the initial resection of CRC primary tumour is not recommended.	3 retrospective series		Very low
SIGN	[55]	January 2001	Colorectal cancer	For patients with totally inoperable rectal cancer, and who are fit for an aggressive approach to treatment, CT-RT should be offered as for potentially resectable disease. Initial combination CT, including oxaliplatin, should be considered in patients fit for hepatic resection, but who have inoperable hepatic metastases that might become resectable on treatment.			Very low

Does first-line chemotherapy alone as compared to observation have an impact on prognosis in patients with resectable primary tumour with non resectable metastases?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[263]	May 2005	Advanced colorectal cancer	For patients with advanced colorectal cancer receiving 5-FU-based chemotherapy as first-line therapy, the addition of bevacizumab, at a dose of 5mg/kg every two weeks, is recommended to improve overall survival in patients with no contraindications to bevacizumab. The addition of bevacizumab to 5-FU-based chemotherapy is also recommended for patients with advanced colorectal cancer receiving second-line therapy if they did not received bevacizumab as a part of their initial treatment.	RCT		High
FNCLCC	[262]	2005	Metastatic colorectal cancer	Chemotherapy has to be proposed in patients in good condition.	3 MA (cfr Simmonds et al. Cochrane)		High
NICE	[54]	March 2003	Colorectal cancer	Idem Conroy et al.	2 MA		High
Lazorthes 2003	[59]	Unsure	Metastatic colorectal cancer	Systemic CT: Delays apparition of symptoms linked to the metastases Improves QOL Prolongs OS In comparison to observation (grade A)	3 MA		High
SIGN	[55]	January 2001	Colorectal cancer	All patients with mCRC should be considered for CT.	2 SR		High

Study ID	Ref	Population	Intervention	Ouctomes	Results	Comments	Study type	Level of evidence
Au 2003	[264]	Elderly patients with CRC	Management of colorectal cancer in elderly patients		Patients of 80 have same OS benefit with palliative first-line monotherapy (5-FU) as younger patients Increased toxicity with bolus 5-FU regimens		SR	High

Study ID	Ref	Population	Intervention	Ouctomes	Results	Comments	Study type	Level of evidence
Folprecht 2004	[265]	3825 elderly pts with metastatic CRC	5-FU-based CT	OS, RR, PFS	Equal in elderly pts and younger patients Infusional 5-FU more effective than bolus in both age groups		Pooled analysis of RCTs	High
Mitry 2004	[271]	Pts with mCRC in first or second line (602 pts)	Irinotecan	Predictive factors of survival in advanced CRC	Irinotecan independently associated with better survival in pts with advanced CRC		Sub-analysis of 2 RCT	Low

Does second-line chemotherapy alone as compared to observation have an impact on prognosis in patients with resectable primary tumour with non resectable metastases?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
Lazorthes 2003	[59]	Unsure	Metastatic colorectal cancer	In case of progressive disease, the first-line therapy will be interrupted. The second-line therapy is therefore recommended. - Additional effect of Irinotecan monotherapy in 2nd line in patients resistant to 5-FU - After progression under 1st line, taking into account the benefit in survival and QOL, a 2nd line has to be proposed to informed patients in good condition.			High
SIGN	[55]	January 2001	Colorectal cancer	Carefully selected patients with good performance status, normal liver function tests and no evidence of GI obstruction with metastasic colorectal cancer, who have progressive disease despite treatment with 5-FU/FA, should be considered for second-line treatment with irinotecan.			High

Study ID	Ref	Population	Intervention	Ouctomes	Results	Comments	Study type	Level of evidence
Mitry et al.	[271]	Pts with mCRC in first or second line (602 pts)		Determine predictive factors of survival in advanced CRC	Irinotecan independently associated with better survival in pts with advanced CRC		Subanalysis of 2 RCT	Low

Which combinations of chemotherapy should be considered in first- and second-line?

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
CCO	[263]	May 2005	Advanced colorectal cancer	For patients with advanced colorectal cancer receiving 5-FU-based chemotherapy as first-line therapy, the addition of bevacizumab, at a dose of 5mg/kg every two weeks, is recommended to improve overall survival in patients with no contraindications to bevacizumab. The addition of bevacizumab to 5-FU-based chemotherapy is also recommended for patients with advanced colorectal cancer receiving second-line therapy if they did not received bevacizumab as a part of their initial treatment.			
CCO	[266]	February 2003	Adult patients with metastatic colorectal cancer for whom chemotherapy is being considered as a first-line treatment	It is reasonable to offer the patient a choice between irinotecan/5-FU/LV and 5-FU/LV. Survival and response improvements with irinotecan/5-FU/LV must be alanced against the increased toxicity. Excess thrombotic events are also seen with irinotecan.			
				For patients offered irinotecan therapy, careful monitoring of adverse effects and early intervention for diarrhea should be part of the treatment process.			
CCO	[274]	January 2004	Adult pts with clinically resectable rectal cancer	It is appropriate to offer irinotecan monotherapy as second-line treatment to patients following failure of first-line treatment with infusional 5-FU/LV and oxaliplatine (Folfox), with bolus or infusional 5-FU/LV (Mayo or de Gramont schedule), with oral capecitabine or with raltitrexed.			
				Although based on non-randomized controlled trial evidence, second-line treatment with irinotecan is supported, either alone or in combination with infusional 5-FU/LV, as second-line treatment to patients following failure of first-line treatment with infusional 5-FU/LV and oxaliplatin (Folfox).			
CCO	[267]	June 2003	Adult patients with metastatic colorectal cancreceived prior chemotherapy for metastatic disease, in whom mofluoropyrimidines or other thymidylate synthase inhibitors is	In appropriate patients, standard combination chemotherapy consists in infusional 5-FU/LV with either irinotecan or oxaliplatin.			
				If this option is not reasonable, then treatment using oral capecitabine is appropriate.			
				The standard dose for capecitabine is 2500mg/m²/day in two divided doses for 14 days every three weeks.			
				As always, the choice of treatment should be based on the various system factors, patient's preferences, and convenience.			

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
			favoured				
CCO	[270]	February 2005	Adult patients with metastatic colorectal cancer for whom chemotherapy is indicated	For patients with previously untreated metastatic colorectal cancer in whom chemotherapy is indicated, a combination of 5-fluorouracil (5-FU) plus leucovorin (LV) and irinotecan is now the standard treatment regimen.			
				For patients with previously untreated metastatic colorectal cancer where monotherapy with fluoropyrimidines or other thymidylate synthase inhibitors (e.g. 5-FU/LV) or capecitabine) appears appropriate, it is reasonable to offer raltitrexed as a therapeutic option. Suitable patients would include those from whom toxicity from 5-FU is a concern or for whom the more convenient administration schedule of raltitrexed is important.			
				At this time, there is insufficient evidence to make a recommendation for or against the use of raltitrexed in patients who progress on 5-FU/LV.			
FNCLCC	[262]	2005	Metastatic colorectal cancer	Are considered as standard: the chemotherapies which improves survival without decreasing QOL or with an acceptable toxicity from randomized phase III studies.			
				Decisions must be taken after disc ussion with the patient about the toxicities and the expected benefits. The standard is to propose a continuous 5-FU based regimen, modulated by folinic acid (Type LV5-FU2), with or without irinotecan or oxaliplatin.			
				Irinotecan, oxaliplatin or raltitrexed can be proposed alone or in combination to the patients who have contra-indication to 5-FU.			
				Oral fluoropyrimidines can be proposed as alternative for the convenience.			
				The choice between the different options must be taken in function of patient's wishes, toxicity and patien's characteristics.			
				A biotherapy should be preferred for the eventually resectable patients.			
				The implantation of an implantable catheter is recommended.			
				Evaluation of the tumour response every 2 to 3 months.			
				Irinotecan versus Oxaliplatin: no argument to use preferentially Folfox or Folfiri (same results in terms of efficacy and toxicity in first-line). Folfox4 is superior to IFL.			

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				IFL-Bevacizumab is superior than IFL in terms of OS, PFS, RR, TTP.			
				The addition of bevacizumab to 5-FU/FA improves RR but not OS compared to 5-FU/FA			
NICE	[54]	March 2003	Colorectal cancer	Initial CT treatment should normally be based on either infused FUFA or an oral fluoropyrimidine. Whatever form of CT is used, patients should be given full information about its nature, possible adverse effects, and what action they should take if problems develop.			
				Palliative CT is normally given for a period of months, followed be radiological assessment of response. Intermittent use of 5-FU based CT may be as effective as continuous treatment until disease progression.			
				Oncologists should discuss second-line CT with patients whose cancer continues to progress.			
DGVS	[52]	Unsure	Colorectal cancer	First line: - De gramont - Capecitabine monotherapie - Folfiri - Folfox - In combination: if 5-FU/FA not possible intravenous: replace by capecitabine Second line: - Irinotecan Mono - Folfox - Folfiri - Cetux-Iri after progression under Irinotecan			
SIGN	[55]	January 2001	Colorectal cancer	Initial combination chemotherapy, including oxaliplatin, should be considered in patients fit for hepatic resection, but who have inoperable hepatic metastases that might become resectable on treatment			
				Bolus 5-FU regimens are not recommended as routine first-line CT for advanced disease			
				Outside a clinical trial, the choice of an appropriate regimen includes continuous infusional fluorouracil, de Gramont or capecitabine			
				Raltitrexed is not recommended as first-line therapy but may be considered as an alternative in those patients intolerant of 5-FU			

CPG ID	Ref	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
				regimens or in whom 5-FU is contraindicated due to cardiotoxicity			
				Carefully selected patients with good performance status, normal liver function tests and no evidence of GI obstruction with metastasic colorectal cancer, who have progressive disease despite treatment with 5-FU/FA, should be considered for second-line treatment with irinotecan			

Study ID	Ref	Population	Intervention	Ouctomes	Results	Comments	Study type	Level of evidence
Cunnigham 2004	[259]	Metastatic colorectal cancer refractory to irinotecan	Cetuximab and irinotecan or cetuximab monotherapy		Cetuximab has clinically significant activity when given alone or in combination with irinotecan in patients with irinotecan-refractory colorectal cancer.		RCT	High
Goldberg 2006	[321]	305 pts, previously untreated for metastatic CRC	Folfox4 vs. rIRL	TTP RR, OS, toxicity	Folfox4 superior RR, TTP and OS Benefice idem with equal use of irinotecan or oxaliplatin in 2nd line; Favourable toxicity profile for Folfox4		RCT	High
Tournigand 2006	[255]	Previously untreated metastatic CRC (620 pts)	Folfox4 vs. sequential Folfox7	PFS, OS, RR	Oxaliplatin can be safely stopped after six cycles in a Folfox regimen.		RCT	High
Hospers 2006		First-line advanced CRC	5-FU/LV/Oxaliplatin vs. bolus 5-FU/LV		Increase RR and PFS for 5-FU/LV/Oxali with less grade 3/4 mucositis/diarrea Same OS	Low cross over rate	RCT	Moderate
EORTC chronotherapy group 2006		Untreated metastatic colorectal cancer	564 pts Patients were treated every 2 weeks with intrapatient dose escalation		Both regimens achieved similar median survival times more than 18 months with an acceptable toxicity.		RCT	High

Study ID	Ref	Population	Intervention	Ouctomes	Results	Comments	Study type	Level of evidence
Fuchs 2003		Previously treated colorectal cancer	Two irinotecan regimens (once a week for 4 weeks followed by a 2-week rest period [weekly] vs. once every 3 weeks)		Irinotecan schedules of weekly and of once every 3 weeks demonstrated similar efficacy and quality		RCT	High
Gibson 2006		Patients with previously untreated metastatic CRC	Panitumumab as a single agent vs. best supportive care	OS	46% reduction in the risk of tumour progression and partial response rate of 8%.		RCT	High
Goldberg 2006		305 pts previously untreated mCRC	Folfox4 versus rIFL	TTP RR, OS, toxicity	Folfox4 superior to rIFL in RR, TTP and OS	Comparable?	RCT	
Souglakos 2006		283 chemonaive CRC patients	FOLFOXIRI vs. FOLFIRI as first line	OS, toxicity	No difference		RCT	High
Hurwitz 2005		Previously untreated metastatic CRC 923 pts	3 arms: IFL, FU/LV/BV, IFL/BV	Efficacy and safety of FU/LV/BV regimen compared to IFL regimen			RCT	High
Folprecht 2004	[265]	3825 elderly pts with metastatic CRC	5-FU-based CT	OS, RR, PFS	Equal in elderly pts and younger patients Infusional 5-FU more effective than bolus in both age groups		Pooled analysis of RCTs	High
Kabbinavar 2005	[268]	490 pts with previously untreated mCRC	FU/LV vs. IFL and FU/LV/Beva	RR, PFS, OS	The addition of bevacizumab gives a statistically significant and clinically relevant benefit		Analysis from 3 RCT	High
Au 2003	[264]	Elderly patients with CRC	Management of colorectal cancer in elderly patients		Patients of 80 have same OS benefit with palliative first-line monotherapy (5-FU) as younger patients Increased toxicity with bolus 5-FU regimens		SR	High

What is the management of isolated peritoneal carcinomatosis

Study ID	Ref	Population	Intervention	Ouctomes	Results	Comments	Study type	Level of evidence
Verwaal 2003	[280]	Patients with peritoneal carcinomatosis of colorectal cancer.	Standard treatment consisting of systemic chemotherapy (fluorouracil-leucovorin) with or without palliative surgery vs. experimental therapy consisting of aggressive cytoreduction with HIPEC, followed by the same systemic chemotherapy regimen.	Survival	Cytoreduction followed by HIPEC improves survival in patients with peritoneal carcinomatosis of colorectal origin. However, patients with involvement of six or more regions of the abdominal cavity, or grossly incomplete cytoreduction, had still a grave prognosis.		RCT	Low
Yan TD 2006	[276]	Pts with peritoneal carcinomatosis from colorectal origin confirmed by pathologic examination	Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy	OS	Improved survival as compared with systemic CT	Low level of evidence in 13/14 studies	SR	Low

Has follow-up an impact on survival and quality of life in patients curatively treated for rectal cancer?

CPG ID	Ref	Search date	Population	Recommendations	Supporting Evidence	Comments	Level of evidence
ASCO	[225]	June 2005	CRC patients	More Intensive follow-up is recommended because of survival benefit	3 meta-analysis of RCT (1 MA of 6 RCT's, 2 MA of 5 RCT's)		High
CCO	[74]	January 2004	Adult patients with curatively resected colorectal cancer	Patients should be alerted to the future risk of disease recurrence, which is related to tumour stage, and to the development of a second colorectal cancer. There is evidence of a small survival benefit with more intensive follow-up compared to less intensive follow-up.	1 meta-analysis of 4 non randomized studies 1 meta-analysis that included two randomized trials and three non-randomized comparative cohort studies 2 meta-analysis who examined the same 5 RCT's		Moderate
SIGN	[55]	January 2001	Colorectal cancer	Formal follow-up in order to facilitate the early detection of metastatic disease	5 RCT's , 2 meta-analyses, 1 cohort study	Individual randomised trials show no advantage of follow-up measured by survival. Meta-analyses indicate that follow-up can offer survival benefit by means of earlier detection of metastatic disease	Moderate
ACS	[227]	January 2005	Colorectal cancer	Endoscopic surveillance	RCT's and cohort studies	No survival benefit from the original primary tumour by performing colonoscopy at annual or shorter intervals.	Moderate
DGVS	[52]	Unsure	Colorectal cancer	Surveillance is indicated for UICC stadium II and III	6 meta-analyses and 6 RCT's	In CRC stadium UICC I is FU not recommended (in case of Ro-resection, low recurrence rate and good prognosis)	High
CCO	[68]	September 2004	CRC patients stage IIb and III	Follow-up is recommended	6 RCT's		High
NICE	[54]	March 2003	Colorectal cancer	Decrease in mortality due to intensive follow-up	4 systematic reviews, 1 RCT	Not clear which elements of the follow-up programme are important	High

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Jeffrey 2007	[322]	CRC patients	Intensive follow-up vs. less intensive follow-up	Survival Quality of life	Higher survival rates Small increase in QoL associated with more frequent follow-up visits	Weighted mean difference for the time to recurrence was significantly reduced No difference in disease free survival	Systematic review (Cochrane) of 5 RCT's	High
Rodriguez-Moranta 2006	[226]	259 stage II and III RC patients	Intensive follow-up (Physical examination, CEA, Liver imaging, chest x-ray, colonoscopy) vs. less intensive follow-up (Physical examination and CEA)	Overall survival	Higher OS with intensive follow-up. In patients with stage II CRC HR=0.34, 95% CI 0.12 to 0.98 P=0.045. Patients with rectal lesions HR=0.09 95% CI 0.01 to 0.81 p=0.03.	44% of the resectable recurrences were detected by colonoscopy	RCT	High

Which clinical, biochemical or technical investigations have to be done in terms of local recurrence, distance recurrence and resectability of recurrence in patients curatively treated for rectal cancer?

CPG ID	Ref	Search date	Population	Recommendations	Supporting Evidence	Comments	Level of evidence
ASCO	[225]	June 2005	CRC patients	CT scanning should not be routinely ordered in patients who would or could not undergo curative liver or pulmonary resection.	3 meta-analysis of RCT's (1 MA of 6 RCT's, 2 MA of 5 RCT's)		High
				Pelvic CT scan is recommended only for patients with several poor prognostic factors, including those who have not been treated with radiation.			
				Flexible proctosigmoidoscopy is only recommended for patients who have not been treated with radiation.			
				Routine blood tests and laboratory derived prognostic and predictive factors are not recommended.			
				Fecal occult blood test is not recommended.			
				Chest X-ray is not recommended.			

CPG ID	Ref	Search date	Population	Recommendations	Supporting Evidence	Comments	Level of evidence
CCO	[74]	January 2004	Adult patients with curatively resected colorectal cancer	Patients have to be fit and willing to undergo investigations and treatment	1 meta-analysis of 4 non randomized studies 1 meta-analysis that included two randomized trials and three non-randomized comparative cohort studies 2 meta-analysis who examined the same 5 RCT's		Moderate
				When recurrences of disease are detected, patients should be assessed by a multidisciplinary oncology team including surgical, radiation, and medical oncologists to determine the best treatment options.			
SIGN	[55]	January 2001	Colorectal cancer	There is no evidence that FOBT is of any value in follow-up	5 RCT's , 2 meta-analyses, 1 cohort study		Moderate
				As carried out for adenomatous polyps; when there is suspicion of local recurrence			
ACS	[227]	January 2005	Colorectal cancer	Performance of fecal occult blood test is discouraged in patients undergoing colonoscopic surveillance.	RCT's and cohort studies		Moderate
				Discontinuation of surveillance colonoscopy should be considered in persons with advanced age or comorbidities (-10 years life expectancy), according to the clinician's judgment.			
				Chromoendoscopy and magnification endoscopy are not established as essential to screening or surveillance.			
				Computed tomography colonography (virtual colonoscopy) is not established as a surveillance modality.			
DGVS	[52]	Unsure	Colorectal cancer	Chest X-ray is not recommended.	6 meta-analyses and 6 RCT's		High
				Routine blood examination (liverfunctiontests) and FOBT are not recommended.			
				Endoscopic ultrasound is a good tool for diagnosing local recurrence but is not recommended in routine follow-up.			

CPG ID	Ref	Search date	Population	Recommendations	Supporting Evidence	Comments	Level of evidence
				Barium enema, virtual colonoscopy and PET scan are not recommended.			
				CT is not recommended in routine follow-up, only in patients with rectal cancer and postoperatively			
CCO	[68]	September 2004	CRC patients stage IIb and III	CT or MRI are indicated following a changing clinical picture or rising biochemical markers (i.e., carcinoembryonic antigen) for patients with rectal cancer.	6 RCT's		High
				There is no evidence of a marked difference between CT and MRI for detecting recurrence though MRI imaging is more useful due to a higher theoretical ability to differentiate scar tissue from recurrence.			
				Ultrasound is less accurate versus CT or MRI at predicting liver metastases at presentation. This is likely also true for liver metastases that develop after curative surgery. As well, ultrasound is unable to assess for recurrent pelvic disease following rectal or sigmoid surgery.			
NICE	[54]	March 2003	Colorectal cancer	CT in routine follow-up is useful.	2 systematic reviews, 1 meta-analysis, 4 RCT's, 2 cohort studies	Detection of more asymptomatic livermetastases but no increase in number of curative hepatectomies	Moderate

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Jeffrey 2007	[322]	CRC patients	Intensive follow-up vs. less intensive follow-up		The exact details of the optimal follow-up regimen still need clarification	Due to the heterogeneity between the studies	Systematic review (Cochrane) of 5 RCT's	High
Rodriguez-Moranta 2006	[226]	259 stage II and III RC patients	Intensive follow-up (Physical examination, CEA, Liver imaging, chest x-ray, colonoscopy) vs. less intensive follow-up (Physical examination and CEA)	Recurrence Resectability (recurrence amenable to curative-intent surgery)	Recurrence: *Intensive fu* 27% - 11% metachronous - 32% locoregional - 57% distant metastases *Less intensive fu* 26% - 6% metachronous - 38% locoregional - 56% distant metastases		RCT	High

How frequently and until how long clinical, biochemical or technical investigations have to be done in terms of local recurrence, distance recurrence and resectability of recurrence in patients curatively treated for rectal cancer?

CPG ID	Ref	Search date	Population	Recommendations	Supporting Evidence	Comments	Level of evidence
ASCO	[225]	June 2005	CRC patients	History + physical examination every 3 to 6 months first 3 years, every 6 months during years 4 and 5.	3 meta-analyses of RCT (1 MA of 6 RCT, 2 MA of 5 RCT)	No formal studies but necessary to determine symptoms, to coordinate follow-up and to offer counselling.	High
				CEA every 3 months for at least 3 years after diagnosis.			
				Annual CT of chest and abdomen first 3 years.		No meta-analyses addressed chest CT surveillance specifically, 3 reasons why it is included: - the largest proportion of resectable recurrences were found on thoracic CT - pulmonary recurrences are less likely to have elevated CEA tests - lung recurrences are as common as liver relapse in rectal cancer	
				Pelvic CT scan annually during the first 3 years, only for patients with several poor prognostic factors, including those who have not been treated with radiation.			
				Colonoscopy pre- or perioperatively, 3 years after surgery and then if normal every 5 years.			
				Flexible procto-sigmoidoscopy every 6 months for 5 years, only if the patient did not receive pelvic radiation.			
CCO	[74]	January 2004	Adult patients with curatively resected colorectal cancer	Clinical assessment when symptoms occur or at least every six months the first three years and yearly for at least five years.	1 meta-analysis of 4 non randomized studies 1 meta-analysis that included two randomized trials and three non-randomized comparative cohort studies 2 meta-analysis who examined the same 5 RCT's		Moderate
				CEA, chest X-ray, liver ultrasound should be done during the same visits of clinical assessment.			
				Colonoscopy before or within six months			

CPG ID	Ref	Search date	Population	Recommendations	Supporting Evidence	Comments	Level of evidence
				of initial surgery, repeated yearly if villous or tubular adenomas >1 cm are found; otherwise, repeat every three to five years.			
SIGN	[55]	January 2001	Colorectal cancer	Not mentioned			
ACS	[227]	January 2005	Colorectal cancer	Colonoscopy should be done preoperative, 1 year after the resection (or 1year following the performance of the colonoscopy that was performed to clear the colon of synchronous disease). If the examination performed at 1 year is normal, then the interval before the next subsequent examination should be 3 years. If that colonoscopy is normal, then the interval before the next subsequent examination should be 5 years.	RCT's and cohort studies		Moderate
				Rigid proctoscopy, flexible proctoscopy, or rectal endoscopic ultrasound at 3- to 6-month intervals for the first 2 or 3 years.			
DGVS	[52]	Unsure	Colorectal cancer	History + physical examination every 6 months during 2 years, than yearly until 5 years.	6 meta-analyses and 6 RCT's		High
				CEA every 6 months during 2 years, than yearly until 5 years.			
				Colonoscopy preoperatively or within 6 months after operation, thereafter after 3 and 5 years.			
				Flexible procto-sigmoidoscopy every 6 months during the first 2 years			
				Liver ultrasound every 6 months during 2 years, than yearly until 5 years.		Only in patients with rectal cancer UICC stadium II or III who did not receive neoadjuvant or adjuvant CRT	
				Spiral CT chest, abdomen and pelvis 3 months postoperatively.		Only for patients with rectal cancer and before starting adjuvant therapy	

CPG ID	Ref	Search date	Population	Recommendations	Supporting Evidence	Comments	Level of evidence
						(as a starting point)	
CCO	[68]	September 2004	CRC patients stage IIb and III	Clinical assessment is recommended when symptoms occur or at least every six months for the first three years and yearly for at least five years.	6 RCT's		High
				Ultrasound abdomen at 6, 18 and 30 months.			
				Abdominal CT or MRI yearly for at least 5 years.			
				Clinical assessment when symptomatic or yearly.			
				Colonoscopy pre-operatively or within 6 months after operation.			
NICE	[54]	March 2003	Colorectal cancer	Frequency of examinations is not mentioned	2 systematic reviews, 1 meta-analysis, 4 RCT's, 2 cohort studies		Moderate

Study ID	Ref	Population	Intervention	Outcomes	Results	Comments	Study type	Level of evidence
Rodriguez-Moranta 2006	[226]	259 stage II and III RC patients	Intensive follow-up (Physical examination, CEA, Liver imaging, chest x-ray, colonoscopy) vs. less intensive follow-up (Physical examination and CEA)	Recurrence Resectability (recurrence amenable to curative-intent surgery)	Recurrence: *Intensive fu* 27% - 11% metachronous - 32% locoregional - 57% distant metastases *Less intensive fu* 26% - 6% metachronous - 38% locoregional - 56% distant metastases		RCT	High

5 REFERENCES

1. Stichting Kankerregister. *Kanker in België 2003.* Available from: http://www.kankerregister.org.
2. Capet, F., et al., *Colorectale kanker: huidige toestand en bijdrage van informatie voor het opbouwen van een gezondheidsbeleid.* 1999, CROSP Wetenschappelijk Instituut Volksgezondheid, Administratie Gezondheidszorg. Ministerie van de Vlaamse Gemeenschap.
3. Hewitt, M. and J.V. Simone, *Ensuring Quality Cancer Care.* 1999: National Academy Press.
4. O'Malley, A.S., et al., *Clinical practice guidelines and performance indicators as related–but often misunderstood–tools.* Jt Comm J Qual Saf, 2004. **30**(3): p. 163-71.
5. McGory, M.L., P.G. Shekelle, and C.Y. Ko, *Development of quality indicators for patients undergoing colorectal cancer surgery.* J Natl Cancer Inst, 2006. **98**(22): p. 1623-33.
6. Walter, L.C., et al., *Pitfalls of converting practice guidelines into quality measures: lessons learned from a VA performance measure.* JAMA, 2004. **291**(20): p. 2466-70.
7. Beauduin, M., et al., *The management of rectal cancer in Belgium: a survey of our practice.* Acta Gastroenterol Belg, 2004. **67**(1): p. 9-13.
8. Penninckx, F., *Surgeon-related aspects of the treatment and outcome after radical resection for rectal cancer.* Acta Gastroenterol Belg, 2001. **64**(3): p. 258-62.
9. Penninckx, F., et al., *Survival of rectal cancer patients in Belgium 1997-98 and the potential benefit of a national project.* Acta Chir Belg, 2006. **106**(2): p. 149-57.
10. Beets-Tan, R.G., et al., *Accuracy of magnetic resonance imaging in prediction of tumour-free resection margin in rectal cancer surgery.* Lancet, 2001. **357**(9255): p. 497-504.
11. Brown, G., et al., *Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging.* Br J Surg, 2003. **90**(3): p. 355-64.
12. Penninckx, F. and E. Danse, *On the role of radiologists in the Belgian PROject on CAncer of the REctum, PROCARE.* Jbr-Btr, 2006. **89**(1): p. 19-22.
13. Hermanek, P. and P.J. Hermanek, *Role of the surgeon as a variable in the treatment of rectal cancer.* Semin Surg Oncol, 2000. **19**(4): p. 329-35.
14. Kapiteijn, E. and C.J. van de Velde, *Developments and quality assurance in rectal cancer surgery.* Eur J Cancer, 2002. **38**(7): p. 919-36.
15. Wexner, S.D. and N.A. Rotholtz, *Surgeon influenced variables in resectional rectal cancer surgery.* Dis Colon Rectum, 2000. **43**(11): p. 1606-27.
16. Sobin, L.H., C. Wittekind, and International Union Against Cancer (UICC), *TNM classification on malignant tumours.* 5th Ed. 1997, New York: Wiley-Liss Publications.
17. Radice, E. and R.R. Dozois, *Locally recurrent rectal cancer.* Dig Surg, 2001. **18**(5): p. 355-62.
18. Beattie, G.C., et al., *Improvement in quality of colorectal cancer pathology reporting with a standardized proforma–a comparative study.* Colorectal Dis, 2003. **5**(6): p. 558-62.
19. Nagtegaal, I.D. and J.H. van Krieken, *The role of pathologists in the quality control of diagnosis and treatment of rectal cancer-an overview.* Eur J Cancer, 2002. **38**(7): p. 964-72.
20. Edge, S.B., D.L. Cookfair, and N. Watroba, *The role of the surgeon in quality cancer care.* Curr Probl Surg, 2003. **40**(9): p. 511-90.
21. Hodgson, D.C., et al., *Relation of hospital volume to colostomy rates and survival for patients with rectal cancer.* J Natl Cancer Inst, 2003. **95**(10): p. 708-16.

22. Meyerhardt, J.A., et al., *Impact of hospital procedure volume on surgical operation and long-term outcomes in high-risk curatively resected rectal cancer: findings from the Intergroup 0114 Study.* J Clin Oncol, 2004. **22**(1): p. 166-74.

23. Porter, G.A., et al., *Surgeon-related factors and outcome in rectal cancer.* Ann Surg, 1998. **227**(2): p. 157-67.

24. Rabeneck, L., et al., *Surgical volume and long-term survival following surgery for colorectal cancer in the Veterans Affairs Health-Care System.* Am J Gastroenterol, 2004. **99**(4): p. 668-75.

25. Schrag, D., et al., *Hospital and surgeon procedure volume as predictors of outcome following rectal cancer resection.* Ann Surg, 2002. **236**(5): p. 583-92.

26. Schrag, D., et al., *Surgeon volume compared to hospital volume as a predictor of outcome following primary colon cancer resection.* J Surg Oncol, 2003. **83**(2): p. 68-78.

27. Wibe, A., et al., *Effect of hospital caseload on long-term outcome after standardization of rectal cancer surgery at a national level.* Br J Surg, 2005. **92**(2): p. 217-24.

28. Harling, H., et al., *Hospital volume and outcome of rectal cancer surgery in Denmark 1994-99.* Colorectal Dis, 2005. **7**(1): p. 90-5.

29. Smith, J.A., et al., *Evidence of the effect of 'specialization' on the management, surgical outcome and survival from colorectal cancer in Wessex.* Br J Surg, 2003. **90**(5): p. 583-92.

30. Martling, A., et al., *Impact of a surgical training programme on rectal cancer outcomes in Stockholm.* Br J Surg, 2005. **92**(2): p. 225-9.

31. McArdle, C.S. and D.J. Hole, *Influence of volume and specialization on survival following surgery for colorectal cancer.* Br J Surg, 2004. **91**(5): p. 610-7.

32. Holm, T., et al., *Influence of hospital- and surgeon-related factors on outcome after treatment of rectal cancer with or without preoperative radiotherapy.* Br J Surg, 1997. **84**(5): p. 657-63.

33. Dowdall, J.F., D. Maguire, and O.J. McAnena, *Experience of surgery for rectal cancer with total mesorectal excision in a general surgical practice.* Br J Surg, 2002. **89**(8): p. 1014-9.

34. Smedh, K., et al., *Reduction of postoperative morbidity and mortality in patients with rectal cancer following the introduction of a colorectal unit.* Br J Surg, 2001. **88**(2): p. 273-7.

35. Seow-Choen, F., *Adjuvant therapy for rectal cancer cannot be based on the results of other surgeons.* Br J Surg, 2002. **89**(8): p. 946-7.

36. Dominitz, J.A., et al., *Race, treatment, and survival among colorectal carcinoma patients in an equal-access medical system.* Cancer, 1998. **82**(12): p. 2312-20.

37. Dignam, J.J., et al., *Outcomes among African-Americans and Caucasians in colon cancer adjuvant therapy trials: findings from the National Surgical Adjuvant Breast and Bowel Project.* J Natl Cancer Inst, 1999. **91**(22): p. 1933-40.

38. Boyd, C., et al., *Associations between community income and cancer survival in Ontario, Canada, and the United States.* J Clin Oncol, 1999. **17**(7): p. 2244-55.

39. Gorey, K.M., et al., *An international comparison of cancer survival: Toronto, Ontario, and Detroit, Michigan, metropolitan areas.* Am J Public Health, 1997. **87**(7): p. 1156-63.

40. Ramsey, S.D., et al., *Quality of life in survivors of colorectal carcinoma.* Cancer, 2000. **88**(6): p. 1294-303.

41. Porter, G.A. and J.M. Skibber, *Outcomes research in surgical oncology.* Ann Surg Oncol, 2000. **7**(5): p. 367-75.

42. Gagliardi, A.R., et al., *Development of quality indicators for colorectal cancer surgery, using a 3-step modified Delphi approach.* Can J Surg, 2005. **48**(6): p. 441-52.

43. Fervers, B., et al., *Adaptation of clinical guidelines: literature review and proposition for a framework and procedure.* Int J Qual Health Care, 2006. **18**(3): p. 167-76.

44. Guyatt, G., et al., *Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force.* Chest, 2006. **129**(1): p. 174-81.

45. Kapiteijn, E., et al., *Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer.* New Engl J Med, 2001. **345**: p. 638-646.

46. Ross, H.M., N. Mahmoud, and R.D. Fry, *The current management of rectal cancer.* Curr Probl Surg, 2005. **42**(2): p. 72-131.

47. Sebag-Montefiore, D., et al., *Routine short course pre-op radiotherapy or selective post-op chemoradiotherapy for resectable rectal cancer? Preliminary results of the MRC CR07 randomised trial.* Journal of Clinical Oncology. ASCO Annual Meeting Proceedings Part I., 2006. **24**(18S): p. 3511.

48. American Joint Committee on Cancer, *Cancer staging handbook.* 5th Ed. 1998: Lippincott-Raven.

49. Ueno, H., et al., *Risk factors for an adverse outcome in early invasive colorectal carcinoma.* Gastroenterology, 2004. **127**(2): p. 385-94.

50. Roels, S., et al., *Definition and delineation of the clinical target volume for rectal cancer.* Int J Radiat Oncol Biol Phys, 2006. **65**(4): p. 1129-42.

51. ACPGBI, *Guidelines for the management of colorectal cancer.* 2001, The Association of Coloproctology of Great Britain and Ireland.

52. Schmiegel, W., et al., *[S3-guideline conference "Colorectal Cancer" 2004].* Dtsch Med Wochenschr, 2005. **130 Suppl 1**: p. S5-53.

53. Barillari, P., et al., *Effect of preoperative colonoscopy on the incidence of synchronous and metachronous neoplasms.* Acta Chir Scand, 1990. **156**(2): p. 163-6.

54. NICE, *Guidance on Cancer Services. Improving outcomes in colorectal cancers.* 2004, National Institute for Clinical Excellence.

55. SIGN, *Management of colorectal cancer: a national clinical guideline*. 2003, Scottish Intercollegiate Guidelines Network (SIGN).

56. Halligan, S., et al., *CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting.* Radiology, 2005. **237**(3): p. 893-904.

57. Mulhall, B.P., G.R. Veerappan, and J.L. Jackson, *Meta-analysis: computed tomographic colonography.* Ann Intern Med, 2005. **142**(8): p. 635-50.

58. Locker, G.Y., et al., *ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer.* J Clin Oncol, 2006. **24**(33): p. 5313-27.

59. Lazorthes, F., et al., *[Therapeutic management of hepatic metastases from colorectal cancers].* Gastroenterol Clin Biol, 2003. **27 Spec No 2**: p. B7.

60. Bipat, S., et al., *Colorectal liver metastases: CT, MR imaging, and PET for diagnosis–meta-analysis.* Radiology, 2005. **237**(1): p. 123-31.

61. Bentrem, D.J., et al., *T1 adenocarcinoma of the rectum: transanal excision or radical surgery?* Ann Surg, 2005. **242**(4): p. 472-7.

62. Mellgren, A., et al., *Is local excision adequate therapy for early rectal cancer?* Dis Colon Rectum, 2000. **43**(8): p. 1064-71.

63. Nascimbeni, R., et al., *Long-term survival after local excision for T1 carcinoma of the rectum.* Dis Colon Rectum, 2004. **47**(11): p. 1773-9.

64. You, Y., et al., *Is Local Excision Adequate For T1 Rectal Cancer? A Nationwide Cohort Study From The National Cancer Database (NCDB).* J Clin Oncol, 2005. **23**(16S): p. 3526.

65. Worrell, S., et al., *Endorectal ultrasound detection of focal carcinoma within rectal adenomas.* Am J Surg, 2004. **187**(5): p. 625-9.

66. Kwok, H., I.P. Bissett, and G.L. Hill, *Preoperative staging of rectal cancer.* Int J Colorectal Dis, 2000. **15**(1): p. 9-20.

67. Will, O., et al., *Diagnostic precision of nanoparticle-enhanced MRI for lymph-node metastases: a meta-analysis.* Lancet Oncol, 2006. **7**(1): p. 52-60.

68. Simunovic, M., et al., *Cross-Sectional Imaging in Colorectal Cancer. Recommendations Report.* 2006, Cancer Care Ontario.

69. Lahaye, M.J., et al., *Imaging for predicting the risk factors–the circumferential resection margin and nodal disease–of local recurrence in rectal cancer: a meta-analysis.* Semin Ultrasound CT MR, 2005. **26**(4): p. 259-68.

70. *Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study.* Bmj, 2006. **333**(7572): p. 779.

71. Fuchsjager, M.H., et al., *Comparison of transrectal sonography and double-contrast MR imaging when staging rectal cancer.* AJR Am J Roentgenol, 2003. **181**(2): p. 421-7.

72. Burton, S., et al., *MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins?* Br J Cancer, 2006. **94**(3): p. 351-7.

73. Knaebel, H.P., et al., *Diagnostics of rectal cancer: endorectal ultrasound.* Recent Results Cancer Res, 2005. **165**: p. 46-57.

74. Figueredo, A., et al., *Follow-up of Patients with Curatively Resected Colorectal Cancer. Practice Guideline Report #2-9.* 2004, Cancer Care Ontario.

75. Bosset, J.-F., et al., *Chemotherapy with preoperative radiotherapy in rectal cancer.* N Engl J Med, 2006. **355**(11): p. 1114-23.

76. Gerard, J.P., et al., *Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203.* J Clin Oncol, 2006. **24**(28): p. 4620-5.

77. Marijnen, C.A., et al., *Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial.* J Clin Oncol, 2002. **20**(3): p. 817-825.

78. Marijnen, C.A., et al., *Radiotherapy does not compensate for positive resection margins in rectal cancer patients: report of a multicenter randomized trial.* Int J Radiat Oncol, 2003. **55**: p. 1311-1320.

79. Marijnen, C.A., et al., *No downstaging after short-term preoperative radiotherapy in rectal cancer patients.* J Clin Oncol, 2001. **19**: p. 1976-1984.

80. Marijnen, C.A., et al., *Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial.* J Clin. Oncol, 2005. **23**: p. 1847-1858.

81. Quirke, P., et al., *Local recurrence after rectal cancer resection is strongly related to the plane of surgical dissection and is further reduced by pre-operative short course radiotherapy. Preliminary results of the Medical Research Council (MRC) CR07 trial.* 2006. **24**(18S): p. 3512.

82. Sauer, R., et al., *Preoperative versus postoperative radiochemotherapy for rectal cancer.* N Engl J Med, 2004. **351**: p. 1731-1740.

83. Bosset, J.F., et al., *Determination of the optimal dose of 5-fluorouracil when combined with low dose D,L-leucovorin and irradiation in rectal cancer: results of three consecutive phase II studies.* Eur J Cancer, 1993. **29A**(10): p. 1406-1410.

84. Lokich, J.J., et al., *A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program Study.* J Clin Oncol, 1989. **7**(4): p. 425-32.

85. Rich, T.A., et al., *Preoperative infusional chemoradiation therapy for stage T3 rectal cancer.* Int J Radiat Oncol Biol Phys, 1995. **32**(4): p. 1025-1029.

86. O'Connell, M.J., et al., *Improving adjuvant therapy for rectal cancer by combining protracted-infusion Fluorouracil with radiation therapy after curative surgery.* N Engl J Med, 1994. **331**: p. 502–7.

87. Kim, J.S., et al., *Comparison of the efficacy of oral capecitabine versus bolus 5-FU in preoperative radiotherapy of locally advanced rectal cancer.* J Korean Med Sci, 2006. **21**(1): p. 52-7.

88. Kim, N.K., et al., *Intravenous 5-fluorouracil versus oral doxifluridine as preoperative concurrent chemoradiation for locally advanced rectal cancer: prospective randomized trials.* Jpn J Clin Oncol, 2001. **31**(1): p. 25_29.

89. Bujko, K., et al., *Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer.* British Journal of Surgery, 2006. **93**: p. 1215–1223.

90. Francois, Y., et al., *Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial.* J Clin Oncol, 1999. **17**: p. 2396-2402.

91. Gerard, J.P., et al., *Improved sphincter preservation in low rectal cancer with high dose preoperative radiotherapy: the LYON R96-02 randomized trial.* J Clin Oncol, 2004. **22**: p. 2404-2409.

92. Vuong, T., et al., *Conformal preoperative endorectal brachytherapy treatment for locally advanced rectal cancer: early results of a phase I/II study.* Dis Colon Rectum, 2002. **45**(11): p. 1486-93.

93. Ahmad, N.R., G. Marks, and M. Mohiuddin, *High-dose preoperative radiation for cancer of the rectum: Impact of radiation dose on patterns of failure and survival.* Int J Radiat Oncol Biol Phys, 1993. **27**: p. 773–778.

94. Chan, A.J.P., A.O.W.a.J. Langevin, and et al., *Preoperative chemotherapy and pelvic radiation for tethered or fixed rectal cancer: A Phase II dose escalation study.* Int J Radiat Oncol Biol Phys, 2000. **48**: p. 843–856.

95. Janjan, N.A., C.N.C.a.B.W. Feig, and et al., *Prospective trial of preoperative concomitant boost radiotherapy with continuous infusion 5-fluorouracil for locally advanced rectal cancer.* Int J Radiat Oncol Biol Phys, 2000. **47**: p. 713–718.

96. Mohiuddin, M., W.F.R.a.W.J. John, and et al., *Preoperative chemoradiation in fixed distal rectal cancer: Dose time factors for pathological complete response.* Int J Radiat Oncol Biol Phys, 2000. **46**: p. 883–888.

97. Movsas, B., et al., *Phase I dose escalating trial of hyperfractionated pre-operative chemoradiation for locally advanced rectal cancer.* Int J Radiat Oncol Biol Phys., 1998. **42**(1): p. 43-50.

98. Myerson, R.J., et al., *A phase I/II trial of three-dimensionally planned concurrent boost radiotherapy and protracted venous infusion of 5-FU chemotherapy for locally advanced rectal carcinoma.* Int J Radiat Oncol Biol Phys, 2001. **50**: p. 1299–1308.

99. Freedman, G.M., et al., *Phase I trial of preoperative hypofractionated intensity-modulated radiotherapy with incorporated boost and oral capecitabine in locally advanced rectal cancer.* Int J Radiat Oncol Biol Phys, 2007. **67**(5): p. 1389-93.

100. Kim, J.Y., et al., *Intensity-modulated radiotherapy with a belly board for rectal cancer.* Int J Colorectal Dis., 2007. **22**(4): p. 373-9.

101. Andreola, S., et al., *Adenocarcinoma of the lower third of the rectum: metastases in lymph nodes smaller than 5 mm and occult micrometastases; preliminary results on early tumor recurrence.* Ann Surg Oncol., 2001. **8**(5): p. 413-7.

102. Oberg, A., et al., *Are lymph node micrometastases of any clinical significance in Dukes Stages A and B colorectal cancer?* Dis Colon Rectum., 1998. **41**(10): p. 1244-9.

103. Perez, R.O., et al., *Lymph node micrometastasis in stage II distal rectal cancer following neoadjuvant chemoradiation therapy.* Int J Colorectal Dis., 2005(5): p. 434-9.

104. Habr-Gama, A., et al., *Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy.* J Gastrointest Surg., 2006. **10**(10): p. 1319-28.

105. Bosset, J.F., et al., *Preoperative chemoradiotherapy versus preoperative radiotherapy in rectal cancer patients: assessment of acute toxicity and treatment compliance. Report of the 22921 randomised trial conducted by the EORTC Radiotherapy Group.* Eur J Cancer, 2004. **40**: p. 219–24.

106. Bosset, J.F., et al., *Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results--EORTC 22921.* J Clin Oncol, 2005. **23**(24): p. 5620-7.

107. Bujko, K., et al., *Does rectal cancer shrinkage induced by preoperative radio(chemo)therapy increase the likelihood of anterior resection? A systematic review of randomised trials.* Radiother Oncol. Epub, 2006. **80**(1): p. 4-12.

108. Bujko, K., et al., *Postoperative complications in patients irradiated pre-operatively for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs chemoradiation.* Colorectal Dis, 2005. **7**(4): p. 410-416.

109. Bujko, K., et al., *Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomized trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy.* Radiother Oncol, 2004. **72**: p. 15-24.

110. Bedrosian, I., et al., *Predicting the node-negative mesorectum after preoperative chemoradiation for locally advanced rectal carcinoma.* J Gastrointest Surg, 2004. **8**(1): p. 56-62.

111. Benzoni, E., et al., *The predictive value of clinical evaluation of response to neoadjuvant chemoradiation therapy for rectal cancer.* Tumor, 2005. **91**(5): p. 401-5.

112. Bernini, A., et al., *Preoperative adjuvant radiation with chemotherapy for rectal cancer: its impact on stage of disease and the role of endorectal ultrasound.* Ann Surg Oncol, 1996. **3**: p. 131–135.

113. Calvo, F.A., et al., *18F-FDG positron emission tomography staging and restaging in rectal cancer treated with preoperative chemoradiation.* Int J Radiat Oncol Biol Phys, 2004. **58**(2): p. 528-35.

114. Capirci, C., et al., *Restaging after neoadjuvant chemoradiotherapy for rectal adenocarcinoma: role of F18-FDG PET.* Biomed Pharmacother, 2004. **58**(8): p. 451-7.

115. Capirci, C., et al., *Long-term prognostic value of 18F-FDG PET in patients with locally advanced rectal cancer previously treated with neoadjuvant radiochemotherapy.* Ajr, 2006. **187**: p. 20220.

116. Chen, C.C., et al., *How Accurate is Magnetic Resonance Imaging in Restaging Rectal Cancer in Patients Receiving Preoperative Combined Chemoradiotherapy?* Dis Colon Rectum, 2005. **48**: p. 722-728.

117. Fleshman, J.W., et al., *Accuracy of transrectal ultrasound in predicting pathologic stage of rectal cancer before and after preoperative radiation therapy.* Dis Colon Rectum, 1992. **35**(9): p. 823-9.

118. Gavioli, M., et al., *Usefulness of endorectal ultrasound after preoperative radiotherapy in rectal.* Dis Colon Rectum, 2000. **43**(8): p. 1075-83.

119. Guillem, J.G., et al., *Clinical examination following preoperative chemoradiation for rectal cancer is not a reliable surrogate end point.* J Clin Oncol., 2005. **23**(15): p. 3475-9.

120. Hiotis, S.P., et al., *Assessing the predictive value of clinical complete response to neoadjuvant therapy for rectal cancer: an analysis of 488 patients.* J Am Coll Surg, 2002. **194**(2): p. 131-5 discussion 135-6.

121. Houvenaeghel, G., et al., *Staging of rectal cancer: a prospective study of digital examination and endosonography before and after preoperative radiotherapy.* Acta Chir Belg, 1993. **93**(4): p. 164-8.

122. Kahn, H., et al., *Preoperative staging of irradiated rectal cancers using digital rectal examination, computed tomography, endorectal ultrasound, and magnetic resonance imaging does not accurately predict T0,N0 pathology.* Dis Colon Rectum, 1997. **40**(2): p. 140-4.

123. Kuo, L.J., et al., *Interpretation of magnetic resonance imaging for locally advanced rectal carcinoma after preoperative chemoradiation therapy.* Dis Colon Rectum, 2005. **48**(1): p. 23-28.

124. Liersch, T., et al., *Präoperative Diagnostik beim lokal fortgeschrittenen Rektumkarzinom (= T3 oder N+).* Chirurg, 2003. **74**: p. 224-234.

125. Maor, Y., et al., *Endoscopic ultrasound staging of rectal cancer: diagnostic value before and following chemoradiation.* J Gastroenterol Hepatol, 2006. **21**: p. 454-458.

126. Romagnuolo, J., et al., *Predicting residual rectal adenocarcinoma in the surgical specimen after preoperative brachytherapy with endoscopic ultrasound.* Can J Gastroenterol, 2004. **18**(7): p. 435-40.

127. Vanagunas, A., D.E. Lin, and S.J. Stryker, *Accuracy of endoscopic ultrasound for restaging rectal cancer following neoadjuvant chemoradiation therapy.* Am J Gastroenterol, 2004. **99**(1): p. 109-12.

128. Williamson, P.R., et al., *Endorectal ultrasound of T3 and T4 rectal cancers after preoperative chemoradiation.* Dis Colon Rectum, 1996. **39**: p. 45–49.

129. Frykholm, G.J., L. Pahlman, and B. Glimelius, *Combined chemo- and radiotherapy vs. radiotherapy alone in the treatment of primary, nonresectable adenocarcinoma of the rectum.* Int J Radiat Oncol Biol Phys., 2001. **50**(2): p. 427-34.

130. Bosset, J.F., et al., *Preoperative radiochemotherapy in rectal cancer: long-term results of a phase II trial.* Int J Radiat Oncol Biol Phys, 2000. **46**(2): p. 323-327.

131. Chari, R.S., et al., *Preoperative radiation and chemotherapy in the treatment of adenocarcinoma of the rectum.* Ann Surg, 1995. **221**(6): p. 778-786.

132. Habr-Gama, A., et al., *Low rectal cancer: impact of radiation and chemotherapy on surgical treatment.* Dis Colon Rectum, 1998. **41**(9): p. 1087-1096.

133. Janjan, N.A., et al., *Improved overall survival among responders to preoperative chemoradiation for locally advanced rectal cancer.* Am J Clin Oncol., 2001. **24**(2): p. 107-112.

134. Ngan, S.Y., et al., *Early toxicity from preoperative radiotherapy with continuous infusion 5-fluorouracil for resectable adenocarcinoma of the rectum: a Phase II trial for the Trans-Tasman Radiation Oncology Group.* Int J Radiat Oncol Biol Phys., 2001. **50**(4): p. 883-887.

135. Borschitz, T., W. Kneist, and T. Junginger, *[Evaluation of residual urine volume by ultrasound for detection of urinary bladder dysfunction after surgical therapy of rectal cancer].* Chirurg, 2005. **76**(7): p. 696-701; discussion 701-2.

136. Kneist, W. and T. Junginger, *Residual urine volume after total mesorectal excision: an indicator of pelvic autonomic nerve preservation? Results of a case-control study.* Colorectal Dis, 2004. **6**(6): p. 432-7.

137. Grumann, M.M., et al., *Comparison of quality of life in patients undergoing abdominoperineal extirpation or anterior resection for rectal cancer.* Ann Surg, 2001. **233**(2): p. 149-56.

138. Gosselink, M.P., et al., *Quality of life after total mesorectal excision for rectal cancer.* Colorectal Dis, 2006. **8**(1): p. 15-22.

139. Jess, P., J. Christiansen, and P. Bech, *Quality of life after anterior resection versus abdominoperineal extirpation for rectal cancer.* Scand J Gastroenterol, 2002. **37**(10): p. 1201-4.

140. Pachler, J. and P. Wille-Jorgensen, *Quality of life after rectal resection for cancer, with or without permanent colostomy.* Cochrane Database Syst Rev, 2005(2): p. CD004323.

141. Schmidt, C.E., et al., *Prospective evaluation of quality of life of patients receiving either abdominoperineal resection or sphincter-preserving procedure for rectal cancer.* Ann Surg Oncol, 2005. **12**(2): p. 117-23.

142. Bucher, P., et al., *Mechanical bowel preparation for elective colorectal surgery: a meta-analysis.* Arch Surg, 2004. **139**(12): p. 1359-64.

143. Platell, C. and J. Hall, *What is the role of mechanical bowel preparation in patients undergoing colorectal surgery?* Dis Colon Rectum, 1998. **41**(7): p. 875-82.

144. Slim, K., et al., *Meta-analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation.* Br J Surg, 2004. **91**(9): p. 1125-30.

145. Wille-Jorgensen, P., et al., *Pre-operative mechanical bowel cleansing or not? an updated meta-analysis.* Colorectal Dis, 2005. **7**(4): p. 304-10.

146. Borly, L., P. Wille-Jorgensen, and M.S. Rasmussen, *Systematic review of thromboprophylaxis in colorectal surgery – an update.* Colorectal Dis, 2005. **7**(2): p. 122-7.

147. Chaudhri, S., et al., *Preoperative intensive, community-based vs. traditional stoma education: a randomized, controlled trial.* Dis Colon Rectum, 2005. **48**(3): p. 504-9.

148. Mynster, T., et al., *Blood loss and transfusion after total mesorectal excision and conventional rectal cancer surgery.* Colorectal Dis, 2004. **6**(6): p. 452-7.

149. Bulow, S., et al., *Recurrence and survival after mesorectal excision for rectal cancer.* Br J Surg, 2003. **90**(8): p. 974-80.

150. Kapiteijn, E., et al., *Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands.* Br J Surg, 2002. **89**(9): p. 1142-9.

151. Maeda, K., et al., "*On table*" *positioning for optimal access for cancer excision in the lower rectum.* World J Surg, 2004. **28**(4): p. 416-9.

152. Martling, A., et al., *Prognostic significance of both surgical and pathological assessment of curative resection for rectal cancer.* Br J Surg, 2004. **91**(8): p. 1040-5.

153. Nagtegaal, I.D., et al., *Low rectal cancer: a call for a change of approach in abdominoperineal resection.* J Clin Oncol, 2005. **23**(36): p. 9257-64.

154. Peeters, K.C.M.J., et al., *Risk factors for anastomotic failure after total mesorectal excision of rectal cancer.* Br J Surg, 2005. **92**(2): p. 211-6.

155. Kanemitsu, Y., et al., *Survival benefit of high ligation of the inferior mesenteric artery in sigmoid colon or rectal cancer surgery.* Br J Surg, 2006. **93**(5): p. 609-15.

156. Kim, J.C., et al., *The clinicopathological significance of inferior mesenteric lymph node metastasis in colorectal cancer.* Eur J Surg Oncol, 2004. **30**(3): p. 271-9.

157. Nagawa, H., et al., *Randomized, controlled trial of lateral node dissection vs. nerve-preserving resection in patients with rectal cancer after preoperative radiotherapy.* Dis Colon Rectum, 2001. **44**(9): p. 1274-80.

158. Araujo, S.E.A., et al., *Conventional approach x laparoscopic abdominoperineal resection for rectal cancer treatment after neoadjuvant chemoradiation: results of a prospective randomized trial.* Rev Hosp Clin Fac Med Sao Paulo, 2003. **58**(3): p. 133-40.

159. Aziz, O., et al., *Laparoscopic versus open surgery for rectal cancer: a meta-analysis.* Ann Surg Oncol, 2006. **13**(3): p. 413-24.

160. Breukink, S., J. Pierie, and T. Wiggers, *Laparoscopic versus open total mesorectal excision for rectal cancer.* Cochrane Database Syst Rev, 2006(4): p. CD005200.

161. Jayne, D.G., et al., *Bladder and sexual function following resection for rectal cancer in a randomized clinical trial of laparoscopic versus open technique.* Br J Surg, 2005. **92**(9): p. 1124-32.

162. Quah, H.M., et al., *Bladder and sexual dysfunction following laparoscopically assisted and conventional open mesorectal resection for cancer.* Br J Surg, 2002. **89**(12): p. 1551-6.

163. Schwenk, W., et al., *Short term benefits for laparoscopic colorectal resection.* Cochrane Database Syst Rev, 2005(3): p. CD003145.

164. Zhou, Z.G., et al., *Laparoscopic versus open total mesorectal excision with anal sphincter preservation for low rectal cancer.* Surg Endosc, 2004. **18**(8): p. 1211-5.

165. Chapuis, P.H., et al., *Risk factors for tumour present in a circumferential line of resection after excision of rectal cancer.* Br J Surg, 2006. **93**(7): p. 860-5.

166. Eriksen, M.T., et al., *Inadvertent perforation during rectal cancer resection in Norway.* Br J Surg, 2004. **91**(2): p. 210-6.

167. Wibe, A., et al., *Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: anterior vs. abdominoperineal resection.* Dis Colon Rectum, 2004. **47**(1): p. 48-58.

168. Maeda, K., et al., *Irrigation volume determines the efficacy of "rectal washout".* Dis Colon Rectum, 2004. **47**(10): p. 1706-10.

169. Terzi, C., et al., *Is rectal washout necessary in anterior resection for rectal cancer? A prospective clinical study.* World J Surg, 2006. **30**(2): p. 233-41.

170. Laurent, A., et al., *Colonic J-pouch-anal anastomosis for rectal cancer: a prospective, randomized study comparing handsewn vs. stapled anastomosis.* Dis Colon Rectum, 2005. **48**(4): p. 729-34.

171. Park, J.-G., et al., *Colonic J-pouch anal anastomosis after ultralow anterior resection with upper sphincter excision for low-lying rectal cancer.* World J Gastroenterol, 2005. **11**(17): p. 2570-3.

172. Sailer, M., et al., *Randomized clinical trial comparing quality of life after straight and pouch coloanal reconstruction.* Br J Surg, 2002. **89**(9): p. 1108-17.

173. Furst, A., et al., *Colonic J-pouch vs. coloplasty following resection of distal rectal cancer: early results of a prospective, randomized, pilot study.* Dis Colon Rectum, 2003. **46**(9): p. 1161-6.

174. Jiang, J.-K., S.-H. Yang, and J.-K. Lin, *Transabdominal anastomosis after low anterior resection: A prospective, randomized, controlled trial comparing long-term results between side-to-end anastomosis and colonic J-pouch.* Dis Colon Rectum, 2005. **48**(11): p. 2100-8.

175. Pimentel, J.M., et al., *Transverse coloplasty pouch and colonic J-pouch for rectal cancer–a comparative study.* Colorectal Dis, 2003. **5**(5): p. 465-70.

176. Machado, M., et al., *Similar outcome after colonic pouch and side-to-end anastomosis in low anterior resection for rectal cancer: a prospective randomized trial.* Ann Surg, 2003. **238**(2): p. 214-20.

177. Machado, M., et al., *Functional and physiologic assessment of the colonic reservoir or side-to-end anastomosis after low anterior resection for rectal cancer: a two-year follow-up.* Dis Colon Rectum, 2005. **48**(1): p. 29-36.

178. Ulrich, A., et al., *Functional results of the colon J-pouch versus transverse coloplasty pouch in Heidelberg.* Recent Results Cancer Res, 2005. **165**: p. 205-11.

179. Amin, A.I., et al., *Comparison of transanal stent with defunctioning stoma in low anterior resection for rectal cancer.* Br J Surg, 2003. **90**(5): p. 581-2.

180. Matthiessen, P., et al., *Population-based study of risk factors for postoperative death after anterior resection of the rectum.* Br J Surg, 2006. **93**(4): p. 498-503.

181. Poon, J.T.C., W.-L. Law, and K.-W. Chu, *Small bowel obstruction following low anterior resection: the impact of diversion ileostomy.* Langenbecks Arch Surg, 2004. **389**(4): p. 250-5.

182. Brown, S.R., et al., *A prospective randomised study of drains in infra-peritoneal rectal anastomoses.* Tech Coloproctol, 2001. **5**(2): p. 89-92.

183. Matthiessen, P., et al., *Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial.* Ann Surg, 2007. **246**(2): p. 207-14.

184. Law, W.L., K.W. Chu, and H.K. Choi, *Randomized clinical trial comparing loop ileostomy and loop transverse colostomy for faecal diversion following total mesorectal excision.* Br J Surg, 2002. **89**(6): p. 704-8.

185. Winde, G., et al., *Surgical cure for early rectal carcinomas (T1). Transanal endoscopic microsurgery vs. anterior resection.* Dis Colon Rectum, 1996. **39**(9): p. 969-76.

186. Lezoche, E., et al., *Transanal endoscopic versus total mesorectal laparoscopic resections of T2-N0 low rectal cancers after neoadjuvant treatment: a prospective randomized trial with a 3-years minimum follow-up period.* Surg Endosc, 2005. **19**(6): p. 751-6.

187. Nascimbeni, R., et al., *Risk of lymph node metastasis in T1 carcinoma of the colon and rectum.* Dis Colon Rectum, 2002. **45**(2): p. 200-6.

188. Nagtegaal, I.D., et al., *Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control.* J Clin Oncol, 2002. **20**(7): p. 1729-34.

189. Marr, R., et al., *The modern abdominoperineal excision: the next challenge after total mesorectal excision.* Ann Surg, 2005. **242**(1): p. 74-82.

190. Maughan, N.J. and P. Quirke, *Modern management of colorectal cancer–a pathologist's view.* Scand J Surg, 2003. **92**(1): p. 11-9.

191. Quirke, P., *Training and quality assurance for rectal cancer: 20 years of data is enough.* Lancet Oncol, 2003. **4**(11): p. 695-702.

192. Quirke, P. and M.F. Dixon, *The prediction of local recurrence in rectal adenocarcinoma by histopathological examination.* Int J Colorectal Dis, 1988. **3**(2): p. 127-31.

193. Quirke, P., et al., *Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision.* Lancet, 1986. **2**(8514): p. 996-999.

194. Jouret-Mourin, A., *Recommendations for pathological examination and reporting for colorectal cancer. Belgian consensus.* Acta Gastroenterol Belg, 2004. **67**(1): p. 40-5.

195. Compton, C.C., et al., *Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999.* Arch Pathol Lab Med, 2000. **124**(7): p. 979-94.

196. Becouarn, Y., et al., *Cancer of the rectum.* Br J Cancer, 2001. **84 Suppl 2**: p. 69-73.

197. Nelson, H., et al., *Guidelines 2000 for colon and rectal cancer surgery.* J Natl Cancer Inst, 2001. **93**(8): p. 583-96.

198. Quirke, P., et al., *The future of the TNM staging system in colorectal cancer: time for a debate?* Lancet Oncol, 2007. **8**(7): p. 651-7.

199. Parfitt, J.R. and D.K. Driman, *The total mesorectal excision specimen for rectal cancer: a review of its pathological assessment.* Journal of Clinical Pathology, 2007. **60**(8): p. 849-55.

200. Wheeler, J.M., et al., *Quantification of histologic regression of rectal cancer after irradiation: a proposal for a modified staging system.* Dis Colon Rectum, 2002. **45**(8): p. 1051-6.

201. Mandard, A.M., et al., *Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations.* Cancer, 1994. **73**(11): p. 2680-6.

202. Dworak, O., L. Keilholz, and A. Hoffmann, *Pathological features of rectal cancer after preoperative radiochemotherapy.* Int J Colorectal Dis, 1997. **12**(1): p. 19-23.

203. Compton, C.C., *Updated protocol for the examination of specimens from patients with carcinomas of the colon and rectum, excluding carcinoid tumors, lymphomas, sarcomas, and tumors of the vermiform appendix: a basis for checklists. Cancer Committee.* Arch Pathol Lab Med, 2000. **124**(7): p. 1016-25.

204. Compton, C.C., *Key issues in reporting common cancer specimens: problems in pathologic staging of colon cancer.* Arch Pathol Lab Med, 2006. **130**(3): p. 318-24.

205. Jass, J.R., et al., *Recommendations for the reporting of surgically resected specimens of colorectal carcinoma.* Hum Pathol, 2007. **38**(4): p. 537-545.

206. Germond, C., et al., *Postoperative adjuvant radiotherapy and/or chemotherapy for resected stage II or III rectal cancer* in *Practice Guideline Report*. 2001, Cancer Care Ontario.

207. De Placido, S., et al., *Modulation of 5-fluorouracil as adjuvant systemic chemotherapy in colorectal cancer: the IGCS-COL multicentre, randomised, phase III study.* Br J Cancer, 2005. **93**(8): p. 896-904.

208. Tsavaris, N., et al., *Leucovorin and fluorouracil vs levamisole and fluorouracil as adjuvant chemotherapy in rectal cancer.* Oncol Rep, 2004. **12**(4): p. 927-32.

209. Kotake, K., et al., *A multicenter randomized study comparing 5-fluorouracil continuous infusion (ci) plus 1-hexylcarbamoyl-5-fluorouracil and 5-FU ci alone in colorectal cancer.* Oncol Rep, 2005. **14**(1): p. 129-34.

210. Iwagaki, H., et al., *Post-operative adjuvant chemotherapy for colorectal cancer with 5-fluorouracil (5-FU) infusion combined with 1-hexylcarbamoyl-5-fluorouracil (HCFU) oral administration after curative resection.* Anticancer Res, 2001. **21**(6A): p. 4163-8.

211. Watanabe, M., et al., *Randomized controlled trial of the efficacy of adjuvant immunochemotherapy and adjuvant chemotherapy for colorectal cancer, using different combinations of the intracutaneous streptococcal preparation OK-432 and the oral pyrimidines 1-hexylcarbamoyl-5-fluorouracil and uracil/tegafur.* Int J Clin Oncol, 2004. **9**(2): p. 98-106.

212. James, R.D., et al., *Randomized clinical trial of adjuvant radiotherapy and 5-fluorouracil infusion in colorectal cancer (AXIS).* Br J Surg, 2003. **90**(10): p. 1200-12.

213. *Adjuvant therapy for patients with colon and rectum cancer.* Consens Statement, 1990. **8**(4): p. 1-25.

214. Bosset, J.F., et al., *Postoperative pelvic radiotherapy with or without elective irradiation of para-aortic nodes and liver in rectal cancer patients. A controlled clinical trial of the EORTC Radiotherapy Group.* Radiother Oncol, 2001. **61**(1): p. 7-13.

215. Cafiero, F., et al., *Randomised clinical trial of adjuvant postoperative RT vs. sequential postoperative RT plus 5-FU and levamisole in patients with stage II-III resectable rectal cancer: a final report.* J Surg Oncol, 2003. **83**(3): p. 140-6.

216. Akasu, T., et al., *Adjuvant chemotherapy with uracil-tegafur for pathological stage III rectal cancer after mesorectal excision with selective lateral pelvic lymphadenectomy: a multicenter randomized controlled trial.* Jpn J Clin Oncol, 2006. **36**(4): p. 237-44.

217. Taal, B.G., et al., *Adjuvant 5FU plus levamisole in colonic or rectal cancer: improved survival in stage II and III.* Br J Cancer, 2001. **85**(10): p. 1437-43.

218. Glimelius, B., et al., *Adjuvant chemotherapy in colorectal cancer: a joint analysis of randomised trials by the Nordic Gastrointestinal Tumour Adjuvant Therapy Group.* Acta Oncol, 2005. **44**(8): p. 904-12.

219. Kato, T., et al., *Efficacy of oral UFT as adjuvant chemotherapy to curative resection of colorectal cancer: multicenter prospective randomized trial.* Langenbecks Arch Surg, 2002. **386**(8): p. 575-81.

220. Sakamoto, J., et al., *Efficacy of oral adjuvant therapy after resection of colorectal cancer: 5-year results from three randomized trials.* J Clin Oncol, 2004. **22**(3): p. 484-92.

221. Smalley, S.R., et al., *Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144.* J Clin Oncol, 2006. **24**(22): p. 3542-7.

222. Lundby, L., et al., *Long-term anorectal dysfunction after postoperative radiotherapy for rectal cancer.* Dis Colon Rectum, 2005. **48**(7): p. 1343-9; discussion 1349-52; author reply 1352.

223. Dencausse, Y., et al., *Adjuvant radio-chemotherapy in stage II-III rectal cancer with 24-hour infusion of high-dose 5-fluorouracil and folinic acid: evaluation of feasibility.* Onkologie, 2001. **24**(5): p. 476-80.

224. Miller, R.C., et al., *Acute diarrhea during adjuvant therapy for rectal cancer: a detailed analysis from a randomized intergroup trial.* Int J Radiat Oncol Biol Phys, 2002. **54**(2): p. 409-13.

225. Desch, C.E., et al., *Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline.* J Clin Oncol, 2005. **23**(33): p. 8512-9.

226. Rodriguez-Moranta, F., et al., *Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: a prospective, multicenter, randomized, controlled trial.* J Clin Oncol, 2006. **24**(3): p. 386-93.

227. Rex, D.K., et al., *Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer.* Gastroenterology, 2006. **130**(6): p. 1865-71.

228. Garden, O.J., et al., *Guidelines for resection of colorectal cancer liver metastases.* Gut, 2006. **55 Suppl 3**: p. iii1-8.

229. Pawlik, T.M., et al., *Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases.* Ann Surg, 2005. **241**(5): p. 715-22, discussion 722-4.

230. Adam, R., et al., *Two-stage hepatectomy: A planned strategy to treat irresectable liver tumors.* Ann Surg, 2000. **232**(6): p. 777-85.

231. Farges, O., et al., *Portal vein embolization before right hepatectomy: prospective clinical trial.* Ann Surg, 2003. **237**(2): p. 208-17.

232. Neeleman, N. and R. Andersson, *Repeated liver resection for recurrent liver cancer.* Br J Surg, 1996. **83**(7): p. 893-901.

233. Oshowo, A., et al., *Radiofrequency ablation extends the scope of surgery in colorectal liver metastases.* Eur J Surg Oncol, 2003. **29**(3): p. 244-7.

234. Nordlinger, B., et al., *Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group.* Eur J Cancer, 2007. **43**(14): p. 2037-45.

235. Rau, B. and M. Hunerbein, *Diagnostic laparoscopy: indications and benefits.* Langenbecks Arch Surg, 2005. **390**(3): p. 187-96.

236. Wiering, B., et al., *The impact of fluor-18-deoxyglucose-positron emission tomography in the management of colorectal liver metastases.* Cancer, 2005. **104**(12): p. 2658-70.

237. Nordlinger, B., et al., *Final results of the EORTC Intergroup randomized phase III study 40983 [EPOC] evaluating the benefit of peri-operative FOLFOX4 chemotherapy for patients with potentially resectable colorectal cancer liver metastases.* J Clin Oncol (Meeting Abstracts), 2007. **25**(18_suppl): p. LBA5.

238. Adam, R., et al., *Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal.* Ann Surg Oncol, 2001. **8**(4): p. 347-53.

239. Tournigand, C., et al., *FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study.* J Clin Oncol, 2004. **22**(2): p. 229-37.

240. Delaunoit, T., et al., *Chemotherapy permits resection of metastatic colorectal cancer: experience from Intergroup N9741.* Ann Oncol, 2005. **16**(3): p. 425-9.

241. Folprecht, G., et al., *Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates.* Ann Oncol, 2005. **16**(8): p. 1311-9.

242. Van Cutsem, E., et al., *Towards a pan-European consensus on the treatment of patients with colorectal liver metastases.* Eur J Cancer, 2006. **42**(14): p. 2212-21.

243. Portier, G., et al., *Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial.* J Clin Oncol, 2006. **24**(31): p. 4976-82.

244. Mitry, E., et al., *[Importance of a multidisciplinary approach to metastatic cancer of the rectum].* Bull Cancer, 1998. **85**(8): p. 716-20.

245. Jonker, D.J., J.A. Maroun, and W. Kocha, *Survival benefit of chemotherapy in metastatic colorectal cancer: a meta-analysis of randomized controlled trials.* Br J Cancer, 2000. **82**(11): p. 1789-94.

246. Simmonds, P.C., *Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. Colorectal Cancer Collaborative Group.* Bmj, 2000. **321**(7260): p. 531-5.

247. Douillard, J.Y., et al., *Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial.* Lancet, 2000. **355**(9209): p. 1041-7.

248. Saltz, L.B., et al., *Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group.* N Engl J Med, 2000. **343**(13): p. 905-14.

249. de Gramont, A., et al., *Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer.* J Clin Oncol, 2000. **18**(16): p. 2938-47.

250. Giacchetti, S., et al., *Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer.* J Clin Oncol, 2000. **18**(1): p. 136-47.

251. Hoff, P.M., et al., *Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study.* J Clin Oncol, 2001. **19**(8): p. 2282-92.

252. Van Cutsem, E., et al., *Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study.* J Clin Oncol, 2001. **19**(21): p. 4097-106.

253. Hurwitz, H., et al., *Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.* N Engl J Med, 2004. **350**(23): p. 2335-42.

254. Cunningham, D., *Mature results from three large controlled studies with raltitrexed ('Tomudex').* Br J Cancer, 1998. **77 Suppl 2**: p. 15-21.

255. Tournigand, C., et al., *OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer–a GERCOR study.* J Clin Oncol, 2006. **24**(3): p. 394-400.

256. Cunningham, D., et al., *Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer.* Lancet, 1998. **352**(9138): p. 1413-8.

257. Rougier, P., et al., *Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer.* Lancet, 1998. **352**(9138): p. 1407-12.

258. Giantonio, B.J., et al., *Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200.* J Clin Oncol, 2007. **25**(12): p. 1539-44.

259. Cunningham, D., et al., *Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer.* N Engl J Med, 2004. **351**(4): p. 337-45.

260. Wiseman, L.R., et al., *Oxaliplatin: a review of its use in the management of metastatic colorectal cancer.* Drugs Aging, 1999. **14**(6): p. 459-75.

261. Rothenberg, M.L., et al., *Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial.* J Clin Oncol, 2003. **21**(11): p. 2059-69.

262. Conroy, T., et al., *[Recommendations for clinical practice: management with first-line palliative chemotherapy for patients with metastatic colorectal cancer].* Bull Cancer, 2006. **93**(2): p. 197-200.

263. Welch, S., et al., *The Role of Bevacizumab (Avastin™) Combined With Chemotherapy in the Treatment of Patients With Advanced Colorectal Cancer: A Clinical Practice Guideline.* 2005, Cancer Care Ontario.

264. Au, H.J., K.E. Mulder, and A.L. Fields, *Systematic review of management of colorectal cancer in elderly patients.* Clin Colorectal Cancer, 2003. **3**(3): p. 165-71.

265. Folprecht, G., et al., *Efficacy of 5-fluorouracil-based chemotherapy in elderly patients with metastatic colorectal cancer: a pooled analysis of clinical trials.* Ann Oncol, 2004. **15**(9): p. 1330-8.

266. Gastrointestinal Cancer Disease Site Group, *Use of Irinotecan (Camptosar®, CPT-11) Combined with 5-Fluorouracil and Leucovorin (5FU/LV) as First-Line Therapy for Metastatic Colorectal Cancer. Practice Guideline Report #2-16b.* 2003, Cancer Care Ontario.

267. Kocha, W., et al., *Oral Capecitabine (Xeloda) in the First-line Treatment of Metastatic Colorectal Cancer: A Clinical Practice Guideline.* 2005, Cancer Care Ontario.

268. Kabbinavar, F.F., et al., *Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer.* J Clin Oncol, 2005. **23**(16): p. 3706-12.

269. Zondor, S.D. and P.J. Medina, *Bevacizumab: an angiogenesis inhibitor with efficacy in colorectal and other malignancies.* Ann Pharmacother, 2004. **38**(7-8): p. 1258-64.

270. Germond, C., et al., *Use of Raltitrexed (Tomudex) in the Management of Metastatic Colorectal Cancer. Practice Guideline Report #2-17.* 2005, Cancer Care Ontario.

271. Mitry, E., et al., *Predictive factors of survival in patients with advanced colorectal cancer: an individual data analysis of 602 patients included in irinotecan phase III trials.* Ann Oncol, 2004. **15**(7): p. 1013-7.

272. Chau, I., et al., *Elderly patients with fluoropyrimidine and thymidylate synthase inhibitor-resistant advanced colorectal cancer derive similar benefit without excessive toxicity when treated with irinotecan monotherapy.* Br J Cancer, 2004. **91**(8): p. 1453-8.

273. Frieze, D.A. and J.S. McCune, *Current status of cetuximab for the treatment of patients with solid tumors.* Ann Pharmacother, 2006. **40**(2): p. 241-50.

274. Figueredo, A., et al., *Use of Irinotecan in the Second-Line Treatment of Metastatic Colorectal Carcinoma. Practice Guideline Report #2-16.* 2004, Cancer Care Ontario.

275. Khot, U.P., et al., *Systematic review of the efficacy and safety of colorectal stents.* Br J Surg, 2002. **89**(9): p. 1096-102.

276. Yan, T.D., et al., *Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma.* J Clin Oncol, 2006. **24**(24): p. 4011-9.

277. Elias, D., et al., *Treatment of peritoneal carcinomatosis from colorectal cancer: impact of complete cytoreductive surgery and difficulties in conducting randomized trials.* Ann Surg Oncol, 2004. **11**(5): p. 518-21.

278. Kavanagh, M. and J.F. Ouellet, *[Clinical practice guideline on peritoneal carcinomatosis treatment using surgical cytoreduction and hyperthermic intraoperative intraperitoneal chemotherapy].* Bull Cancer, 2006. **93**(9): p. 867-74.

279. Verwaal, V.J., et al., *Recurrences after peritoneal carcinomatosis of colorectal origin treated by cytoreduction and hyperthermic intraperitoneal chemotherapy: location, treatment, and outcome.* Ann Surg Oncol, 2004. **11**(4): p. 375-9.

280. Verwaal, V.J., et al., *Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer.* J Clin Oncol, 2003. **21**(20): p. 3737-43.

281. Verwaal, V.J., et al., *Predicting the survival of patients with peritoneal carcinomatosis of colorectal origin treated by aggressive cytoreduction and hyperthermic intraperitoneal chemotherapy.* Br J Surg, 2004. **91**(6): p. 739-46.

282. Figueredo, A., et al., *The use of preoperative radiotherapy in the management of patients with clinically resectable rectal cancer: a practice guideline.* BMC Med, 2003. **1**(1): p. 1.

283. Anthony, T., et al., *Practice parameters for the surveillance and follow-up of patients with colon and rectal cancer.* Dis Colon Rectum, 2004. **47**(6): p. 807-17.

284. Bast, R.C., Jr., et al., *2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology.* J Clin Oncol, 2001. **19**(6): p. 1865-78.

285. National Cancer, I.

286. National Comprehensive Cancer Network, *Rectal Cancer*. 2006.

287. *[Therapeutic choices for rectal cancer].* Gastroenterol Clin Biol, 2006. **30**(1): p. 59-69.

288. Tjandra, J.J., et al., *Practice parameters for the management of rectal cancer (revised).* Dis Colon Rectum, 2005. **48**(3): p. 411-23.

289. Davila, R.E., et al., *ASGE guideline: the role of endoscopy in the diagnosis, staging, and management of colorectal cancer.* Gastrointest Endosc, 2005. **61**(1): p. 1-7.

290. Scholefield, J.H. and R.J. Steele, *Guidelines for follow up after resection of colorectal cancer.* Gut, 2002. **51 Suppl 5**: p. V3-5.

291. *[Recommendations on the diagnosis and multimodal primary therapy of rectal carcinomas 2004].* Wien Klin Wochenschr, 2005. **117**(4): p. 154-71.

292. Tveit, K.M. and V.V. Kataja, *ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of rectal cancer.* Ann Oncol, 2005. **16 Suppl 1**: p. i20-1.

293. Van Cutsem, E.J., J. Oliveira, and V.V. Kataja, *ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of advanced colorectal cancer.* Ann Oncol, 2005. **16 Suppl 1**: p. i18-9.

294. Purkayastha, S., et al., *Diagnostic precision of magnetic resonance imaging for preoperative prediction of the circumferential margin involvement in patients with rectal cancer.* Colorectal Dis, 2007. **9**(5): p. 402-11.

295. van Erkel, A.R., et al., *Hepatic metastases in patients with colorectal cancer: relationship between size of metastases, standard of reference, and detection rates.* Radiology, 2002. **224**(2): p. 404-9.

296. Dietrich, C.F., et al., *Assessment of metastatic liver disease in patients with primary extrahepatic tumors by contrast-enhanced sonography versus CT and MRI.* World J Gastroenterol, 2006. **12**(11): p. 1699-705.

297. Kulig, J., et al., *The role and value of endorectal ultrasonography in diagnosing T1 rectal tumors.* Ultrasound Med Biol, 2006. **32**(4): p. 469-72.

298. Bipat, S., et al., *Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging–a meta-analysis.* Radiology, 2004. **232**(3): p. 773-83.

299. Marusch, F., et al., *Routine use of transrectal ultrasound in rectal carcinoma: results of a prospective multicenter study.* Endoscopy, 2002. **34**(5): p. 385-90.

300. Poon, F.W., et al., *Accuracy of thin section magnetic resonance using phased-array pelvic coil in predicting the T-staging of rectal cancer.* Eur J Radiol, 2005. **53**(2): p. 256-62.

301. Tatli, S., et al., *Local staging of rectal cancer using combined pelvic phased-array and endorectal coil MRI.* J Magn Reson Imaging, 2006. **23**(4): p. 534-40.

302. Kulinna, C., et al., *Local staging of rectal cancer: assessment with double-contrast multislice computed tomography and transrectal ultrasound.* J Comput Assist Tomogr, 2004. **28**(1): p. 123-30.

303. Mathur, P., et al., *Comparison of CT and MRI in the pre-operative staging of rectal adenocarcinoma and prediction of circumferential resection margin involvement by MRI.* Colorectal Dis, 2003. **5**(5): p. 396-401.

304. Branagan, G., et al., *Can magnetic resonance imaging predict circumferential margins and TNM stage in rectal cancer?* Dis Colon Rectum, 2004. **47**(8): p. 1317-22.

305. Bianchi, P.P., et al., *Endoscopic ultrasonography and magnetic resonance in preoperative staging of rectal cancer: comparison with histologic findings.* J Gastrointest Surg, 2005. **9**(9): p. 1222-7; discussion 1227-8.

306. Hsieh, P.S., et al., *Comparing results of preoperative staging of rectal tumor using endorectal ultrasonography and histopathology.* Chang Gung Med J, 2003. **26**(7): p. 474-8.

307. Strassburg, J., *Magnetic resonance imaging in rectal cancer: the MERCURY experience.* Tech Coloproctol, 2004. **8 Suppl 1**: p. s16-8.

308. Martling, A., et al., *The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study.* Cancer, 2001. **92**: p. 896-902.

309. Holm, T., et al., *Tumour location and the effects of preoperative radiotherapy in the treatment of rectal cancer.* Br J Surg, 2001. **88**(6): p. 839-843.

310. Folkesson, J., et al., *Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate.* J Clin Oncol, 2005. **23**(24): p. 5644-5650.

311. Birgisson, H., et al., *Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial.* J Clin Oncol, 2005. **23**(34): p. 8697-8705.

312. Petersen, S., et al., *Brief preoperative radiotherapy in surgical therapy of rectal carcinoma. Long-term results of a prospective randomized study.* Chirurg, 1998. **69**(7): p. 759-765.

313. Kapiteijn, E., et al., *Total mesorectal excision (TME) with or without preoperative radiotherapy in the treatment of primary rectal cancer. Prospective randomised trial with standard operative and histopathological techniques. Dutch ColoRectal Cancer Group.* Eur J Surg, 1999. **165**(5): p. 410-420.

314. Rodel, C., et al., *Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer.* J Clin Oncol, 2005. **23**(34): p. 8688-8696.

315. Hyams, D.M., E.P. Mamounas, and N. Petrelli, *A clinical trial to evaluate the worth of preoperative multimodality therapy in patients with operable carcinoma of the rectum: a progress report of National Surgical Breast and Bowel Project Protocol R-03.* Dis Colon Rectum 1997. **40**: p. 131–139.

316. Roh, M.S.R., et al., *Response to preoperative multimodality therapy predicts survival in patients with carcinoma of the rectum.* Journal of Clinical Oncology. ASCO Annual Meeting Proceedings (Post-Meeting Edition). 2004. **22**(14S): p. 3505.

317. Bujko, K., et al., *Prediction of mesorectal nodal metastases after chemoradiation for rectal cancer: results of a randomised trial: implication for subsequent local excision.* Radiother Oncol, 2005. **76**(3): p. 234-40.

318. Glehen, O., et al., *Long-term results of the Lyons R90-01 randomized trial of preoperative radiotherapy with delayed surgery and its effect on sphincter-saving surgery in rectal cancer.* Br J Surg., 2003. **90**(8): p. 996-8.

319. Chaudhri, S., et al., *Successful voiding after trial without catheter is not synonymous with recovery of bladder function after colorectal surgery.* Dis Colon Rectum, 2006. **49**(7): p. 1066-70.

320. Nowacki, M.P., et al., *Prospective, randomized trial examining the role of gentamycin-containing collagen sponge in the reduction of postoperative morbidity in rectal cancer patients: early results and surprising outcome at 3-year follow-up.* Int J Colorectal Dis, 2005. **20**(2): p. 114-20.

321. Goldberg, P.A., et al., *Long-term results of a randomized trial of short-course low-dose adjuvant pre-operative radiotherapy for rectal cancer: reduction in local treatment failure.* Eur J Cancer, 1994. **30A**: p. 1602-1606.

322. Jeffery, M., B.E. Hickey, and P.N. Hider, *Follow-up strategies for patients treated for non-metastatic colorectal cancer.* Cochrane Database Syst Rev, 2007(1): p. CD002200.

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