Methodology

1 General methodology

1.1 RARECARE Selection Rare Tumours

During recent years, rare cancers have been intensively studied by RARECARE, a research group to estimate the burden of rare cancers in Europe [1]. They defined a cancer as rare when the incidence is lower than 6 per 100,000. Based on this criterion, a list of common and rare cancers has been created and publically made available. The definition of each tumour entity is done based on a combination of morphology and topography codes. The list is organised into three layers: bottom, middle and top layers [2]. The bottom layer corresponds to the WHO names of the individual cancers with their corresponding ICD-O-3 codes, for example mucinous adenocarcinoma of colon [3]. These bottom layers are grouped into middle layers that are considered to require similar clinical management and research, for example adenocarcinoma with variants of colon. The middle layers are further grouped to top layers that are considered to involve the same clinical expertise and patient referral structure, for example epithelial tumours of colon. To select the rare cancers for this study, we used the RARECARE list published online in march 2011 [4]. From this list, we selected the top layers and underlying middle layers for the analyses. Bottom layers were not taken into account in this report.

It should be noted that these layers are not exhaustive. For example, not all tumours included in a top layer, are also included in one of the underlying middle layers. This means that the sum of the number of tumours in the different middle layers is often smaller than the number of tumours included in the related top layer.

1.2 Incidence

Incidence is the number of new cases arising in a given period in a specified population. This measure provides a direct estimate of the probability or risk of illness, and it can be expressed in different ways. In this report, it is expressed as:

- Crude incidence rate (CR): calculated by dividing the number of new cases observed during a given time period by the corresponding number of people in the population at risk. The crude rate is expressed as a number of new cases per 100,000 persons per year.
- Age specific incidence rate: the number of newly diagnosed cases in a particular 5-year age group over a specified time period and expressed per 100,000 persons per year.
- Age standardised incidence rate: a weighted average of the individual age specific rates using an external standard population. It is the incidence that would be observed if the population had the age structure of the standard population (European or World Standard population). Since age has a powerful influence on the risk of cancer, this standardisation is

necessary when comparing several populations that differ with respect to their age structure. Age standardised incidence rates are expressed as the number of new cases per 100,000 persons per year.

1.3 Trends

Trends over the incidence years are studied by calculating the Estimated Annual Percentage Change (EAPC). In this method, a regression line is fitted to the natural logarithm of the rates using calendar years as a regressor variable, i.e. y=mx + b where y = ln (rate) and x = calendar year. Then the EAPC = 100 x (e^m-1). Testing the hypothesis that the EAPC is equal to zero is equivalent to testing the hypothesis that the slope of the line in the above equation is equal to zero. The latter hypothesis is tested using the t-distribution of m/SEm, while the number of degrees of freedom equals the number of calendar years minus two. The standard error of m, i.e. SEm, is obtained from the fit of the regression line. This calculation assumes that the rates increased/decreased at a constant rate over the entire period, although the accuracy of this assumption has not been tested [5].

1.4 Survival

For the adequate calculation of survival results, some patients were removed from the selection:

- Cases with uncertain date of diagnosis
- Cases without a unique national number. The vital status was retrieved from the Kruispuntbank van de Sociale Zekerheid/Banque Carrefour de la Sécurité Social based on patients' unique social security number (INSZ/NISS).
- Second and subsequent tumours. For each person, only the first diagnosed cancer (known to the Belgian Cancer Registry, non-melanoma skin cancers not taken into account) was considered for the analyses, consistent with other (inter)national cancer survival analyses [6, 7,8].
- Cases with a date of diagnosis equal to the date of death
- Cases lost to follow-up at the date of incidence

Two types of survival are reported: observed survival and relative survival.

Because of these additional exclusion criteria used for the survival analyses compared with the analyses on incidence, the number of patients included in the survival analyses is most often lower.

It should be noted that the interpretation of survival analyses is uncertain if the number of patients is smaller than 35. Therefore, survival analyses are restricted to groups of 35 or more patients at the start of the observation period (i.e. the number at risk equal to or higher than 35). If the numbers at risk are lower than 35, an asterisk (*) is used and no results are shown.

1.4.1 Observed Survival

Observed survival is the proportion of patients that is still alive after a specified period of time. In this study, we report the observed survival rates until ten years of follow-up for the first part and until five years of follow-up for the second part. Patients whose observation period was shorter than the

maximum time for which survival probability was calculated (i.e., ten years or five years for the first and second part, respectively) were censored at the date of the last information on vital status. Observed survival was calculated with the Kaplan-Meier method [9] using a semi-complete analysis approach [10]. The 1-, 3- , 5- and 10-year observed survival is the proportion of patients that is still alive one, three , five and ten years after their diagnosis, respectively.

1.4.2 Relative Survival

A problem with measuring observed survival is that the estimates do not only include deaths due to the cancer itself, but also deaths due to other causes, including older age, other diseases, trauma and any other possible causes of death. Calculation of a disease-specific survival (which takes only the cancer itself into account as a cause of death) is impossible because the exact cause of death for each individual is unknown in this study and is hard to achieve at a population level.

To overcome this problem, relative survival has been developed as a proxy for net survival which is defined as the survival that would occur if mortality from other causes of death is removed [11]. Relative survival is calculated as the ratio of the observed survival to the expected survival (=survival that would be expected if the cancer patients had the same age and sex specific mortality in each period as the general population). Relative survival is widely used for comparisons between different populations and countries. Life tables are required to estimate the expected survival. For the survival analyses performed in this study, expected survival calculations were based on sex-, age-, region- and calendar-year-specific Belgian lifetables [12], according to the Ederer II method [13]. Relative survival rates were estimated using a SAS code written by Paul Dickman from the Karolinska Institute, Stockholm Sweden using a semi-complete analysis approach [14].

1.4.3 Staging

Staging is done according the TNM classification as defined by the International Union Against Cancer (5^{th} edition for the incidence years 2001-2002 [15], 6^{th} edition for the incidence years 2003-2009 [16], 7^{th} edition for the incidence year 2010 [17]). Stage can be reported as the clinical stage, the pathological stage or the combined stage. The combined stage is a compilation of the pathological (pTNM) and the clinical (cTNM) stage. If both the pTNM and the cTNM are available, pTNM is used for the combined stage. An exception to this rule is a case with clinical metastases (cM=1): in this case, the combined stage is IV. If either the pathological or the clinical stage is available, the combined stage is derived from the available stage. If both pStage and cStage are absent, the combined stage is considered unknown ('X'). For some tumours TNM staging is not applicable because of their morphology (e.g. sarcoma) or because of their localisation (e.g. some sublocalisations for anal canal). These tumours are reported as 'NA' and are excluded from the analyses by stage. Note that in the current report, 'stage' refers to the combined stage, unless specified otherwise.

2 Methodology of Part III: Rare Cancers in the Flemish Region, 2001-2010: Incidence, Trends and Survival

2.1 Selection of Tumours

Because of the goal to give a broad overview in this first part of the study, a broad range of tumours was selected. The following inclusion- and exclusion criteria were used:

2.1.1 Inclusion Criteria

- Tumours first diagnosed during the years 2001-2010 (incidence date)
- Patients with their official residence in the Flemish Region
- The topography/morphology combinations from the RARECARE list are used to define the tumour entities

2.1.2 Exclusion Criteria

- The following tumours are excluded:
    - All types of sarcoma
    - The embryonal neoplasms
    - The extragonadal germ tumours
    - All central nervous system tumours
    - All haematological malignancies
    - Rare skin tumours

2.2 Common versus Rare Cancers

To be able to compare the results for rare cancers to those for common cancers, incidence, trends and survival results are also shown for the common cancers. However, because of the goal of this study to report on rare cancers, rare cancers are described in more detail. This implies that if a top layer (e.g. epithelial tumours of colon) has only common middle layers which can be described (because the rare middle layers hardly contain any patients, e.g. squamous cell carcinoma with variants of colon), only general results and no detailed results are provided.

2.3 Incidence

- Incidence is reported in terms of the raw numbers, the crude rate and the age standardised rate using the world population (WSR).
- An additional column was added next to the incidence rates to indicate whether a cancer type (top or middle layer) is rare (R) or common (C) according to the selection of included incidence years (2001- 2010), region (Flemish Region) and sex (both sexes together, males or females) based on the crude rate.

2.4 Trends

- Results are only displayed when at least one patient is diagnosed in each included incidence year.
- Because of the small numbers of patients for several tumours, trends are often calculated making use of the technique of three year moving averages. Using this technique, the preceding and following year are taken into account to calculate the age standardised rates. For example, to calculate the rate for 2004, the years 2003, 2004 and 2005 are taken into account. As a consequence, trend curves become smoother.

2.5 Survival

For all survival analyses reported in this part, a minimum follow-up was guaranteed until June 30, 2012. This implies that for the majority of patients, no complete ten year follow-up was available and censoring was needed. If the 10-year observed and relative survival could not be calculated because none of the patients had a follow-up period of ten years or more, this is indicated with a hyphen ('-'). Because the number of patients with a follow-up of ten years is rather limited (this is only the case for patients diagnosed between January 1, 2001 and June 30, 2002), 10-year survival is only reported for the overall survival and not for the more detailed analyses.

The following survival analyses are reported (not necessary all for all tumours):

- Overall survival: survival for both sexes together. 1-, 3-, 5- and 10-year observed and relative survival results are reported, together with the confidence interval (CI) for the 5-year survival (observed and relative).
- Survival by sex: 1-, 3- and 5-year observed and relative survival by sex, together with the CI for the 5-year survival (observed and relative) are reported.
- Survival by stage: 5-year relative survival analyses were performed for the different stages.
- Survival by age group: 5-year relative survival analyses were performed for three different age groups. The age groups were chosen to have three groups of more or less the same size.

3 Methodology of Part IV: Clinical Care for Selected Rare Cancers in the Flemish Region, 2004-2007

3.1 Selection of Tumours

3.1.1 Inclusion Criteria

To be able to conduct in depth analyses on the clinical care of rare cancers in the Flemish Region, inclusion criteria for this second part are different from the inclusion criteria for the first part of this study:

- Tumours first diagnosed during the years 2004-2007 (incidence date)
- Patients with their official residence in the Flemish Region

- Eleven tumours were selected based on the RARECARE list (see Appendix A for the selected topography and morphology codes per tumour). In alignment with the original project application, the major focus was on cancers of the head and neck region. This reflection led to the following list of studied tumour types:
    - Head and Neck Tumours (because of the original project demand):
        - Nasopharynx
        - Salivary Glands
        - Hypopharynx
        - Larynx
        - Oropharynx
        - Oral Cavity
        - Lip
    - Anal Canal
    - Vulva
    - Vagina
    - Mesothelioma

3.1.2 Exclusion criteria

The following tumours were excluded:

- Patients without a national security number (INSZ) available
- Second and subsequent tumours. For each person, only the first diagnosed cancer (known to the Belgian Cancer Registry, non-melanoma skin cancers not taken into account) was considered for the analyses.
- Cases with a date of diagnosis equal to the date of death
- Patients younger than 15 years because treatment in children can differ from treatment in adults
- Patients that could not be linked with the health insurance data

3.2 Linkage of cancer registry data with health insurance data

To enable analyses on the diagnosis and treatment of the patients, the BCR data are linked to the health insurance data. Since 2009, the Belgian Cancer Registry is authorised to link data from the BCR database with data on cancer-related diagnostic and therapeutic procedures and pharmaceuticals [18], which are obtained from all seven Belgian health insurance companies (HIC) via the Intermutualistic Agency (IMA/AIM). Via this linkage procedure, the Cancer Registry receives for each registered patient, health insurance data starting from January 1 of the year preceding the incidence year, until December 31 of the third year after the incidence year (further mentioned as HIC data). At the start of the final analyses, HIC data were available to the Cancer Registry until 2009. Because at least two years of follow-up could be guaranteed for each individual patient, it was decided that the available HIC data were sufficient to analyse the clinical care.

3.3 Limitations Concerning the Use of Health Insurance Data to Analyse Clinical Care

The use of HIC data to analyse the medical acts concerning diagnosis and treatment of cancer patients has some limitations. A first limitation is that only medical acts that are charged are available in the HIC data. For example, acts that are not charged because they took place in the context of a sponsored clinical study are not available in the HIC dataA second limitation is that the description of the registered medical acts does not directly refer to the diagnosis. A third shortcoming is that small deviations are possible in both the incidence date and the date of invoice of the medical act. To overcome the two latter limitations, timeframes are used to restrict the possibility of including medical acts that were conducted for other purposes than the ones of interest.

For diagnosis and staging, a timeframe of three months before until three months after the incidence date is taken (one month is always defined as 30 days). For the medical oncological consult (MOC), a timeframe of one month before until three months after the incidence date is taken. The timeframes taken into account for treatment (surgery, radiotherapy and chemotherapy) are different per tumour type and are therefore summarized in Appendix C. When multiple acts took place, the act closest to the incidence date is always chosen. It should be noted that for radiotherapy, the date of the last radiotherapy session is registered in the HIC data. For MOC and treatment acts, priority is given for those acts that took place from one month before the incidence date onwards.

Nomenclature codes were selected for all studied medical acts per tumour, and are reported in Appendix D. It should be noted that nomenclature codes are often rather unspecific and can be used for different techniques or different parts of the body. For example, no specific nomenclature codes are available for a CT scan of the neck or the thorax: for both regions, the same code is registered. On the other hand, no specified code is available for some medical acts. In sum, the use of health insurance data gives a good indication of the medical acts that took place but may show some minor deviations to the true values.

3.4 Patient Characteristics

Incidence is reported both in terms of the raw numbers, but also in terms of age standardised rates, using the European Standard Population (ESR)

3.5 Tumour Characteristics

- Sublocalisation is reported based on the ICD-10 codes
- The observed morphology codes are grouped into morphology groups. For an overview of the observed morphology codes per tumour: see Appendix B.

3.6 Diagnostic and Staging Procedures

For each tumour, all diagnostic and staging procedures are reported for the whole observation period, and by incidence year. It should be noted that for histological diagnosis, both nomenclature codes for taking biopsies and codes for the anatomo-pathological examination are included.

3.7 Multidisciplinary Oncological Consult

For each tumour, the proportion of patients discussed at a multidisciplinary oncological consult is calculated for the whole observation period, and by incidence year.

3.8 Therapeutic Procedures

3.8.1 Surgery

Different types of surgery are included for the different tumours. For most of the tumours, these can be divided into major surgery, minor surgery and lymphadenectomy. The nomenclature codes for the surgeries that are included in these three categories can be found in Appendix D. Within each type of surgery, the surgery closest to the incidence date is selected (with a restriction that the surgery could not have had taken place more than one month before the incidence date).When different types of surgery had taken place (e.g. major surgery and lymphadenectomy), priority rules are used to choose one of the surgeries (as such, only one surgery is withheld for each patient). Major surgery always received priority when performed within the studied timeframe because this type of surgery is most likely used for curative purposes. Minor surgeries received less priority because these surgeries are more aspecific (e.g. no localisation is defined in the nomenclature code) and can be done for diagnostic purposes. Therefore, these minor surgeries are only taken into account when no major surgery was performed within the timeframe.

Lymphadenectomies can most of the time not be curative on their own, but may be performed together with a curative surgery. Because only one surgery (the one with the highest reimbursement) can be charged when different surgeries have taken place together in the same anatomical region [19], it is possible that the curative surgery was not registered in the HIC data. Therefore for all head and neck cancers except nasopharynx and lip, patients without major surgery but with a lymphadenectomy are also considered to have undergone surgery. These surgeries are taken into account with a lower priority. When both a minor surgery and a lymphadenectomy took place within the timeframe, the surgery closest to the incidence date is selected.

An exception to these rules is laryngeal cancer for which minor surgeries are regarded as important as major surgeries and are therefore treated with the same priority. When both a major and a minor surgery took place within the defined timeframe, the surgery closest to the incidence date was selected. When none of them took place, lymphadenectomies are taken into.

A second exception is salivary glands cancer, for which the surgeries are divided into salivary gland surgery and head and mouth surgery. In line with laryngeal cancer, both types of surgeries are treated with the same priority. When both types of surgery took place within the defined timeframe,

the surgery closest to the incidence date was selected. When none of them took place, lymphadenectomies are taken into.

For lip cancer, no distinction was made between major and minor surgery. However, nomenclature codes for surgery were taken together with codes for plastic surgery (Appendix D). The decision to group these codes has been made because for several patients, nomenclature codes for plastic surgery were found within the studied timeframe, without the occurrence of nomenclature codes for oncological surgery. Plastic surgery in lip cancer patients without oncological surgery is very unlikely. Therefore, it is supposed that also these patients had received oncological surgery at the time of plastic surgery or before. For lip cancer, lymphadenectomies are not taken into account for surgery.

For anal canal cancer and nasopharyngeal cancer which are both primarily treated with radiotherapy, surgery is studied in relation to radiotherapy (i.e. before or after radiotherapy). For vagina, surgery and radiotherapy are regarded independently.

3.8.2 Radiotherapy (RT)

Radiotherapy is (unless otherwise stated) analysed for all types of RT (external RT, brachytherapy and combined external and brachytherapy) together. The timeframes used to study RT are different for the different tumours and are reported in Appendix C.

3.8.3 Chemotherapy

Chemotherapy products are selected based on the ATC (Anatomical Therapeutic Chemical Classification System) codes. For this study, all cytostatics (level L01) are included for analyses. For an overview of all included products, see Appendix D. For an overview of all timeframes used to study chemotherapy for the different tumours, see Appendix C.

3.8.4 Treatment Schemes

Information on surgery, radiotherapy and chemotherapy is combined into treatment schemes. The description of treatment schemes differs for the different tumours and is based on the literature. Only treatment schemes that were observed are presented. It should be noted that based on the nomenclature, it is very difficult to find out whether for a patient who underwent both radiotherapy and chemotherapy this is given in the setting of concomitant chemoradiotherapy. Therefore, we report that the patient has had chemoradiotherapy when both chemotherapy and radiotherapy took place within the predefined timeframe.

3.9 Survival

For all survival analyses reported in this part, a minimum follow-up was guaranteed until May 18, 2013. This implies that for all patients, a complete five year follow-up was available and censoring was only needed for patients lost to follow-up within the first five years after diagnosis. Additionally to the above mentioned exclusion criteria for this part of the study, patients who were lost to follow-up at the day of incidence were removed from the survival analyses.

The following survival analyses are reported when at least two subgroups have a number at risk of 35 patients or more:

- Overall survival: survival for both sexes together
- Relative survival by sex (if applicable)
- Relative survival by age group
- Relative survival by stage
- Relative survival by sublocalisation (ICD-10)
- Relative survival by primary treatment

3.10 Analyses by Volume

3.10.1 Assignment of each patient to one centre

To analyse hospital volume, it was for methodological reasons necessary to identify one centre per patient, although patients might have consulted different physicians in different hospitals. Specific algorithms were designed to identify for each patient the centre with the most important impact on the quality of care. The following medical acts were taken into account in the algorithms:

- Surgery (major surgery, minor surgery and lymphadenectomy)
- Radiotherapy
- Chemotherapy
- The centre were the patient was discussed at a MOC

For each type of those medical acts the identified centre was the one where the medical act that was closest to the incidence date (or the date of major surgery in case of adjuvant treatment) and within a certain timeframe around the incidence date (or date of major surgery) was performed (Appendix C). When both neoadjuvant and adjuvant chemotherapy, or both neoadjuvant and adjuvant radiotherapy were performed in a different centre, the centre of the neoadjuvant therapy prevailed over the centre of the adjuvant therapy. For tumours for which the primary treatment was radiotherapy, the surgery or chemotherapy conducted before RT received priority above the surgery or chemotherapy performed after RT if both took place in a different centre.

Hospital merges were taken into account until the end of the most recent incidence year that was included in this study, i.e. December 2007.

A set of rules was used to assign each patient to one centre. The order indicates the priority between the rules (1 = highest priority):

1. When only one centre could be identified for surgery, chemotherapy, radiotherapy and/or discussion at the multidisciplinary oncological consult (MOC), this centre was always chosen (NB: to apply this rule, not all of these medical acts should have taken place)

If more than one centre was identified for these acts:

2. The centre where the major surgery (if applicable) took place was chosen.
3. The centre where RT took place.

4. The centre where minor surgery or lymphadenectomy took place when no major surgery was performed.
5. The centre where chemotherapy took place.

An exception to these rules is nasopharyngeal cancer, for which the second rule was not applied. The other rules are applied in the same order, and all nasopharyngeal surgeries are treated as minor surgeries or lymphadenectomies in the centre assignment. Another exception is lip cancer, for which all surgeries are taken into account in the second rule and the fourth rule was not taken into account. For salivary gland cancer, the second rule applies for salivary gland surgery and for head and mouth surgery while the fourth rule only applies for lymphadenectomies.

3.10.2 Analyses by Volume

To compare the volume of the different hospitals, all Flemish centres were selected. However, as it is possible that patients with an official residence in the Brussels-Capital Region or in the Walloon Region are treated in Flemish centres, these patients are also taken into account in the calculation of the centre's volume.

To study whether the volume of the centre has an influence on the treatment of the patient, centres are divided into high-volume and low-volume centres. Because the literature concerning the threshold to consider a centre as high- or low-volume is scarce , the threshold is arbitrarily set for each tumour with a minimum of ten patients per year (40 patients for the period 2004-2007). Tumours for which none or only one of the centres has treated ten or more patients per year are not divided into high- and low-volume hospitals and therefore no further analyses were performed. Because RT got a rather high priority in the rules to assign a patient to a centre, RT- centres are often over represented in the group of high-volume centres. This may to some extent influence the results.

4 References

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