

Discussion and Conclusion

After previous publications on cancer incidence and survival by cancer type in Belgium and by region [1-4], the current publication provides a detailed inventory of rare cancers in the Flemish Region. To identify rare cancers, we used the definition provided by RARECARE, considering malignancies with an incidence rate lower than 6/100,000 per year as rare [5].

The **first part** of the issue describes the incidence, trends and survival of a wide variety of rare cancers in different organs systems. All Belgian patients living in the Flemish Region, with a new cancer diagnosis between 2001 and 2010, are included.

Generally it can be stated that rare cancers are a minority within each group of cancers of a specific organ or organ system. However, there is a marked diversity in incidence amongst the group of rare cancers. Some rare cancers are not so uncommon such as for example squamous cell carcinoma of the larynx (5.94/100,000 per year), other are very rare and have not even been reported during the observation period such as for example lymphoepithelial carcinoma of the thymus. It is also important to mention that in the RARECARE list both sexes are combined to determine a rare cancer. In the present study, the RARECARE definition has been applied to the incidences of both sexes together, but also of each sex separately. In the case of laryngeal cancer, this tumour is a common cancer in males (10.77/100,000 per year) but a rare cancer in females (1.23/100,000 per year). Additionally, not all tumours listed as rare in the RARECARE list, are rare in the Flemish Region, as for example the squamous cell carcinoma of the cervix uteri which is common in the Flemish Region (9.11/100,000 per year) but rare according to the RARECARE list.

Besides testicular and trophoblastic cancer, incidences are very low in young patients between the age of 15 and 40 years. In most cases there is a continuous increase in age specific incidence, starting at ages between 40 and 60 years. As a consequence, most tumours mainly occur in older patients. In some cases however, as for example in papillary serous cystadenocarcinoma of the ovary, there is a peak around 65-70 years followed by a decline thereafter.

The availability of the tumour stage is highly dependent on the cancer type. For example, mesothelioma have a very high percentage of tumours with an unknown stage, in contrast with hypopharyngeal cancers. Besides this variation between cancer types, some variation can also be observed between the different histological subtypes within a cancer entity. For example, the proportion of tumours with an unknown stage is 17.4% for squamous cell carcinoma of the bladder, while this is nearly double (33.5%) for the adenocarcinoma of the bladder.

Concerning the trends in incidence, there is no clear trend in general: some tumours (e.g. squamous cell carcinoma with variants of nasopharynx) show an increase in incidence, some (e.g large cell

carcinoma of lung) a decrease and others (e.g. squamous cell carcinoma with variants of oral cavity) remain stable. It is however important to note that trend analyses in this study might be complicated by the low incidences.

Concerning survival, different points have to be highlighted. First of all, a worse prognosis for rare cancers, compared with common cancers is a known phenomenon: in literature, a 5-year relative survival of 65% for common cancers and of 47% for rare cancers is mentioned [5]. Higher ages are associated with a worse prognosis: the survival of the two youngest age groups are frequently comparable, while the oldest patients have a poorer outcome. The more advanced stages are also associated with a worse prognosis and in the majority of rare cancer entities, females have a better prognosis. Detailed analyses often show differences in survival for different histological subgroups. In lung cancer for example, poorly differentiated endocrine carcinomas clearly have a worse outcome than squamous cell carcinomas. This difference in survival is often related to differences in stage distribution at diagnosis: histological subtypes with lower 5-year survival probabilities present more frequently at more advanced stage.

In the **second part**, a selection of 11 rare cancers is studied more in detail, with particular attention to clinical care including diagnosis and staging, multidisciplinary consultations and treatment, and to the diversity in clinical management. To this purpose, all Belgian patients living in the Flemish Region, with an incidence of a rare cancer between 2004 and 2007 are considered.

Large differences in the availability of the differentiation grade and the stage are observed for the different tumours. The percentage of tumours with an unknown differentiation grade ranges between 13.1% for oral cavity cancers to 45.9% for salivary gland cancers. This proportion is even higher for mesothelioma which are not ordinarily graded: 89.2% of these tumours are registered without differentiation grade. Large differences are also observed in the proportion of unknown stages. For head and neck cancers, this ranges from 8.1% for hypopharyngeal cancers to 51.5% for lip cancers. For non-head and neck cancers, high percentages of unknown stages are reported for cancers of the vagina (49.2%).

No clear trend can be observed in the sex or age-dependent differences in stage distribution for the different tumours: for some tumours the stage distribution is the same for both sexes (e.g. oropharyngeal cancer), for others females have less favourable stages (e.g. nasopharyngeal cancer), while the reverse has also been observed (e.g. salivary gland cancer). For most tumours, older patients have a less favourable stage distribution, although the opposite is also observed (lip and hypopharynx). In laryngeal and oropharyngeal cancer, no difference in stage distribution can be observed between the age groups.

Diagnostic and therapeutic procedures for the selected rare cancers are studied by means of administrative data on medical acts (nomenclature and pharmaceutical specialties), provided by the health insurance companies (HIC). Given the obligatory health insurance for residents of the Flemish Region, HIC data have the enormous advantage of being population-based. Moreover, retrospective studies prevent the costs and efforts associated with prospective registration projects. On the other hand, the use of HIC databases inevitably entails some limitations. A first limitation is that only

charged medical acts are available in the HIC data. For example, acts which are not charged because they took place in the context of a sponsored clinical trial, are not available in the HIC data. A 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 invoice date 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.

Across all different rare cancer types, the clinical suspicion of a malignancy is proven by pathology tissue examination in almost 100% of cases. Different staging procedures have been used, but beside lip and vulvar cancer, more than 80% of the patients undergo an examination by CT scanning. It should be noted that within the studied period, nomenclature for CT scanning was not diversified between different anatomical regions. The proportion of patients having undergone CT scanning may therefore be artificially high. A chest X-ray is also performed in a majority of the patients. However, due to the lack of specificity of nomenclature codes as described above, it is not clear if the X-ray is performed in the course of staging or for other reasons such as pre-operatively or to exclude pulmonary infections. Other technical studies are performed at different frequencies depending on the primary tumour, such as endoscopic examinations, PET-scan, MRI... Screening for second primary malignancies of the upper aerodigestive tract is often performed for head and neck cancers. In all studied tumour types, more than 40% of the patients have been screened for a tumour of the upper digestive tract.

For most cancer types, a multidisciplinary oncological consult (MOC) has been charged to more than half of the patients, ranging from 55% to 73%. A major exception to this rule is cancer of lip, for which a MOC is only found in 27.5% of patients. This cancer type may often be treated in a pure ambulatory setting without referral to a hospital and may therefore not be discussed at a MOC. Although an increase in the percentage of patients discussed at the MOC is noted during the observation period for most cancers, the proportion of multidisciplinary discussed patients remains lower than expected. A previous study has shown that the proportion of patients discussed at a MOC is underestimated when making use of HIC data [6]. The absence of a nomenclature code for a MOC in the health insurance database does not always imply that no MOC has taken place within the defined timeframe. It only indicates that no MOC was charged during that timeframe. In this previous study, it has been confirmed that for some patients there is no MOC charged although the meeting has taken place, or that another MOC outside the timeframe has been charged [6].

For each rare cancer entity which has been investigated in detail, treatment schemes have been reconstructed based on HIC data. Certain methodological decisions should be kept in mind when interpreting these results.

Concerning surgery, it is important to mention that patients might have had more surgeries than those that have been selected as basis for the build-up of the treatment schemes. For oral cavity cancers for example, priority has been given to the major surgeries. As a consequence, patients for which major surgery has been selected as the cornerstone of the treatment might also have undergone lymphadenectomy.

For chemotherapy analyses, all antineoplastic and immunomodulating agents (ATC code L01) have been considered together. This choice implies that differences between chemotherapeutic drugs and targeted agents, or the usage of different chemotherapy schedules have not been investigated within the current project. Such detailed analyses might be the subject of future studies.

As for radiotherapy, nomenclature enables a distinction between external radiotherapy, brachytherapy or a combination of both. This differentiation has been taken into account in the analyses of tumour types that are regularly treated with brachytherapy such as lip cancer. On the other hand, nomenclature descriptions for radiotherapy are not referring to the target region for which the radiation has been charged. It is therefore impossible to discriminate between radiotherapy for a local or regional treatment. In addition, detailed data on the fraction size and number of delivered fractions cannot be retrieved from HIC data.

Concerning the combined use of radiotherapy and chemotherapy, it is hard to retrieve the order in which these modalities have been administrated. Therefore, combined use has always been described as chemoradiotherapy.

Taken these methodological issues into account, the treatment schemes that have been retrieved from the HIC data show in general that most tumour types are treated according to international guidelines. This is not the case for vaginal cancer, for which in contrast to what we expected, surgery is more frequently the cornerstone of the treatment than radiotherapy.

For a certain proportion of patients, no information could be found concerning treatment. This proportion varies between 1.8% and 23.4% for lip cancer and mesothelioma, respectively. For all head and neck cancers and for vulvar cancer no treatment was found in HIC data for less than 10% of patients, for anal canal and vaginal cancer this was the case for more than 15% of the cases. Multiple reasons can be put forward to explain this variance. Some patients who present in very poor performance with an advanced or metastatic cancer, might only be offered supportive care without active oncological treatment. This can especially be the case for mesothelioma as no good therapeutic options are available for this cancer type. On the other hand, no charged medical acts are found for patients who are included in clinical trials with fully sponsored therapeutic regimens.

As head and neck cancers constitute the majority of the cancers which have been studied in detail, we have a further look at the treatment schemes that were set up for these cancer types.

It is clear that for head and neck cancer, treatment greatly depends on the primary localization of the concerned tumour. Lip cancers are almost exclusively treated with surgery. For cancers of the larynx, the oral cavity and the salivary glands, surgery is the treatment of choice, in a majority of the patients followed by adjuvant treatment. Hypopharyngeal and oropharyngeal cancer are most frequently treated with (chemo)radiotherapy although surgery as the cornerstone of the treatment seems to be an alternative for a large amount of patients. As expected, almost all nasopharyngeal cancers are primarily treated with radiotherapy.

Survival results presented in this booklet are frequently hampered by the low numbers at risk at start of the observation period. For nasopharyngeal cancer and vaginal cancer, this problem prevents all further subgroup analyses. For other cancers, certain subgroups are not presented in survival analyses (e.g. stage I and II in hypopharyngeal cancer) or are regrouped to enable estimations of survival (e.g. stages I to III in cancer of salivary glands). Almost all cancers that occur in both sexes

have a better prognosis in females. This is not the case for laryngeal cancer, for which males have a better 5-year relative survival than females. Beside in lip cancers for which younger patients have a slightly worse stage distribution, survival for the analysed rare cancers is poorest for the oldest patients. Analyses by stage confirm an inverse relation between the stage of the disease and the outcome of the patients: more advanced cancers have a poorer prognosis. Notably, survival rates of stage IV cancers of the head and neck region are generally higher than for other tumour types. This finding is related with the classification of head and neck cancers, in which some locally or regionally advanced diseases are diagnosed as stage IVA and IVB. Stage IV disease is not always designated incurable, especially in the absence of distant metastases (stage IVC).

In spite of the low numbers at risk, detailed survival analyses have been performed for several tumour types. These results show a prognostic advantage for certain histology groups as for example low grade cancers in salivary gland tumours, and epithelioid morphologies in mesothelioma.

Of all head and neck cancers, cancer of the lip has the best prognosis and hypopharyngeal cancer the poorest (5-year relative survival of 91.0% versus 29.6%). Besides this difference in survival between the major head and neck cancer regions, variable prognoses are also observed for sublocalisations within some head and neck cancer entities. In oropharyngeal cancer for example, the best survival is seen in lesions of the soft palate and the uvula.

The analyses concerning the distribution of patients by centre show a large spread in the management of patients with rare cancers. The number of hospitals in the Flemish Region taking care of rare cancers ranges from 15 (nasopharyngeal cancer) to 55 (laryngeal cancer). On one hand, this wide range might be related with the large differences in incidence between the rare cancer entities. On the other hand, treatment options might play a role for certain tumour types: the care for nasopharyngeal cancer is probably less dispersed because the main treatment for this tumour type (radiotherapy) is not available in every centre.

Distribution of patients by hospital is unequal, and often large deviations are seen between the mean and median number of patients by hospital. This is for example the case for hypopharyngeal cancer which have been treated in 29 Flemish hospitals during the concerned observation period, with a mean value of 13.5 patients per centre, a mean of 2 and a range between 1 and 56 patients per centre. These data confirm that some hospitals clearly treat more patients with a certain rare cancer entity than others.

In the absence of published reference values, the cut-off to discern low- from high-volume hospitals has been chosen arbitrarily based on the observed patient distribution. Due to the low number of patients diagnosed and treated in a wide variety of hospitals, analyses of differences in used treatment schemes between low- and high-volume centres are not possible for a number of tumour types (cancer of salivary gland, anal canal cancer, lip cancer, nasopharyngeal cancer, vaginal and vulvar cancer). For hypopharyngeal and oral cavity cancer, treatment schemes are comparable between low- and high-volume hospitals. This is not the case for laryngeal and oropharyngeal cancer and mesothelioma, for which surgery seems to be less frequently considered as the primary treatment in high-volume hospitals compared with their low-volume counterparts. This finding may be confounded by the fact that radiotherapy has been considered in the process of assigning patients to a centre.

In conclusion, the present project is the first to give a detailed insight in the epidemiology and clinical care for rare cancers in the Flemish Region. As registration data at the Belgian Cancer Registry are complete for the Flemish Region from 1999 onwards, the current results can be considered population-based. In view of the obligatory health insurance in our country, the diagnostic and therapeutic acts described by means of HIC data also completely cover the studied population. Despite possible drawbacks associated with their use, HIC data are proven suitable for analyses of cancer care.

We hope that this project may enhance knowledge on rare cancer epidemiology and clinical care, and may be useful in future discussions concerning health care organization for rare cancer management. In line with international initiatives such as RARECARENET, the current results can stimulate further research on these malignancies which are still associated with a poorer outcome than their common counterparts.

References

1. Cancer Incidence in Belgium, 2004-2005, Belgian Cancer Registry, Brussels 2008
2. Cancer Incidence in Belgium, 2008, Belgian Cancer Registry, Brussels 2011
3. Cancer in Children and Adolescents, Belgian Cancer Registry, Brussels 2013
4. Cancer Survival in Belgium, Belgian Cancer Registry, Brussels 2012
5. Gatta G, van der Zwan JM, Casali PG, Siesling S, Dei Tos AP, Kunkler I et al. Rare cancers are not so rare: The rare cancer burden in Europe. *Eur J Cancer* 2011; 47: 2493-2511.
6. Vlayen J, De Gendt C, Stordeur S, Schillemans V, Camberline C, Vrijens F, Van Eycken E, Lerut T. Quality indicators for the management of upper gastrointestinal cancer. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). 2013. KCE Reports 200. D/2013/10.273/15.