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Deliverable nr D7.2

Title **Recommendations on requirements for long-term surveillance of rare cancer patients (for each family of rare cancers)**

Contents

DESCRIPTION

Joint Action on Rare Cancers

The Joint Action on Rare Cancers (JARC) is aimed to integrate and maximize efforts of the European Union (EU) Commission, EU Member States and all stakeholders to advance quality of care and research on rare cancers.

The public health challenges posed by rare cancers include the limited professional expertise in the community, the difficulties in clinical research, the need of a timely and appropriate diagnosis and optimal treatment from the very beginning of the patient's journey. An accurate clinical, pathologic and biological assessment of the disease of the individual patient is key to survival and cure, as well as an expert clinical decision provided by a multidisciplinary team. To this end, proper referral of patients and effective clinical networking are crucial in rare cancers. This is the main reason why JARC decided to shape its efforts around the new European Reference Networks (ERNs) with the following objectives:

1. Improving epidemiological surveillance of rare cancers in the EU
2. Identifying standards of care for all families of rare cancers to ensure sharing of best practices and equality of care for rare cancers across Europe, particularly through clinical networking
3. Improving the implementation at local level and within ERNs of clinical practice guidelines on rare cancers
4. Promoting integration of translational research innovations into rare cancer care
5. Improving education on rare cancers for medical and non-medical experts to ameliorate management of rare cancers and to improve rare cancer patients' empowerment in the EU
6. Identifying core strategies to incorporate in National cancer plans and Rare disease plans to address the specific needs of rare cancers across EU MSs

The JARC is structured in 10 work packages (WPs). Three cross cutting WPs (WP1 coordination, WP2 dissemination, WP3 evaluation) and 7 specific WPs based on the JARC objectives: WP4 epidemiology, WP5 quality of care, WP6 clinical practice guidelines, WP7 innovation and access to innovation, WP8 medical education, WP9 childhood cancers and, WP10 rare cancers policy. Patients work across all work packages, driving the JARC efforts to ensure the need of the end users are integral to everything we can do, in care and research as well.1.2

Work Package 7

The goal of WP7 is to establish optimal ways to bring the best treatment and care to patients by advancing translational and clinical research on rare cancers through ERNs.

The main objectives of this workpackage are:

- to stimulate translational research on RCs by exploiting networking, namely through the new ERNs, as a means to promote tissue banking to promote exploitation of "big data", namely those generated through the new ERNs, as a means to advance our knowledge on rare cancers to provide:
    - recommendations on how to optimize long-term surveillance of rare cancer patients in an effort to
    - address the many survivorship~~'s~~ issues to make proposals on how to exploit available regulations across the EU, and/or how to improve them, on collaborative prospective interventional clinical research, especially academic clinical research joining national collaborative groups (inter-group research, etc.).

Aim and purpose of deliverable

The goal of WP7 is to establish optimal ways to bring the best treatment and care to patients by advancing translational and clinical research on rare cancers through ERNs.

Objectives:

- to stimulate translational research on RCs by exploiting networking, namely through the new ERNs, as a mean to promote banking of tissue samples associated with rich clinical data on patient and tumour demographics, treatment and outcomes
- to promote exploitation of "big data", namely those generated through the new ERNs, as a mean to advance our knowledge on rare cancers to provide recommendations on how to optimize long-term surveillance of rare cancer patients in an effort to address the many survivorship~~'s~~ issues
- to make proposals on how to exploit available regulations across the EU, and/or how to improve them, for collaborative prospective interventional and non-interventional (observational) clinical research, especially academic clinical research joining national collaborative groups (inter-group research, etc.).Recommendations will be provided with regard to the requirements for long-term surveillance of rare cancer patients, given the peculiarities of their natural history and treatments, so that these criteria may be added to those which are relevant to accreditation of ERNs and reference centres on rare cancers.

Thus, this task addresses the many regulatory and legal issues posed by clinical big data. It will address the issues concerning the harmonization of these data, especially in terms of their semantics. The goal was to explore the possibility to set up a clinical epidemiology framework program for outcome research in rare cancers. Conceptual optimized models to integrate big data from pathology files, tumor registries, electronic patient records and administrative health data bases were assessed. The use of patient-reported outcomes, including quality of life end-points, were explored theoretically.
Finally the theoretical and methodological issues posed by the use of these data to advance medical knowledge (in a framework which is radically divergent from the one of clinical trials) were addressed.

This deliverable covers the results of the pilots conducted in this JA on 'exploiting available regulations across the EU, and/or how to improve them, on collaborative prospective interventional clinical research" especially academic clinical research joining national collaborative group'

The target group of the specific deliverable

The main target group of this deliverable are the members of the European Reference Networks, especially the responsibles/principal investigators for clinical trials within the context of rare cancers. In addition, policy makers involved in facilitating, controlling or authorizing clinical trials and studies are a key target public.

Summary of the main conclusions of the deliverable

The main conclusion from the activities in the task 7.2 are:

- Cancer Registries have to exploit different alternative data sources and establish a good collaboration with the clinical experts on the field

- Efforts are needed to strengthen the links between population-based cancer registries, clinical registries, electronic clinical records, administrative databases and healthcare data so that cancer registries enrich their database with relevant clinical data
- In order to facilitate data extraction and data exchange, implementation of structured detailed information in the electronic medical records is necessary
- If relevant clinical data is not available in a structured way cancer registries need to invest in innovative techniques, e.g. artificial intelligence, to extract relevant clinical data from text reports
- National Cancer Registries have to reflect together with the ERNs how to harmonize the registration modalities in order to avoid double work
- Actions are needed to anticipate and implement quickly evolving knowledge in terms of the molecular features and ~~his~~ complexity of different cancers in a structured way and on a population level
- Need of infrastructural and financial resources for the Cancer Registries to develop and implement the above mentioned points
- In the process of every step need to take into account the privacy regulations to be compliant to the General Data Protection Regulation
- Recommendations were made that Toronto stage should be requested in the next data call (2020) of the ENCR for the European Cancer Intelligence System (ECRIS) and that the CRs should work together to apply for funding to exploit use of the enhanced datasets available at a European level.

INTRODUCTION

Population-based cancer registries have, next to the well-known epidemiological descriptive role (serve public health by monitoring changes in cancer occurrence and prognosis) also an important role in the quality of care and cancer control. This is due to the growing interest in real-world data, i.e. population based data on diagnoses, treatment enriched with more relevant clinical data and linkage to long term health outcomes, including patient-reported data. More in general, larger and larger amounts of data will be automatically generated by electronic patient records, as well as other administrative and research databases. Cancer Registries (CRs) are well positioned to bring these data together because of their experience in data handling, the so-called 'big data'. The objective in task 7.2 was to explore the possibility to set up a platform for a clinical epidemiological framework program for outcome research in rare cancers. This is performed by means of two pilot studies: HPV oropharyngeal cancer and Toronto principle and guidelines for staging of major childhood malignancies.

Head and neck cancers are a heterogeneous group of tumor entities arising in the upper aerodigestive tract. For oropharyngeal cancer, the presence of high-risk HPV has gained tremendous interest over the last years. On the one hand, HPV infection has been identified as a principal cause of the increasing incidence rates for oropharyngeal cancers in a non-smoking and non-alcohol drinking population (1). On the other hand, patients affected by HPV-related cancers have been demonstrated to have better survival rates (2, 3). In the pilot study we would like to examine the availability of tumor stage, HPV status, and treatment modalities, and its influence on the adherence to guidelines and outcome in oropharyngeal cancer.

Childhood cancers are defined in epidemiological terms as those arising in children aged 0-14 yrs, though they also occur rarely in older adolescents and young adults. Their biology is very different from the common adult cancers, with 12 major categories and many more sub-categories (1). Their pathological classification is not always based on anatomical organ of origin and the typical adult Tumour-Node-Metastases (TNM) staging system is not clinically useful or relevant in many. Hence, data quality and comparability between registries can be highly variable unless specific efforts are made to apply age-appropriate cancer classifications. Furthermore, choice of treatment intensity for an individual child or young person is often based on risk stratification factors that include tumour response to pre-operative chemotherapy and, increasingly, molecular analysis of the tumour tissue or quantification of minimal residual disease.

Collaborative cancer registry research has demonstrated differences in overall survival rates for childhood cancers between European countries, however, without systematic knowledge of tumour stage at diagnosis, it is difficult to interpret the reasons for this variation. In the pilot study, we aimed to test the abilities of CRs to apply a recently agreed global consensus set of principles and guidelines for assigning tumour stage in childhood cancers (the 'Toronto' staging guidelines) to two index childhood solid tumours, so that survival by stage could be calculated. We also assessed the availability to CRs of the additional clinical data required to determine clinical risk stratification and success of first line therapy. This is expected to aid interpretation of existing survival benchmarking studies and to form the basis for future analyses of treatment and outcomes (including relapse) according to 'risk group' that will also integrate tumour biology.

MATERIAL AND METHODS

In this workpackage we applied following methods:

1. **Pilot study: Develop a model for longitudinal follow-up of HPV ororpharynx carcinoma patients through cancer registries enriched with additional medical/pathology information**

1.a. The Belgian Cancer Registry developed a questionnaire with questions about information available on patient and tumor characterisctics, information on risk factors, tumor stage, HPV status and related testing, treatment data, follow-up data, different disposable data sources, data linkage possibilities and privacy issues

1.b. 10 CRs of member states participating in the JARC, were invited by mail to take part in the questionnaire. When interested a telephone conversation or skype call was fixed to go through the questionnaire orally.

1.c. 7 of the invited CRs consented and additonal information was received.

2. **A pilot study to test how the Toronto paediatric cancer staging information can be adopted by population-based cancer registries in one or more major childhood tumour types**

2.a The protocol for the pilot project was developed jointly between a paediatric oncologist (KPJ) and epidemiologist (Gemma Gatta), in close iterative consultation with the Cancer Registries (both general and specialist paediatric) who have a long-established collaborative research relationship in childhood cancers epidemiological research.

2.b All interested Cancer Registries were invited to participate in the pilot project, not only those registries already participating in the JARC, by providing tumour stage on two index solid tumours (neuroblastoma and Wilms tumour, the two commonest extra-cranial solid tumours of childhood). A teleconference call with all interested parties was held in Oct 2017 to finalise the protocol, subsequent questions were dealt with by email or individual phone call.

2.c All invited registries expressed interest and 14 countries (24 CRs) contributed data to the pilot study. Some non-participating countries provided information on the staging data they held and how they would obtain more complete 'Toronto stage', but did not have the resources or were not able to comply with data access permissions in the timeline.

2.d All interested registries (including those who could and **those** who were not able to provide staging data) were invited to a workshop, held **in Brussels,** 5-6 March 2019, to discuss the results of the Toronto pilot study and how collection of staging (and other clinical) data could be made sustainable for new cases. Representatives from 15 countries' CRs and 2 clinical trial groups (neuroblastoma and Wilms tumour) attended and recommendations were made.

The Workpackage partners met on 3 WP meetings to discuss aims of the WP and share work progress.

RESULTS

1. **Pilot study: Develop a model for longitudinal follow-up of HPV ororpharynx carcinoma patients through cancer registries enriched with additional medical/pathology information**

1.a. Data availability

All participating CRs have basic patient and tumor information at their disposal. All but one CR possess detailed information on TNM classification, including separate T-, N- and M-categories. The remaining CR does have stage group information (i.e. local, regional or distant spread). No CR holds data on individual risk factors like alcohol and tobacco consumption. The follow-up data is limited to the date of death, which is available in 6 CRs. Only one CR is (very recently) provided with structured information on p16 testing and HPV status. In all other CRs this information is achievable but not readily accessible in a structured way, and indicated that a great effort would be necessary to obtain this kind of structured information. Two CRs have access to data on imaging modalities. Also here, this information is not readily accessible in a structured way and CRs indicated that efforts are needed to retrieve those data (i.e. resources, time and funding).

All participating CRs have access to data on surgery and radiotherapy performed for the primary tumor, all but one additionally have data on chemotherapy at their disposal, and 2 CRs also have data on targeted therapy available . Various data sources are consulted to obtain the information concerning treatment, mainly medical files followed by hospital discharge data. Other data sources include clinical datasets, reimbursement registry for medical acts, routine primary care registry and administrative databases containing reimbursed medical acts and pharmaceuticals.

1.b. Linkage possibilites

As various data sources are consulted to obtain the detailed clinical data and detailed treatment data linkage is needed form those different data sources with the Cancer Registries. Almost all CRs have the possibility to link, either by means of a unique patient identifer or by indirectly probabilistic coupling.

1.c. Resources and privacy regulation for data linkage and data transfer

In order to participate to a pilot study the CRs have to gather the detailed clinical information from other data sources, entailing issues that have to be tackled such as linkage possibilities and privacy regulations to be compliant to the General Data Protection Regulation.

2. A pilot study to test how the Toronto paediatric cancer staging information can be adopted by population-based cancer registries in one or more major childhood tumour types

2.a. Data availability

Electronic health record data systems are not yet sufficiently mature in most countries for the detailed clinical information needed for Toronto staging to be routinely available to CR staff. Most registries held some staging data already for the two tumour types, but levels of completeness were variable as was the adequacy of data sources used for staging according to the Toronto principles. Most had required more than one data source to complete the Toronto stage. All had had to go back to existing records and/or obtain new data sources in order to perform the task.

14 countries (24 CRs) contributed data on 499 neuroblastomas and 387 Wilms tumours with Toronto stage provided for 97% of cases. Cases were diagnosed in the time period 2000-2016 (mostly 2011-2016) with 3 year follow up data were available for the majority.

2.b. Linkage processes used and possibilities:

In several countries, registry staff are not allowed to visit clinical centres and examine medical records so have to rely on the voluntary efforts and goodwill of the clinical and data management staff in treatment centres and/or clinical registries to provide the necessary data. No registry used an algorithm to assign Toronto stage but did it manually from existing records supplemented by the new data sources they were able to gain access to. There was interest in learning more about the App developed by the Australian national cancer registry to support registry staff in assigning Toronto stage from clinical data (mainly imaging and pathology reports).

2.c. Resources and privacy regulation for data linkage and data transfer

Estimates of staff time to collect the data and assign the Toronto stage varied from 10 mins/case to a few days or even weeks for 20 cases for countries where much more reliance was placed on responses from clinical treatment centres. In some countries, data requires parental consent to be collected, either as part of the authorization of the national children's cancer registry or because the CR is not a statutory government organization but an academically-led initiative. In some countries, linkage between the CR and clinical registries was hampered by the lack of a unique personal identifier at the national level.

There is variation between countries in the requirements for individual projects using enriched datasets to have national regulatory and/or ethical approval in order to provide patient-level data, even if the data are heavily pseudonymised and hence not identifiable to the collaborative project team.

2.d Clinical results and interpretation of the pilot study

The distribution of age at diagnosis for the two index tumours is as expected from previous EUROCARE studies (2). For neuroblastoma, the proportion with metastatic disease at diagnosis was >50% in those aged over 1yr compared to only 12% in those diagnosed as infants < 1yr. For Wilms tumour, 14% had metastases at diagnosis. 76% of the Wilms tumours were noted to have been treated with elective pre-operative chemotherapy. There was evident variation in stage distribution by country. The overall survival for each tumour type was as expected from EUROCARE. Whilst some exploratory analyses of correlations of survival by country and by stage distribution were presented, it was agreed that the cohorts would need to be larger for any statistically robust comparisons.

2.e Potential for additional data items

Several countries had provided data on treatment and relapse, very few had data on imaging used for staging purposes or metastatic response. Whilst data on biological subgroups have been included in pathology reports for several years in many tumour types, they don't have a specific code in the ICD0 and are therefore difficult to register. Some molecular tests used for clinical diagnostic purposes are available to CRs but are often incompletely reported or require special efforts to link to their data source in clinical disease-specific registries.

2.f Mobility of patients and need for a European Patient Identifier

Some registries experienced high rates of migration of cancer patients which made it difficult to have access to a complete record of healthcare activity for each patient or to ensure continuity of surveillance – this highlights the potential need for a unique European patient identifier that CRs could access in a non-disclosive way. All CRs commented on the potential to lose patients to follow up when children transition to young adults (15-19yrs) as they are no longer seen in the paediatric oncology hospitals. For continuity of surveillance of healthcare outcomes, it was recommended that consideration be given to a European Patient Identifier, that could be made available to CRs in a non-disclosive way with modern pseudonymisation methodologies..

DISCUSSION

A: **Develop a model for longitudinal follow-up of HPV ororpharynx carcinoma patients through cancer registries enriched with additional medical/pathology information**

Through this pilot study, we have established that most European cancer registries do not have readily access to the detailed clinical information that is required to identify the individual treatment, prognosis and long-term surveillance. Extra resources and funding will be needed to retrieve this essential detailed information. In addition, data linkage and data transfer require substantial administrative work, and for most of the CRs particular permission processes from authorities are requested.

In order to set up a clincial epidemiological framework program for outcome research in rare cancers following recommendations could be made:

- Cancer Registries have to exploit different alternative data sources and establish a good collaboration with the clinical experts on the field
- Efforts are needed to strengthen the links between population-based cancer registries, clinical registries, electronic clinical records, administrative databases and healthcare data so that cancer registries enrich their database with relevant clinical data
- In order to facilitate data extraction and data exchange, implementation of structured detailed information in the electronic medical records is necessary
- If relevant clinical data is not available in a structured way cancer registries need to invest in innovative techniques, e.g. artificial intelligence, to extract relevant clinical data from text reports
- National Cancer Registries have to reflect together with the ERNs how to harmonize the registration modalities in order to avoid double work
- Actions are needed to anticipate and implement quickly evolving knowledge in terms of the molecular features and ~~his~~ complexity of different cancers in a structured way and on a population level
- Need of infrastructural and financial resources for the Cancer Registries to develop and implement the above mentioned points
- In the process of every step need to take into account the privacy regulations to be compliant to the General Data Protection Regulation

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B. **A pilot study to test how the Toronto paediatric cancer staging information can be adopted by population-based cancer registries in one or more major childhood tumour types**

The pilot study was conducted successfully and demonstrated the current capabilities and enthusiasm of the European CRs to collect additional data in order to be able to assign an international consensus standard tumour stage to a population-based cohort of two solid tumours of childhood. The effort required to obtain the necessary clinical data to assign the Toronto stage was considerable, and it was not possible for all CRs to take part in the pilot – their barriers were the lack of availability of resources and the relatively short timescale of the project if specific data access permissions were required.

In order to set up a clinical epidemiological framework program for cancer outcomes research in children and young people, the following recommendations are proferred:

Toronto stage should be requested in the next data call (2020) of the ENCR for the European Cancer Intelligence System (ECRIS).

ENCR should work towards this being an obligatory field for paediatric cases in the CRs in the future and provide training and tools through the ENCR and JRC.

As well as ENCR endorsement of the Toronto Staging guidelines, SIOP Europe should be asked for a statement endorsing the importance of close cooperation between clinical centres/clinical registries and their population based cancer registries to make staging and other clinical data available.

The offer from the Australian children's cancer registry to share their learning and electronic tool, the TorontoStage App, should be embraced by a coordinated interface with the European CRs.

The CRs interested in childhood cancer should work together to apply for funding to exploit use of the enhanced datasets becoming available at a European level. For statistically meaningful comparisons of tumour stage distribution by childhood cancer type between countries/regions, at least three years of incident cases with complete staging are needed for analysis.

Consideration should be given to the creation of a unique European Patient Identifier, to address the issue of patient migration and also loss to follow up when childhood patients become adults. This will be essential for evaluation of patient outcomes in the PaedCan ERN

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ANNEXES

A.1 Study Report UCL (UK)

Tender – WIV-ISP-2017-PRI094-TOR.

Report for the tender: Abstract, Executive Summary and Report

Evaluate how the "Toronto consensus principles and guidelines" can be adopted by population-based cancer registries for major childhood malignancies – approached by developing and conducting a pilot study to undertake analysis of survival by tumour stage in one or more major childhood solid tumour types.

Abstract

Background: Collaborative cancer registry research has demonstrated differences in overall survival rates for childhood cancers between European countries. Further improvements require more detailed information on patient and tumour demographics, treatment and outcomes than are currently collected by population-based cancer registries (CRs). Childhood cancers require special attention by CRs due to the specific classification systems needed to document their morphology and stage. The Toronto consensus principles and guidelines for staging each of the common childhood cancers were therefore developed to meet this need to improve data quality and comparability (1).

Methods and results: A pilot study was developed jointly between a paediatric oncologist (KPJ) and epidemiologist (Gemma Gatta), in close iterative consultation with the CRs (both general and specialist paediatric), to test how the Toronto paediatric cancer staging guidelines could be implemented for two index tumour types. 14 countries (24 CRs) were able to contribute data, totalling 499 neuroblastomas and 387 Wilms tumours diagnosed consecutively in the time period 2000-2016 (mostly 2011-2016). Toronto stage was provided for 97% of cases. All CRs needed to go back to existing records and/or obtain new data sources in order to perform the task. Data sources used were the pathology report and clinical records. Registry staff usually required two or more data sources to assign tumour stage, particularly for sub-staging of 'localised' disease. Methodology and resources used to access the data varied by country but all required considerable effort to obtain the additional data. Age distribution and survival rates were comparable to those expected from larger population-based registry reports. There was evidence for variation in stage distribution between countries.

Conclusions: Collection of Toronto stage to the highest level of detail (Tier 2) was possible for nearly all patients but required unsustainable effort without specific resourcing for retrospectively diagnosed patients. All CRs were optimistic that their current or imminently planned improvements in processes and datalinkage capabilities would enable this task to become a part of routine staging for newly diagnosed patients. Participation in the pilot study has been a useful stimulus to

strengthen joint working between CRs and clinical treatment centres/clinical registries. This task has catalyzed ambitions to collaborate on a study of survival by stage at a European level and to jointly utilise further enhancement of CR data with information on tumour biology, treatment and relapse and longer term surveillance to create a true framework for outcome research in childhood cancers capable of integrating 'big data'.

Recommendations were made that Toronto stage should be requested in the next data call (2020) of the ENCR for the European Cancer Intelligence System (ECRIS) and that the CRs should work together to apply for funding to exploit use of the enhanced datasets available at a European level.

Executive summary

Background

Childhood cancers are rare (<1% of all cancers), are classified differently to adult cancers due to their specific biology (International Classification of Childhood Cancers-03) and have their own tumour-specific staging systems.

There is variation across Europe in survival rates and the population-based cancer registries (CRs), both specialist paediatric and general, are keen to be part of further work to understand the basis for these differences.

Quality of survival is influenced by the success of first line therapy with optimised overall treatment burden to reduce risk of relapse. This is improved through accurate risk stratification at diagnosis (including tumour stage) and assessment of response during therapy.

The starting point is to be able to document the tumour stage at diagnosis in a standardised comparable way. Tumour stage is a key indicator of the cancer burden at the point of diagnosis and is used in clinical decision making to select the optimum treatment to reduce risk of relapse and maximise chances of survival.

The main method of staging adult cancers (TNM classification) is not suited to paediatric cancers, which have their own staging criteria. These vary by tumour type and in their application - in different countries and in the various clinical trials on which the evidence base for risk stratification largely relies.

In 2014, an international group of clinicians, experts in cancer registration and epidemiologists published the "Toronto consensus principles and guidelines". These provide recommendations on which staging systems should be adopted by population-based cancer registries for each of the major childhood malignancies. The Toronto staging guidelines were endorsed by ENCR in Feb 2019.

Methodology

A pilot project was developed in two exemplar childhood solid tumours (neuroblastoma – a tumour of the sympathetic nervous system that can occur in many sites in the body - and Wilms tumour (nephroblastoma) – a childhood kidney cancer) to test the capabilities of the CRs to apply the Toronto staging guidelines and to be able to share deeply pseudononymised patient-level data for analysis of survival by stage.

A key factor in the success of the project was its joint development by epidemiologists and registry staff in CRs and clinicians with leading roles in the relevant European tumour-specific clinical trials groups.

The pilot study protocol was finalised between Oct-Dec 2017 in conjunction with all CRs in Europe interested to participate. CRs then took until May 2018 to provide their data through the usual data sharing and governance channels used for the EUROCARE studies, coordinated by the Istituto Nazionale del Tumori, Milan.

Preliminary results of the pilot project data analysis were completed in 2018 and discussed in a face to face meeting by the participating and other interested CRs at a 2 day workshop held in conjunction with SIOP Europe staff in March 2019, Brussels to develop recommendations.

Results

14 countries (24 CRs) were able to contribute data on a total of 499 neuroblastomas and 387 Wilms tumours diagnosed consecutively in a recent time period (mostly 2011-2016).

97% of cases could have a Toronto stage defined successfully. In order to achieve this, all CRs needed to make additional specific efforts to obtain review existing records and obtain new data, usually from more than one source.

Preliminary data analysis was completed in 2018 and presented verbally at several epidemiology and clinical research congresses and meetings during autumn 2018.

Data access – in many countries, CR staff are not permitted to go to the hospitals to view records due to data privacy rulings set in national law – even when these are permissive, there may be variable interpretation by hospital administrators, even within the same institutions or regions, that limit data access.

The resources required to obtain the necessary information on each patient to assign Toronto stage varied according to the existing CR data completeness and mechanisms for going back to clinical data sources. The extent of variation was from 10 minutes per case (most data already held by the registry) to a few weeks to stage 20 cases.

Additional time was needed in some countries to obtain ethical and/or regulatory approval for the project, even though the CRs already have authorisation to hold staging data.

Some CRs experienced high levels of population mobility for healthcare and all CRs commented on the potential to lose patients to follow up when children transition to young adult services (aged 15-19yrs).

Conclusions

All CRs are capable of implementing the Toronto staging guidelines, given sufficient time and resources, even with their current processes.

Data exchanges with clinical treatment centres and clinical registries (where they exist) are required to obtain sufficient information to assign Toronto stage and to collect other data items relevant to understanding cancer survival rates at a population level.

The process to access data from clinical and administrative sources is often slow for various reasons e.g. no staff time, data needs 'cleaning' before sending, additional approvals required, etc. Efforts to ensure high quality data is collected once and in a format suitable for sharing are recommended to improve the efficiency of this process.

These efforts include improvements in CR data handling systems and in electronic health records. In many countries these improvements are already occurring in parallel, which should accelerate access to relevant data for CRs if efforts are synergistic and take account of 'big data' needs including molecular and imaging analyses.

With rising overall survival rates in childhood cancer (already exceeding 80%), it is becoming more imperative for cancer intelligence systems to focus on indicators that measure quality of survival not just crude survival rates. Quality of survival is affected by the intensity of therapy given, which is in turn dictated by a combination of the burden of disease at first diagnosis (tumour stage) and the accuracy of risk stratification for choice of first line therapy – increasingly dependent on molecular analyses of tumour tissue and sophisticated imaging not only at point of diagnosis but during therapy. All of these data items sit in hospital clinical records but are not yet easily available to CRs.

All CRs expressed a strong interest in continuing the collaboration initiated by this pilot to collect clinically enriched data sets and use them in future joint studies that would utilise their new data linkage and acquisition capabilities to best effect.

In order to maintain access for continuity of surveillance of healthcare outcomes on an individual patient basis (essential for evaluation of the paediatric cancer ERN), some form of European Patient Identifier is required, to be used in a carefully pseudonymised way to keep track of the outcomes of a whole pathway of treatment for each patient.

Recommendations

Toronto stage should be requested in the next data call (2020) of the ENCR for the European Cancer Intelligence System (ECRIS).

There was agreement amongst attendees that for any comparisons of tumour stage by childhood cancer, at least three years of incident cases with complete staging would be needed for the analysis.

The CRs interested in childhood cancer should work together to apply for funding to exploit use of the enhanced datasets available at a European level.

As well as ENCR endorsement, SIOP Europe should be asked for a statement endorsing the importance of close cooperation betwen clinical centres and clinical registries with their population based cancer registries to make staging and other clinical data available.

The offer from the Australian children's cancer registry to share their learning and electronic tool, the TorontoStage App, should be embraced by a coordinated interface with the European CRs. It should be easy to add the Toronto Stage as an obligatory field for paediatric cases in the CRs but training and tools will be needed and are best offered through the ENCR and JRC.

Consideration should be given to the creation of a unique European Patient Identifier, accessible to CRs in a non-disclosive way, to address the issue of patient migration and also loss to follow up when childhood patients transfer to adult services. This will be essential for evaluation of patient outcomes in the PaedCan ERN.

REPORT

1. BACKGROUND

Population-based cancer registries generate estimates of incidence and survival that are essential for cancer surveillance, research, and control strategies. Although data on cancer stage allow meaningful assessments of changes in cancer incidence and outcomes, tumour stage is not well recorded by many population-based cancer registries. The main method of staging adult cancers is the TNM classification. The criteria for staging paediatric cancers, however, vary by diagnosis, have evolved over time, and sometimes vary by cooperative trial group. Consistency in the collection of staging data on childhood cancers has therefore been challenging for population-based cancer registries.

Developed by an international group of clinicians, experts in cancer registration and epidemiologist and published in 2014, the "Toronto consensus principles and guidelines" provide recommendations on which staging systems should be adopted by population-based cancer registries for each of the major childhood malignancies (appendix 1) (1). Wide adoption of these guidelines in registries is expected to facilitate international comparative incidence and outcome studies. However, pilot investigations are needed to assess the feasibility of applying these recommendations. Thus, a pilot study aimed at assessing the feasibility of using the Toronto recommendations in European cancer registries is the objective of this task.

The task built on the long-established collaborative research relationship in childhood cancers epidemiological research between the European population-based cancer registries in incidence and survival research (2-4). These studies have demonstrated that there is variation across Europe in survival rates and the CRs are keen to be part of further work to understand the basis for these

differences. The starting point is to be able to document the tumour stage at diagnosis in a standardised comparable way.

We had prepared the ground with the CRs during discussions in previous meetings held in 2016 as part of the RARECAREnet project (Valencia, Spain, May 2016) and during a specially convened workshop held in conjunction with the annual meeting of the European Network of Cancer Registries (ENCR) (Baveno, Italy, October 2016). Furthermore, during the preparation of this pilot study, the Australian national childhood cancer registry implemented a protocol to collect Toronto stage on all stageable cancers diagnosed in the period 2006-2014 and were able to publish (in Feb 2019), for the first time at a population level in childhood cancer, survival by stage (5). Their work gave further impetus to our project and they were very generous in sharing their experience and methodological approach throughout our project.

Another key factor in setting up the pilot was to ensure it would strengthen joint working between the epidemiological CRs and clinicians, particularly those leading the European tumour-specific clinical trials groups who were also looking for new ways to undertake outcomes research. Quality of survival is influenced by the success of first line therapy with optimised overall treatment burden to reduce risk of relapse. This is improved through accurate risk stratification at diagnosis and assessment of response during therapy. These increasingly require knowledge of molecular analyses of the tumour tissue, quantification of minimal residual disease and results of sophisticated imaging and other interventions. All of these data items sit in hospital clinical records but are not easily available to CRs. However, several CRs have or are developing their capability to link to sources of 'enhanced' clinical data such as clinical registries held at a national level and routine hospital data sources. The CRs had expressed a strong interest in collaborating in this pilot and future joint studies that would utilise their new data linkage and acquisition capabilities to best effect.

2. METHODOLOGY

The protocol for the pilot project was developed jointly between a paediatric oncologist (KPJ) and epidemiologist (Gemma Gatta), in close iterative consultation with the Cancer Registries (both general and specialist paediatric) and tumour-specific clinical trial group leads. Discussions had been initiated as far back as 2016 (see background) on the two most suitable solid tumours on which to conduct the Toronto staging pilot – neuroblastoma and Wilms tumour (nephroblastoma) - the two commonest extra-cranial solid tumours of childhood.

All interested European Cancer Registries were invited to participate in the pilot project, not only those registries already participating in the JARC. Dr Gemma Gatta coordinated the invitation process through the communication network used for EUROCARE studies.

A teleconference call with all interested parties was held in Oct 2017 to finalise the protocol, subsequent questions were dealt with by email or individual phone call. The 'ask' to registries was to apply the Toronto staging principles to either one full calendar year of cases (large CRs) or 10 consecutively diagnosed cases of each tumour type over a longer time period (smaller CRs), in accordance with any national requirements for ethical and regulatory approvals and the General Data Protection Regulation. CRs were given 6-8 months to obtain the data.

All invited registries expressed interest and 14 countries (24 CRs) contributed data to the pilot study. Some non-participating countries provided information on the staging data they held and how they would obtain more complete 'Toronto stage', but they did not have the resources or were not able to comply with data access permissions in the timeline.

Dr Gatta's group at the INT, Milan, received the pseudonymised data from the CRs and performed the data quality checks and analyses.

All interested registries (including those who did and those who were not able to provide staging data) were invited to a workshop, held at the SIOP Europe office, Brussels, 5-6 March 2019, to discuss the results of the Toronto pilot study and how collection of staging (and other clinical) data could be made sustainable for new cases. The original planned time for this face to face meeting was delayed until March 2019 due to competing time pressures in the autumn (many other conferences) and the need and indeed, clear desire by the registry leaders to have a full discussion of the results and time to consider next steps. Representatives from 15 countries' CRs and 2 clinical trial groups (neuroblastoma and Wilms tumour) attended and recommendations were made.

3 RESULTS

3.a. Data availability

Most registries held some staging data already for the two tumour types, but levels of completeness were variable as was the adequacy of data sources used for staging according to the Toronto principles. Most had required more than one data source to complete the Toronto stage. All had had to go back to existing records and/or obtain new data sources in order to perform the task.

In general, the routine hospital discharge and pathology reports that many registries already have access to did not provide sufficient information to produce the Toronto stage. For example, a CR may know the date that a CT scan has been performed, but did not have access to the scan results. Therefore, many registries had to make active efforts for CR staff members to look at medical records and be supported by someone with clinical knowledge in order to be able to assign a tumour stage to each case.

Ultimately, 14 countries (24 CRs) contributed data to the pilot study, providing data on 499 neuroblastomas and 387 Wilms tumours diagnosed in the time period 2000-2016 (mostly 2011-2016). 3 year follow up data were available for the majority but not all cases. The Toronto stage was provided for 97% of cases, for which all participating registries were congratulated.

Those registries who were unable to provide the appropriate staging data in the required timescale, did provide information about the completeness of the staging data they held for the two tumour types. For example:

- **NL:** the Dutch CR held sufficient stage data to assign tier 1 Toronto stage to 97% of cases (tier 1 distinguishes localised from metastatic disease) but didn't participate as they didn't have the time/resources to collect the additional data required for tier 2 Toronto staging.

- **England:** The National Cancer Registration and Analysis Service (NCRAS) hosted by Public Health England, reported low staging completeness for NBL and WT cases in 2014, improving over time to 80% for NBL and 30% for WT cases diagnosed in 2015. It was not possible for the England CR to join the pilot due to the incompleteness of staging data held and the length of time and resources needed to obtain necessary permissions to link to stage data held in a clinical registry (WT) or by going back to treatment centres (NBL). Similar reasons for non-participation were given by several other CRs, who were all keen to participate in principle and in future joint studies.
- **Romania** has a very recently established children's cancer registry, set up with voluntary funding. Tumour stage is missing in 59% of reported cases currently which have been reported using a registration form that has only TNM staging.

3.b. Linkage processes used and possibilities:

There was national variation in the type of data that CRs had access to on either a routine basis for 'normal' cancer registration or if requested for specific studies such as this pilot. In several countries, registry staff are not allowed to visit clinical centres and examine medical records so have to rely on the voluntary efforts and goodwill of the clinical and data management staff in each treatment centre to complete the clinical staging and imaging data in patient-level datafiles exchanged between the CR and the hospital or clinical registry.

Electronic health record data systems are not yet sufficiently mature in most countries for the detailed clinical information needed for Toronto staging to be routinely available to CR staff. France is amongst the most advanced and can view medical reports electronically, multi-disciplinary team meeting reports and pathology reports. Their national CR doesn't have visibility of the patient's national health insurance number but it can be used in a non-disclosive way for linkage to routine health care records. For the pilot, they extracted all cases of NBL and WT diagnosed in 2014 and a single person with clinical knowledge assigned the Toronto stage from the compiled information. This took about 10 minutes per case. The Toronto staging is now integrated for cases diagnosed since 2016 using routine healthcare reports. About 90% of cases have enough information to be staged. In France nothing is mandatory, but the clinical centres must open the files when asked for info by the national children's cancer registry (RNCE). Germany and Switzerland have similar levels of access to complete staging information but again rely on the responsiveness of clinical registries and treatment centres to make it available to them.

No registry used an algorithm to assign Toronto stage but did it manually from existing records supplemented by the new data sources they were able to gain access to. There was interest in learning more about the Australian approach, and Laura Botta was able to show us some detail she'd received from Joanne Aitken, Director of the Australian national children's cancer registry, on the electronic tool they had developed. The TorontoStage App is aimed at registry staff to support them to assign Toronto stage from the clinical data (mainly imaging and pathology reports) they collect as part of their routine visits to the 9 treatment centres nationally.

3.c. Resources and privacy regulation for data linkage and data transfer

Estimates of staff time to collect the data and assign the Toronto stage varied from 10 mins/case (France) to a few days or even weeks for only 20 cases for countries where much more reliance was placed on responses from clinical treatment centres.

In some countries, data requires parental consent to be collected, either as part of the authorization of the national children's cancer registry (Switzerland) or because the CR is not a statutory government organization but an academically-led initiative (Greece).

In Spain, linkage between the CR and clinical registries was hampered by the lack of a unique personal identifier at the national level.

There is variation between countries in the requirements for individual projects using enriched datasets to have national regulatory and/or ethical approval in order to provide patient-level data, even if the data are heavily pseudonymised and hence not identifiable to the collaborative project team.

3.d Clinical results and interpretation of the pilot study

The first results of the pilot were available in May 2018 and have been presented in oral and poster abstract at several international conferences (see reference list) and meetings attended by European and wider international cancer registry staff and epidemiological and clinical researchers.

The distribution of age at diagnosis for the two index tumours was as expected from previous EUROCARE studies (2). For neuroblastoma, the proportion with metastatic disease at diagnosis was >50% in those aged over 1yr compared to only 12% in those diagnosed as infants < 1yr. For Wilms tumour, 14% had metastases at diagnosis. 76% of the Wilms tumours were noted to have been treated according to SIOP protocols (i.e. with elective pre-operative chemotherapy recommended for the majority of clinical scenarios). There was evident variation in stage distribution by country. The overall survival for each tumour type was as expected from EUROCARE. Whilst some exploratory analyses of correlations of survival by country and by stage distribution were presented, it was agreed that the cohorts would need to be larger for any statistically robust comparisons.

3.e Potential for additional data items

Several countries had provided data on treatment and relapse, very few had data on imaging used for staging purposes or metastatic response. Biological subgroups are becoming standard of care and no longer research items. They have been included in pathology reports for several years in many tumour types but don't have a specific code in the ICD0 and are therefore difficult to register. Switzerland and France have these molecular data items for some tumours. In other countries, results of molecular tests used for clinical diagnostic purposes (e.g. *MYCN* gene copy number in neuroblastoma) are available to the registry but incompletely reported (England) or require special efforts to link to the data items held in clinical disease-specific registries (Germany, Spain).

3.f Mobility of patients and need for a European Patient Identifier

Some regional CRs commented on the high levels of population mobility for healthcare, in and out of their region, which made it difficult to have access to a complete record of healthcare activity for each patient or to ensure continuity of surveillance. All CRs commented on the potential to lose patients to follow up when children transition to young adults (15-19yrs) as they are no longer seen in the paediatric oncology hospitals. For continuity of surveillance of healthcare outcomes, it was recommended that consideration be given to a European Patient Identifier, that could be used in a carefully pseudonymised way to keep track of the patient pathway.

4. DISCUSSION

4.a Completed pilot project and plans for publication

There was mutual acknowledgement of the success of the pilot project, the level of interest it had stimulated, and the desire to continue to work together to collect and analyse clinically enriched datasets for outcomes research in childhood cancers.

It was agreed that the pilot study should be published, with its main message being about the feasibility of provision of tumour stage by many registries for a collaborative study and the effort required and data sources used. Whilst some exploratory analyses of correlations of survival by country and by stage distribution were presented in the workshop, it was agreed that the cohorts would need to be larger to provide statistically robust comparisons. Hence, it was also agreed that such analyses should be the aim of a future collaborative research project that would build on the experience of the pilot in accessing more complete and comparable staging data in each country.

It was emphasized that the publication of the pilot study should include recommendations for some form of quality checks for the Toronto stage implementation if it is to be included in the ENCR guidelines, as well as TNM checks, although the latter apply to fewer childhood cancers. The paper should be useful to clinicians, to highlight the potential for future comparative studies of survival to be able to show them what type of patients they are treating and to show survival rates stratified by stage.

4.b Future plans to improve staging data completeness and collect additional data items

For most CRs, current information on tumour stage was too incomplete in the national registry, whereas clinical stage is a ‘must’ for the clinician. CRs have all decided to focus on improving prospective collection, with a few (e.g. France) planning to also stage retrospective cases.

Several countries were interested in generating the Toronto stage, both tier 1 and tier 2, through use of an algorithm. Some registries will do this to retrospective cases but the majority are focusing on improving their capabilities for staging prospective patients only as part of ongoing or planned updates to their cancer registration systems.

There was also recognition that CRs need to and had already benefitted from much closer working with paediatric oncologists and other clinical staff in the treatment centres and clinical registries. These relationships needed to be sustained and strengthened further. However, it was also clear that the time pressures on clinical front line staff mean that additional resources will be needed to support high quality and complete data collection. Whilst some may come from research funding, there is a need for CRs to be fully linked into the efforts ongoing in most countries to improve routine collection of more detailed healthcare data, and to make it available for multiple purposes from a single point of data collection. The exact processes to achieve these aims varied according to national regulatory processes and resourcing.

There was a discussion about the apparent variation by country in age and Toronto stage at diagnosis that had been observed in the pilot and which mirrors some published data. It was suggested that this might be related to child health practices in each country which could impact on how early cancer is detected and through what route (e.g more likely to be detected as an incidental finding during examination of a child with vague symptoms by paediatricians rather than generalist doctors). Collecting such data by CRs could be challenging, and testing this hypothesis is part of some clinical trials and studies currently ongoing or planned by the European trial groups. Again, this emphasises the importance of increased joint working between CRs and clinical registries/studies.

Discussion on capabilities to collect additional data items included:

- Belgium, difficult to have relapse. Imaging used to stage is a new variable that we want to include.
- France collect treatment but is unable to give it to the ENCR.
- Biological subgroups are becoming standard of care and no longer research items. They have been included in pathology reports for several years in many tumour types but don't have a specific code in the ICD0 and are therefore difficult to register. Switzerland and France have these data items.
- Data on biology and other clinically important data used for risk stratification are more about relapse free than overall survival (i.e. optimizing the success rates of first line therapy to reduce late effects). Therefore will be important to have data on relapse.

There was agreement that the CRs need to keep it simple and take an incremental approach, with Toronto staging being the most important first step for all registries, whilst maintaining the ambition to collect/provide other data items for shared projects where feasible. Many registries are in the process of redesigning their systems and processes and migrating their databases to new environments with increased opportunities for linkage to other routine healthcare data and disease registries.

4.c Training requirements and future plans of the ENCR for children's cancers

The 2014 JRC Technical Report provides for one common procedure for cancer registration with agreement on common standards. Whilst ENCR can make recommendations and offer training, the needs of each cancer registry can be very different. The co-chair of the ENCR suggested that each CR could ask ENCR if they have a specific problem. For children's cancers, the ICCC classification should be used.

It is planned to provide training for cancer registries on the Toronto staging principles as part of the next JRC-ENCR training workshop – to be held 5-6th June 2019, Ispra. The JRC gives some financial support for registries who cannot access training easily. It was noted that the Toronto guidelines have been endorsed by ENCR on their website since February 2019 and it is expected that all registries will make efforts to use them. A proposal was made by the Slovenian CR to run a future longer course, with ENCR involvement, in Slovenia in Autumn 2019, aimed at South and Eastern registries.

There was agreement that specific training of registry staff in applying the Toronto stage from information contained within administrative and clinical reports in childhood cancers was essential. There was great interest in the already planned workshop at the JRC in June and agreement that the CRs could provide some "test cases" that could be used for training purposes, selected from their real life experience in the pilot.

The Romanian CR wished to emphasise the importance of a European-wide statement on a minimum set of variables that have to be collected for childhood cancer cases and which should specify the staging system to be used. The Toronto guidelines are ready to be proposed for this purpose.

Staging systems can be expected to evolve over time as they incorporate the overall 'risk classification' approach that is most useful clinically and which increasingly integrates other data items such as molecular markers. Hence, it is important that the guidelines are reviewed periodically, especially since it was now nearly 5 years since their publication. The original Toronto guidelines working group is planning an update meeting in conjunction with IARC to take place during the next congress of the International Society of Paediatric Oncology (SIOP) in October 2019. It is expected that representatives of several of the CRs who took part in the pilot project will attend and take part in that review process.

Agreement that as an output of the pilot project, the group should make an official request to the ENCR to include Toronto stage in the 2020 call for data. The request will be sent in good time for consideration at the May meeting of the ENCR steering committee. Whilst many registries said they would not be able to provide stage for any but the most recent cases, it was welcomed that including stage in the 2020 data call would be a stimulus for the registries to find the means to collect these data at a national level and share them for international benchmarking purposes.

5. Conclusions

1. The pilot study of the feasibility of implementing the Toronto staging guidelines by cancer registries has been a success.
2. It has highlighted the most useful data sources, the methodology and effort required, both for registries who had been able to provide cases for the pilot and those who had not, for a variety of reasons.
3. All CRs are supportive of including Toronto stage for prospective cases diagnosed from 2018 onwards, there is variable and limited capability to stage retrospective cases over a short time period back to ~ 2015.
4. Inclusion of Toronto stage in the ENCR 2020 data call would be a useful stimulus to strengthen joint working with clinical treatment centres and clinical registries. This working group will

submit a formal request to the ENCR steering committee to include the guidelines and to SIOP Europe asking for their endorsement of their use.

5. This JARC pilot project has highlighted the increasing capability of registries to include 'enhanced' clinical data items in their registration processes and their willingness to use these in joint projects to improve interpretation of international survival comparisons and the European cancer intelligence system for children's cancers. However, specific funding will be needed to enable registries to contribute cases for a larger joint project in the near term.

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Conference presentations of the JARC pilot study on Toronto staging by CRs (all presented by Dr Gemma Gatta):

- XXII Annual congress of the association of Italian cancer registry AIRTUM Venice March 2018 ORAL PRESENTATION
- GRELL Ascension Meeting 2018 16th-18th May, Trento ORAL PRESENTATION
- ENCR Scientific Meeting, Copenhagen, 26-28 Sep 2018 ORAL PRESENTATION

- IACR The 40th Annual Conference of the International Association of Cancer Registries, AREQUIPA, PERU 13-15 November 2018 POSTER

A.2 Study Report Belgian Cancer Registry (Be)

Tender – WIV-ISP-2017-PRI088-HPV

Develop a model for longitudinal follow-up of HPV oropharynx carcinoma patients through cancer registries enriched with additional medical/pathology information

Report for the tender: Abstract, Executive Summary and Report

Abstract

Cancer Registries (CRs) have an increasing involvement in cancer care due to the growing interest in real-world data, i.e. population-based data on diagnosis, treatment and outcome. Head and neck cancers are a heterogeneous group of tumor entities arising in the upper aerodigestive tract. The entities are anatomically close to each other but dissimilar in terms of aetiology, histology, treatment modalities and prognosis. For oropharyngeal cancer, the presence of high-risk HPV has gained tremendous interest over the last years.

In the present study, we examined the availability of information on stage, p16/HPV status, treatment modalities and follow-up for oropharyngeal cancers in CRs of member states participating in the JARC, by means of a questionnaire. Most of the CRs have detailed information on patient and tumor characteristics as well as stage. There is a striking variability in availability of information on imaging and treatment. At the time of the survey, no structured information on p16/HPV status is readily available at the CRs, and substantial efforts are required to retrieve the p16/HPV status from the pathology reports or the medical files. Almost all CRs are using different data sources to obtain information, requesting linkage possibilities with data from the CR.

To some extent efforts to strengthen the links between population-based cancer registration systems, clinical care, research and routine healthcare data are on-going.

Especially for rare cancers, it is important to work towards more accessible and exchangeable data, because of the relatively small numbers per individual country. By pooling the data together, evaluation of quality of care, adherence to guidelines, outcome… becomes a lot more relevant.

Executive Summary

Background

Head and neck cancers are a heterogeneous group of tumor entities arising in the upper aerodigestive tract. For oropharyngeal cancer, the presence of high-risk HPV has gained tremendous interest over

the last years. On the one hand, HPV infection has been identified as a principal cause of the increasing incidence rates for oropharyngeal cancers in a non-smoking and non-alcohol drinking population (1). On the other hand, patients affected by HPV-related cancers have been demonstrated to have better survival rates (2, 3).

Cancer Registries (CRs) have an increasing involvement in cancer care due to the growing interest in real-world data. This data allows to evaluate the adherence to guidelines and outcome of rare cancers, but implies that CRs need more and clinically relevant data. The CRs are well positioned to bring these data together because of their experience in data handling, i.e. the so called “big data”. Therefore the objective is to explore the possibility to set up a clinical epidemiology framework program, to use big data for outcome research in rare cancers.

In the present study we would like to examine the availability of information on stage, HPV status, and treatment modalities in CRs, and its influence on the adherence to guidelines and outcome in oropharyngeal cancer.

Methodology

In order to answer this question the Belgian Cancer Registry has taken the following steps:

- Reflection about the questionnaire, with the purpose of finding the balance between the requested relevant information and the time to spend to fill out the questionnaire.
- Relevant information asked in the questionnaire (see also Annex 1): patient and tumor characteristics, information on risk factors, tumor stage, imaging modalities, p16/HPV status, treatment data in broad categories, different disposable data sources, data linkage possibilities, follow-up data and privacy issues.
- 10 national or regional cancer registries were invited by mail to ask for their contribution: Associazione Italiana Registri Tumori- Airtum (Italy), Unitat d’Epidemiologica i Registre de Cancer de Girona (Spain), Croatian National Cancer Registry (Croatia), National Cancer Registry Ireland (Ireland), Greater Poland Cancer Registry (Poland), English National Registry (United Kingdom), Finnish Cancer Registry (Finland), Malta National Cancer Registry (Malta), FRANCIM (France) and finally the Belgian Cancer Registry (Belgium)
- Finally, 7 national or regional registries consented and further information was retrieved by mail, telephone or skype call : Unitat d’Epidemiologica i Registre de Cancer de Girona (Spain), Croatian National Cancer Registry (Croatia), National Cancer Registry Ireland (Ireland), Greater Poland Cancer Registry (Poland), English National Registry (United Kingdom), FRANCIM (France) and Belgian Cancer Registry (Belgium)

Results

1. *Data availability*

- All participating CRs have basic patient and tumor information (incidence date, location, histology, age, gender) at their disposal.
- No information is available on risk factors such as tobacco and alcohol history.

- Most of the CRs have separate information for the c/p T-, N- and M- categories. The other CRs have stage group information (i.e. local, regional or distant spread).
- The information concerning the p16 immunohistochemistry test and HPV result is extremely rare available in a structured way. All the CRs (who do not have the structured information) indicated that the information is available (in the pathology reports, in medical files, …) but a great effort is needed to retrieve those data (i.e. resources, time and funding).
- Only limited CRs have information available about imaging modalities. Options to obtain those data is to search this information in the medical files or to link with the hospital discharge data, but anyway a great effort is needed to get hold of those data (i.e. resources, time and funding).
- Almost all CRs have information available on treatment modalities (surgery, radiotherapy, chemotherapy) in broad categories. Only a few CRs have information on targeted therapy.
- All CRs have follow-up data available, at least the date of death.
-

2. *Linkage possibilities*

   Almost all CRs are using different data sources to retrieve information and therefore linkage is needed with data from the Cancer Registry. Some of them have a unique patient identifier to link, others are performing a probabilistic coupling, and others have different patient identifiers for different data sources.

3. *Resources and privacy regulation for data linkage and data transfer*

   In order to participate to a pilot study the CRs have to receive the detailed clinical information from other data sources entailing issues that have to be tackled such as linkage possibilities and privacy regulation to be compliant to the General Data Protection Regulation (GDPR).

Conclusion

Through this pilot study, we have established that most European cancer registries do not have readily access to the detailed clinical information that is required to identify the individual treatment and prognosis. Extra resources and funding will be needed to retrieve this essential detailed information. In addition, data linkage and data transfer require substantial administrative work, and for most of the CRs particular permission processes from authorities are requested.

Report

Background

Head and neck cancers are a heterogeneous group of tumor entities arising in the upper aerodigestive tract. The entities are anatomically close to each other but dissimilar in terms of aetiology, histology, therapeutic approach and prognosis. Typically, head and neck cancers develop in a population with chronic excessive tobacco and alcohol consumption. Other risk factors include human papilloma virus (HPV) infection and Epstein-Barr virus infection. About 90% of all head and neck cancers are squamous

cell carcinomas, the other 10% are sarcomas, adenocarcinomas, melanomas and not well specified tumors (1).

For oropharyngeal cancer, the presence of high-risk HPV has gained tremendous interest over the last years. On the one hand, HPV has been identified as a principal cause of the increasing incidence rates for oropharyngeal cancers in a non-smoking and non-alcohol drinking population, mainly in younger but also in older patients. On the other hand, patients affected by HPV-related cancers have been demonstrated to have better survival rates (2,3).

Cancer Registries (CRs) have an increasing involvement in cancer care due to the growing interest in real-world data, i.e. population-based data on diagnosis, treatment and outcome. This data allows to evaluate the adherence to guidelines and outcome of rare cancers but implies that CRs (would) need more and clinically relevant data compared to the classic cancer registration dataset. CRs need to be enriched with information from medical records, pathology reports, clinical registries and administrative health databases.

The CRs are well positioned to bring these data together because of their experience in data handling, i.e. the so called “big data”. Therefore the objective is to explore the possibility to set up a clinical epidemiology framework program, to use big data for outcome research in rare cancers.

For several years, the prognostic impact of HPV status is well recognized. Accordingly, its significance is now translated in the 8th TNM classification where a clear distinction is made between p16+ and p16- oropharyngeal cancers (4). Despite this fact, information regarding HPV/p16-status is currently not part of the standard cancer registration dataset.

In the present study we would like to examine the availability of tumor stage, HPV status, and treatment modalities, and its influence on the adherence to guidelines and outcome in oropharyngeal cancer.

Methods

A questionnaire was prepared by the Belgian Cancer Registry, implicating thorough overthinking in order to select relevant questions for the purpose of the study. The questions were composed, on the one hand focusing on the type of information available (e.g. patient and tumor characteristics, type of treatment etc.) and on the other hand trying to figure out the format of the available data (e.g. structured, electronic etc.). Also, aiming for a quick response rate by the different participating CRs, the survey was kept as concise and to the point as possible.

The ultimate questionnaire included the following topics (see also the documents in Annex 1):

- patient and tumor characteristics (e.g. age, gender, information on risk factors such as tobacco/alcohol use and socio-economic status, incidence date, location, tumor stage and which kind of staging information)
- HPV status and related testing (e.g. p16 immunohistochemistry testing)
- imaging modalities

- treatment data (e.g. surgery, radiotherapy, chemotherapy, targeted therapy) and the related data source
- different disposable data sources
- data linkage possibilities (and if available, direct versus indirect linkage)
- follow-up data
- possibility to participate in a prospective clinical epidemiology framework program for outcome research in rare cancers
- privacy issues

Subsequently 10 CRs, member states participating in the JARC, notably Airtum (Italy), Unitat d'Epidemiologica i Registre de Cancer de Girona (Spain), Croatian National Cancer Registry (Croatia), National Cancer Registry Ireland (Ireland), Greater Poland Cancer Registry (Poland), English National Registry (United Kingdom), Finnish Cancer Registry (Finland), Malta National Cancer Registry (Malta), FRANCIM (France), and finally the Belgian Cancer Registry (Belgium), were invited by mail to take part in the questionnaire. When interested, a telephone conversation or skype call was fixed in order to go through the questionnaire orally.

Finally, 7 of the invited CRs (France, Spain, Croatia, Ireland, Poland, United Kingdom and Belgium) consented and additional information was received afterwards, mainly by means of telephone calls.

Results

All participating CRs have basic patient and tumor information on gender, performance status, incidence date, location and histology at their disposal (Table 1). All but one CR possess detailed information on TNM classification, including separate T-, N- and M-categories, and pathological stage after neo-adjuvant treatment. The remaining CR does have stage group information (i.e. local, regional or distant spread). No CR holds data on individual risk factors like alcohol and tobacco consumption. The follow-up data is limited to the date of death, which is available in 6 CRs. Only one CR is (very recently) provided with structured information on p16 testing and HPV status. In all other CRs this information is achievable but not readily accessible in a structured way, and CRs indicated that a great effort would be necessary to obtain this kind of structured information. Two CRs have access to data on imaging modalities. Also here, this information is not readily accessible in a structured way and CRs indicated that efforts are needed to retrieve those data (i.e. resources, time and funding).

All participating CRs have access to data on surgery and radiotherapy performed for the primary tumor, all but one additionally have data on chemotherapy at their disposal, and 2 CRs also have data on targeted therapy available (Table 2). Various data sources are consulted to obtain the information concerning treatment, mainly medical files (5 CRs) followed by hospital discharge data (4 CRs). Other data sources (each time used by 1 CR) include clinical datasets, reimbursement registry for medical acts, routine primary care registry and administrative databases containing reimbursed medical acts and pharmaceuticals.

In all but one CR the data sources can be linked, of which in 5 CRs at least to some extent directly by means of a unique patient identifier, and in 1 CR indirectly by probabilistic coupling (Table 3).

In order to participate to a pilot study the CRs have to gather the detailed clinical information from other data sources, entailing issues that have to be tackled such as linkage possibilities and privacy regulations to be compliant to the General Data Protection Regulation.

Table 1. Availability of patient and tumor characteristics

	FRANCIM network - France	Unitat d'Epidemiologica i Registre de Cancer de Girona - Spain	Croatian National Cancer Registry – Croatia[a]	National Cancer Registry Ireland – Ireland[b]	Greater Poland Cancer Registry – Poland[c]	English National Registry – United Kingdom	Belgian Cancer Registry - Belgium
Incidence date, gender, location, histology, performance status	x	x	x	x	x	x	x
Risk factors (tobacco and alcohol history, socio-economic status)							
TNM classification by UICC/AJCC	x	x		x	x	x	x
Separate information for cT, cN, cM categories	x	x		x	x	x	x
Separate information for pT, pN, pM categories	x	x		x	x	x	x
Information available on pathological stage after neo-adjuvant treatment?	x	x		x	x	x	x
Information on imaging modalities (chest X-ray,	x						x

PET/CT, endoscopy, MRI)?							
Information on p16 immunohistochemistry test?				x			
HPV status information?				x			
Follow-up data? Date of death	x	x		x	x	x	x

[a]The Croation National Cancer Registry has for the moment only stage group information (local, regional, distant) for the clinical as well as the pathological stage. The intention is as from incidence year 2018 onwards to collect the TNM classification by UICC.

[b]Collecting p16/HPV status as part of the routine data set started from incidence year 2016 (but is not yet complete).

[c]The only information on imaging modalities available is about radiology; all p16/HPV tests are centralized in the laboratory of pathological anatomy. Information about the p16 immunohistochemistry test and the HPV status could be available at the Cancer Registry but with a great effort to retrieve those data.

Table 2: Treatment data: which type of data are available regarding treatment of the primary tumor?

	FRANCIM network - France	Unitat d'Epidemiologica i Registre de Cancer de Girona - Spain	Croatian National Cancer Registry - Croatia	National Cancer Registry Ireland - Ireland	Greater Poland Cancer Registry - Poland	English National Registry – United Kingdom	Belgian Cancer Registry - Belgium
Surgery Radiotherapy Chemotherapy Targeted therapy	x x x x	x x x	x x x	x x x	x x	x x x	x x x x
Data sources for treatment information?	Medical files	Medical files, Hospital discharge registry	Medical files, Hospital discharge registry	Medical files, Hospital discharge registry, Reimbursement registry for medical acts, Routine primary care registry	Medical files, Hospital discharge registry	Clinical datasets	Administrative database (reimbursement medical acts)

Table 3: Linkage possibilities

	FRANCIM network - France	Unitat d'Epidemiologica i Registre de Cancer de Girona – Spain[a]	Croatian National Cancer Registry – Croatia[b]	National Cancer Registry Ireland - Ireland[c]	Greater Poland Cancer Registry - Poland[d]	English National Registry – United Kingdom[e]	Belgian Cancer Registry - Belgium[f]
Linkage possibilities		x	x	x	x	x	x

[a]there is a linkage possibility but the linkage depends on which data sources are used because of different unique identification numbers for different data sources
[b]linkage data sources directly by using unique patient identifier
[c]linkage data sources indirectly, by probabilistic coupling
[d]linkage data sources directly by using unique patient identifier
[e]linkage data sources directly by using unique patient identifier when available, otherwise indirectly by probabilistic coupling
[f]linkage data sources directly by using unique patient identifier

Conclusion

Through this pilot study, we have established that most European cancer registries do not have readily access to the detailed clinical information that is required to identify the individual treatment and prognosis. Extra resources and funding will be needed to retrieve this essential detailed information. In addition, data linkage and data transfer require substantial administrative work, and for most of the CRs particular permission processes from authorities are requested.

Discussion

Cancer Registries (CRs) have an increasing involvement in cancer care due to the growing interest in real-world data, i.e. population-based data on diagnosis, treatment and outcome. This data allows to evaluate the adherence to guidelines and the outcome of rare cancers but implies that CRs (would) need more and clinically relevant data compared to the standard cancer registration dataset. CRs therefore need to be enriched with information coming from medical records, pathology reports, clinical registries and administrative health databases.

CRs should report a defined set of relevant population-based data with the purpose of improving comparisons with other registries and exploring inequities in the burden of cancer between regions or countries. However, there is no clear advice concerning the registration of certain –relevant – tumor characteristics of rare cancers. Besides tumor characteristics, also data regarding stage and treatment is highly valuable, but far from generally well documented.

For oropharyngeal cancer, the presence of high-risk HPV has gained tremendous interest over the last years. On the one hand, HPV infection has been identified as a principal cause of the increasing incidence rates for oropharyngeal cancers in a non-smoking and non-alcohol drinking population, mainly in younger but also in older patients. On the other hand, patients affected by HPV-related cancers have been demonstrated to have better survival rates.

The prognostic relevance of HPV status is well recognized and its impact is now translated in the 8th TNM classification where a clear distinction is made between p16+ and p16- oropharyngeal cancers. Despite this fact, information regarding HPV/p16-testing is currently not part of the standard cancer registration dataset.

In the present study, several cancer registries of participating member states in the JARC project were contacted by mail and/or telephone. This in order to investigate which data are already available in the registries and which data could be retrieved by linking information from other data sources (e.g. medical files, hospital discharge data, pathology reports ...) with a special interest in the p16 immunohistochemistry status and the HPV status.

Despite the fact that the prognostic impact of HPV status is well recognized since several years, not one contacted cancer registry has structured information at its disposal on p16/HPV status for oropharyngeal cancers. Only the National Cancer Registry of Ireland has p16/HPV status information since the incidence year 2016, but this data is not yet complete.

The information concerning the HPV status can be recovered in pathology reports, in medical files of the patients, or in other existing clinical or administrative databases. Possible methods to gain this information

include adding the parameter to the standard registration dataset of the tumor type and/or investment in new technologies such as text-recognition to extract tumor specific information from the pathology reports.

The landscape of organization of data input and the possibilities of cancer registries throughout Europe is very heterogeneous. Obviously, we cannot expect registries to re-organise completely following one ideal example. On the contrary, this heterogeneity can be an advantage and it can be very productive to join forces, learn from each other, and work towards maximal exploitation of the individual already existing possibilities (e.g. clinical versus administrative databases, radiotherapy/radiology/pathology databases, cooperation with clinical experts etc.). The ultimate goal in essence is that data has to become available in a structured way, and somehow cancer registries must have access to these structured data. Linkage to structured data therefore needs to be promoted on the individual scale. Secondly, there should be a firm collaboration with European Reference Networks (ERNs) and reflect together how to harmonize the registration modalities in order to avoid double.

Especially for rare cancers, it is important to work towards more accessible and exchangeable data, because of the relatively small numbers per individual country. By pooling the data together, evaluation of quality of care, adherence to guidelines, outcome… becomes a lot more relevant. By joining forces, a lot of quality of care research becomes more realistic for rare cancers.

Some countries are particularly progressive and/or have the luxury of a substantial history of cancer registration to build on in contrast to other -more often small- countries who are less equipped and/or have a relatively recent starting point. How can we support the latter? There is a need for European investment to enable the -often highly motivated- cancer registries to fully blossom. It is clear that there is a willingness, but a true endorsement by European authorities promoting a good organisation and appropriate methodology on the individual level is necessary. There is a true need for collaboration between the existing European entities, i.e. ERNs, European Union (EU), JARC and European Network of Cancer Registries (ENCR), in which every player has an important role.

Concern and (financial) support of the authorities and various stakeholders are essential if general changes in practice or improvements are pursued. Especially in the climate of evolving knowledge in terms of the molecular features of different cancers and their increasing importance in the adequate staging of cancers, guiding therapeutic choices and determining prognosis (e.g. HPV/p16-status for oropharyngeal cancer), this concern and support is needed as strategies to obtain this kind of information in a structured way on population-level are warranted. An essential part in this regard is the stimulation of innovation, e.g. investing in artificial intelligence.

Also awareness and general support by clinicians in the various hospitals could stimulate and contribute towards comprehensive data collection on rare cancers, especially by delivering high-quality data with a minimal delay. A good relationship between cancer registries, the various stakeholders and clinicians is of mutual interest. On the one hand quality and completeness of data concerning rare cancers at the registries improves, on the other hand feedback regarding the health situation or quality of care in their individual institutes and more research questions can be taken up by the registries.

Ultimately, the privacy rules and ethical framework are an important obstacle in the process towards interexchange ability or accessibility of data. Especially when it comes to rare cancers, privacy matters are at issue, because of the low volume and therefore easier identification of these pathologies.

In many countries, efforts are ongoing or already in place to strengthen the links between population-based cancer registration systems, clinical care, research and routine healthcare data. The aim is to both increase the efficiency of data collection and to enhance the clinical content available to the cancer registries. Once these systems are mature, with robust, sustainable technologies for data linkage in place and compliant with GDPR/Privacy regulations, they should provide the platform for a prospective clinical epidemiology framework program for outcome research in rare cancers.

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Annex 1. Questionnaire performed by the Belgian Cancer Registry

Which data are available in your Cancer Registry regarding HPV oropharynx carcinoma?

A. General information

1. Please indicate the name of your registry and the email address of the person to be contacted if any further question: free text

2. In general, for your database, what incidence years are available? free text

B. Patient and tumour characteristics

1. Does your cancer registry have data available on patient and tumour characteristics in general (incidence date, location, histology, age, gender, performance status,…)?
    - o Yes
    - o No

2. Does your cancer registry have information on risk factors (tobacco history, alcohol history, socio-economic status, comorbidities, …)?
    - o Yes, already available in electronic format
    - o Yes, can be available in electronic format with a minimal effort to retrieve those data
    - o Yes, can be available in electronic format with a great effort to retrieve those data
    - o Not available

3. Does your cancer registry define the staging of the tumour according to the TNM classification by UICC/AJCC?
    - o Yes
    - o No

4. Which kind of staging information is available in your cancer registry? (multiple answers possible)

    - o Clinical stage
    - o Pathological stage
    - o Compilation of clinical and pathological stage
    - o None of the above

    (If box is checked)

        o Already available in electronic format
        o Can be available in electronic format with a minimal effort to retrieve those data
        o Can be available in electronic format with a great effort to retrieve those data
        o Not available in electronic format

5. Does your cancer registry have for the clinical stage?
    - o Separate information for cT, cN, cM categories
    - o Stage group information (local, regional, distant)
    - o No information

6. Does your cancer registry have for the pathological stage?
    - o Separate information for pT, pN, pM categories
    - o Stage group information (local, regional, distant)
    - o No information

7. Does your cancer registry have information on whether **pathological stage was registered after neo-adjuvant treatment** according to UICC/AJCC?
    - o Yes
    - o No

8. Does your cancer registry have information about imaging modalities (chest X-ray, PET/CT, endoscopy, MRI, …) ?
    - o Yes
    - o No

    (If yes is checked)
        - o Already available in electronic format
        - o Can be available in electronic format with a minimal effort to retrieve those data
        - o Can be available in electronic format with a great effort to retrieve those data
        - o Not available in electronic format

9. Does your cancer registry have information on **the p16 immunohistochemistry test**?
    - o Yes but only an indication that it has been done
    - o Yes, the actual test result
    - o Not available

    (If yes is checked)
        - o Already available in electronic format
        - o Can be available in electronic format with a minimal effort to retrieve those data
        - o Can be available in electronic format with a great effort to retrieve those data
        - o Not available in electronic format

10. Does your cancer registry have **HPV status** information?
    - o Yes, already available in electronic format
    - o Yes, can be available in electronic format with a minimal effort to retrieve those data
    - o Yes, can be available in electronic format with a great effort to retrieve those data
    - o Not available

    (If yes is checked)

    Do you know which technique has been used to determine the HPV status (PCR, ISH, IHC,…)?
    - o Yes
    - o No

C. Treatment data *: Which type of data are available regarding treatment of the primary tumour?*

1. Does your cancer registry have treatment information available?
    - o Yes
    - o No

2. Please, check in the following list what treatment procedures performed are available (in any format: electronic, paper,…) (multiple answers possible)
    - o Surgery
    - o Radiotherapy
    - o Chemotherapy
    - o Targeted therapy
    - o Other: (free text)

3. What type of data source do you retrieve treatment information from? (multiple answers possible)
    - o Medical files
    - o Hospital discharge registry
    - o Reimbursement registry for medical acts
    - o Routine primary care registry
    - o Other: (free text)

Data sources

1. Which of the following data sources are available at your cancer registry or are used to gather more information? (multiple answers possible)
    - o Radiotherapy department records
    - o Computerized public hospital discharge recording systems/case listings
    - o Computerized private hospital discharge recording systems/case listings
    - o Cancer/oncology department out−patient records
    - o Public hospital in−patient records
    - o Public hospital out−patient records
    - o Private hospital/clinic in−patient records
    - o Private hospital/clinic out−patient records
    - o Imaging center records
    - o Pathology laboratories
    - o Autopsy services
    - o Hematology laboratories
    - o Death certificates/records mentioning cancer
    - o All death certificates/records
    - o General practitioner records
    - o Health insurance records
    - o Hospice/palliative care records
    - o Clinical laboratory records
    - o Other: (free text)

3. Can you link the data source(s)?
    a. Yes, directly (unique patient identifier) for all data sources
    b. Yes, directly (unique patient identifier) for a part of the data sources and indirectly (probabilistic coupling like using name, date of birth, gender, etc).
    c. Yes, for all type of databases indirectly (probabilistic coupling)

d. No linkage possible

Follow-up data

Which of the following variables are collected for the follow-up of patients ? (multiple answers possible)

- o Date of death
- o Date of last contact
- o Vital status at last contact
- o Cause of death
- o Date of emigration from registry area
- o None of the above

Extra questions

Would you be interested to participate to the pilot study?

- o Yes
- o No

Are there any financial costs to retrieve the data?

- o Yes
- o No

If your cancer registry has no information available concerning imaging and treatment modalities and HPV status would it be a great effort to retrieve those data (for example do you have to go back to the hospital to retrieve the data)

- o Yes
- o No

Are there any privacy issues if your cancer registry would like to transfer data on record/patient level?

- o Yes
- o No