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Review

Improving treatment results with reference centres for rare cancers: where do we stand?

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Abstract Rare adult cancer (RAC) is characterised by an incidence of less than six cases per 100,000 people per annum; 4,300,000 patients in the European Union are living with rare cancer (22% of all new human cancers). These cancers are linked with worse survival rates than 'frequent' tumours (5-year survival: 47% for RAC against 65% for 'common' cancers), mainly because of: (1) delays in obtaining an accurate diagnosis, (2) inadequate treatments given in curative phases and (3) restricted opportunities for patients to participate in clinical trials because of the lack of support for dedicated trials for this disease group from both academic and industrial sponsors. Although quantitative studies to measure the socioeconomic burden of RACs as a whole are still lacking, the increasing fragmentation of all cancers into molecular subgroups implies a substantial increase in the number of RACs and their associated socioeconomic burden. To answer this urgent and growing need, some countries, cooperative groups, and cancer institutes delineated national and/or regional organisations to promote quality management for RACs. Currently, the European Union (EU) is supporting an official EU call to organise a European network dedicated to RACs. The goals will be to pool the vast knowledge and expertise of the 67 EU clinical reference centres and to cover ten rare adult solid cancer

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domains across more than 18 countries in order to deploy an integrated, EU-wide capacity towards accelerated innovative treatments and care for RACs while empowering patients. This article will summarise these experiences and the potential benefit for patients.

1. Introduction

Rare cancers are a challenge to clinical practice. Treatment experience—even in major cancer centres to which rare cancers are usually referred—is often limited, and new treatments are difficult to assess because too few patients are proposed for adequately powered clinical trials to determine the gold standard design of new regimens for establishing treatment efficacy. However, substantial advances in the treatment of some rare cancers have occurred as a result of national and international collaborative trials [1,2].

2. A problem of epidemiology

Problems related to other rare diseases apply to rare tumours as well, and, in principle, rare tumours should be defined in the same way as other rare diseases. But the definition of a rare disease is based on prevalence, and varies from less than 5 in 10,000 in the EU to 7 in 10,000 in the USA [[3]; http://rarediseases.info.nih.gov/RareDiseaseList.aspx].

Collectively, rare cancers account for more than one-fifth of all new cancer diagnoses, more than any of the common cancers alone. However, the natural history of tumours is such that some of them have a high prevalence and are nonetheless rare, and vice versa. Thus prevalence varies substantially depending on life expectancy, although life expectancy obviously has nothing to do with frequency. In addition, several tumours with prevalence below 50/100,000 are not perceived as rare. For these reasons, incidence may be a more useful indicator to select a threshold for rarity of tumours as opposed to non-neoplastic diseases. It should be clear, however, that the conventional definition of a rare disease has regulatory implications, including those on orphan drugs. In addition, the evolution of therapies may well affect the definition. For example, if anticancer therapies could actually be delivered in a chronic way, overcoming the currently limiting factor of tumour resistance, prevalence would become a much more suitable indicator of frequency. The project Surveillance of Rare Cancers in Europe (funded by the European Commission) aimed at providing a definition of 'rare cancer', a list of cancers and rare cancer burden indicators, based on population-based cancer registry data across Europe. An international consensus group agreed that incidence is the most appropriate indicator for measuring rare cancers and set the threshold for rarity at 6/100,000/year. The list of rare cancers was based on the International Classification of Diseases for Oncology (ICD-O 3rd edition) [4].

Thus, given the low survival rates for several cancers, it is more relevant to select a definition based on incidence (<6/100,000/year) to avoid the false inclusion of rare cancers with frequent cancers with high death rates.

In the era of molecular targeted therapies, the molecular profile will also be relevant. International agencies that preside over such classifications are constantly updating them, and genetic and molecular profiles are becoming more and more relevant to tumour partitioning in such classifications. The rare cancer list proposed by RARECARE (a scientific research programme on rare cancers in Europe) is based on the International Classification of Diseases for Oncology (ICD-O, 3rd version) because this is the classification of tumours recognised worldwide. Rare tumour entities are relevant for clinical decision-making and clinical research, while families of tumours are relevant for organisation of health care. This is the list of tumour entities from which rare tumours are identified as those with an incidence of <6/100,000 persons/year. The list (http://www.rarecarenet.eu/rarecarenet/index.php/cancerlist) is derived from the data of 94 population-based cancer registries from 24 European countries adhering to the RARECAREnet project [5].

3. A question of outcomes

Outcomes for patients with rare cancers are worse than for patients with more common cancers. It is well recognised that optimal routine management and research are difficult in rare cancers, and outcomes are improved through research in organisation as well as on nosology and treatment. Altogether, rare cancers are linked with worse survival rates than 'frequent' tumours (5-year survival: 47% for RAC against 65% for 'common' cancers), mainly because of (1) the delays in obtaining accurate diagnoses, (2) inadequate treatments and (3) restricted opportunities for patients to participate in clinical trials.

EUROCARE has published substantial regional differences across EU countries in survival from rare cancers for which there are no effective treatments (e.g. mesothelioma), suggesting variations in the quality of diagnosis and follow-up [6]. For rare cancers that

respond well to treatment, differences in regional survival are of greater concern and are possibly attributable to variations in treatment quality and availability or to cancer awareness in the population. Effective treatments are available for testicular cancer, anal squamous cell carcinoma, sarcoma of extremities and sites of reproductive cancer; further investigation is needed to ascertain why survival from these cancers is low in some European countries, particularly for older patients. Geographical variation in survival for these cancers might therefore reflect differences in the use of effective treatment protocols. By contrast, little or no treatment advances were achieved between 1983 and 1994 for squamous cell carcinoma of the bladder, adrenocortical carcinoma, and mesothelioma. For these cancers, geographical variations in outcome might reflect differences in diagnosis (e.g. accuracy of histological diagnosis) or in quality of follow-up by cancer registries (CRs, e.g. loss of information on death). Adequate knowledge of these neoplasms is crucial for diagnosis and adequate treatment, including surgery, adjuvant therapy and the management of disease relapse [7].

4. A question of clinical trials

The past three decades have seen rapid improvements in the diagnosis and treatment of cancers and consequently in survival and other outcomes for several cancer types. Many factors have contributed to this progress, including public education and screening for earlier diagnosis, better access to diagnostic and treatment services, improved training and quality control in treatment delivery and improved supportive care. The most important contributor to progress has been research, with public and private sector investment in preclinical and clinical research leading to rapid expansion of the evidence base.

Studies of rare tumours present many challenges. Funding is limited; the pharmaceutical industry initially had little incentive to develop drugs for rare cancers; patient accrual to trials is frequently prolonged; there is no consensus about the most efficient clinical trial design methodology, and national regulatory requirements currently significantly impair the ability to conduct international trials.

With regard to clinical research, an interesting example is provided by sarcoma models. The clinical presentations at the sarcoma session of the American Society for Clinical Oncology (ASCO) in 2011 showed data from five randomised clinical trials including 1867 patients; two studies reported an improvement in progression-free survival (PFS). However, an overall survival (OS) benefit was not achieved in any of these studies; this can be explained in part by the inclusion of too heterogeneous a group of patients and probably diseases [8,9]. Looking at the sarcoma group: surprisingly, the first-line treatment options for patients with advanced soft-tissue sarcoma (ASTS) have not progressed substantially in the past 30 years, while the OS for advanced breast cancer increased from 24 months in 1980 to 60 months over the same period of time [10]. To date, only one antiangiogenic molecule, pazopanib, has been approved for the treatment of patients with ASTS (not liposarcoma (LPS)) who have progressive disease after receiving doxorubicin [9], whereas more than ten targeted therapies are available for breast cancer patients [10]. A recent study on metastatic soft-tissue sarcoma estimated a per-patient lifetime medical cost of €65,616, a cost approximately three times greater than that for breast (€23,078) and prostate (€19,710) cancers.

In the case of gynaecological cancers, the past 5 years have seen a major expansion in our understanding of their heterogeneity, so that a global approach is needed to share information and collect data for research. However, improved understanding of the molecular pathogenesis of tumours increases the proportion of rare tumours and creates challenges in optimising the design of clinical trials. In this context, several recent randomised trials dedicated to rare subtypes failed to recruit patients all around the world (mEOC GOG241, GOG 0253, GOG0277, CDK4/CDK6 inhibitor for immature teratoma). Considering this, in 2012 the GCIG (Gynecologic Cancer Intergroup)—an organisation of national gynaecological cancer trial groups—decided to develop a collaborative research initiative and clinical trials in 'moderately rare' and 'very rare' gynaecological cancers. The first step for the GCIG was to develop clinical management guidelines for the major histological subtypes of rare tumours [11]. The next step would be to use these documents to design and develop clinical trials for these tumours to improve the outcome of treatment [12]. More recently—based on national organisation, then EU collaboration, then GCIG collaboration—a GCIG randomised trial (Alienor trial) exploring bevacizumab in combination with weekly paclitaxel or chemotherapy alone for sex-cord stromal tumours, led by the French Group (GINECO) (NCT01770301), has been launched; with the use of a Bayesian statistical plan, only 60 patients are needed to reach conclusions and these were finally randomised in less than 3 years!

To stimulate and facilitate the development of international clinical trials for patients with rare cancers, the International Rare Cancers Initiative (IRCI) was formed in 2011 as a partnership between the National Institute of Health Research Cancer Research Network (NCRN) in England, Cancer Research UK, the European Organisation for Research and Treatment of Cancer (EORTC) and the United States of America (USA) National Cancer Institute Cancer Therapy Evaluation Program (CTEP); in 2013 the French National Institute of Cancer (INCa) joined in. The IRCI is focussed on interventional (usually randomised)

clinical trials aiming to improve outcomes for patients [13]. Of the initial nine groups taken on by IRCI, seven are actively developing ten clinical trials for submission to appropriate funding bodies. Coordinated approaches for cooperative clinical trials therefore need to be improved in 2017.

As an investigative community, we must come to terms with the most efficient clinical trial designs and intergroup collaborations to study drugs in order to allow specific patients to access more rapidly the most active drugs for their diagnosis. In rare cancers, the problems are distinct from those of more common cancers. The pharmaceutical industry is reluctant to invest in the treatment of 'niche' diseases with small market potential [14]. The scientific review process in academic centres is burdened by studies that may accrue only one or a few patients with a rare diagnosis in a year, and regulatory requirements are greater than ever in the conduct of clinical trials [15]. Novel trial designs are needed to take forward the development of new treatments for rare tumours. An emphasis has been put on these cancers at different national and international political levels, recently bringing together different stakeholders and aiming to solve the problem imposed by the rarity of these tumours to allow for new clinical developments. For clinical research, the unresolved problems also include epidemiological aspects, identification of patients, the definition of the most efficient primary end-point, the capability to delineate randomised trials, and new statistical approaches; the latter include cross-over studies, Bayesian statistics or even using the patient as her own control [16], as well as the need for an intergroup setting with associated administrative costs and requirements, and last but not least the development of rigorous partnerships with pharmaceutical companies in this context. This requires international partnerships, harmonisation of treatment, and collaboration to overcome the regulatory barriers to conducting international trials which are mandatory in view of this rarity. Whilst randomised trials can be done for many tumour types, there are some for which conducting even single-arm studies may be challenging. For these tumours robust collection of data through national and/or international registries could lead through audit to improvements in the treatment of rare tumours. Such international partnerships and collection of data need to be built on efficient national organisations to improve quality management and available databases.

5. National organisations and experiences

Several national initiatives to organise care and research for rare cancers are currently operational, some for several years (in Scandinavian countries, UK, France etc.). We present here an example of such initiatives. In France, a second National Plan for Cancers was launched on 2nd November 2009 for the period 2009–2013. A specific plan of action is dedicated to the development of specialised expert centres for rare cancer patients, labelled 'reference centres for rare cancers'. Again, the term 'rare cancers' applies to cancers which are diagnosed in less than 6/100,000 persons per year, or those requiring highly specialised management owing to their unusual location or to their occurrence at a specific or complex site. This organisation implements the creation of a network of regional centres for rare adult cancers referred to national 'expert centres' (reference centres).

Since 2009, 23 national clinical networks for 23 groups of rare adult cancers have been set up and financed. Among their missions, these expert centres have to: (1) ensure diagnostic certainty by implementing a systematic second reading; (2) ensure a multidisciplinary expert discussion of the patient file for the choice of initial and subsequent treatments; and (3) facilitate the enrolment of patients in appropriate clinical trials. After 4 years of activities, national networks have reported all their activities to the Inca website (www.e-cancer.fr). Thus, in 2013, over 12,800 patients with rare cancers benefited from expert care. In 2012, this figure was 8100 (+58%). The overall rate of coverage by the specific organisation for rare cancers, all networks combined, was 74.6% in 2013. However, it varies considerably between the networks. Although eight national reference networks have very strong coverage, with over 70% of new patients discussed at a referral multidisciplinary tumour board (MTB) or recorded in the corresponding databases; eight in contrast have highly inadequate coverage, with fewer than 30% of patients having benefited from this specific organisation in 2013. The organisation for rare cancers with discussion of files at a referral MTB and/or recording of cases in national databases act as a lever for encouraging clinical trials and facilitating access to innovative treatments. Thus, in 2013, 138 clinical trials were started, ongoing or completed during the year, compared to 89 in 2012 (+55%), with a variable distribution depending on the network. Epidemiological surveillance is essential for improving the knowledge of these rare pathologies. Moreover, most of them are excluded from the general statistics provided by CRs. Seventeen of the 23 clinical networks for rare cancers have established a national database for recording cases. However, follow-up data—especially data on survival without recurrence (RFS) and on overall survival (OS)—are usually not recorded. A linkage with CRs could contribute to ensuring the collection of the data on follow-up and life status. Over 135,000 cases were recorded in these 17 dedicated national databases. Finally, 17 websites have been designed by members of the rare cancer network, and these provide high-quality information for health professionals, patients and the general public alike. They provide detail on the organisation of the network, with a list of the experts in each regional centre and the *modus operandi* of the referral

staff; they disseminate recommendations or national guidelines for these pathologies (Support for the decision, INCa, April 2015 http://www.e-cancer.fr/Expertises-et-publications/Catalogue-des-publications/French-national-networks-for-rare-cancers-in-adults-Review-and-Outlook). Some examples published or orally reported in International congresses such as the European Society for Medical Oncology (ESMO) or ASCO also highlight benefits in terms of outcome for patients.

6. Rare ovarian/gynaecological tumours

The rare malignant tumours of the ovary represent less than 10% of the ovarian tumours in adults. They essentially include germ-cell tumours and tumours of the stroma and sex cords, tumours of the granulosa and of Sertoli–Leydig cells, small-cell carcinomas and certain rare epithelial tumours (mucinous, clear-cell, low-grade serous carcinoma, carcinosarcoma and borderline tumours with invasive implants). The age at diagnosis, the initial stage, and the prognosis are different from the most frequent ovarian epithelial high-grade serous carcinomas. Because of the extreme rarity of these tumours, the difficulty of histological diagnosis and the absence of strongly validated prognostic factors and of randomised trials, therapeutic decisions cannot be based on established standards and require multidisciplinary discussion among experts.

In 2010, a national network dedicated to all rare ovarian cancers and other extremely rare gynaecological tumours was established. In this national network, up to 22 centres and three national reference centres covering the whole territory were linked together. Expert pathologists and referral clinicians were able to organise in each region both central histological reviews and dedicated multidisciplinary meetings. Thus each patient with a rare gynaecological tumour could be sent to an expert centre close to their home. This organisation is based on a web site (www.ovaire-rare.org) where the patient's clinical information and the results of the expert pathological diagnosis and expert multidisciplinary meeting decisions are collected. In addition, this website offers clinical medical guidelines for each tumour type as well as information for the patients and their families. Over a 5-year period, 4612 patients have been included in the website database. Patients were included either for a pathological review or for advice from an expert advisory board or both. Their number increased from 553 in 2011 to 1202 in 2015. Expert pathological review and discussions of patients' files in dedicated multidisciplinary tumour boards increased from 166 cases in 2011 (25%) to 538 in 2015 (45%). Pathological review consistently modified the medical strategy in 5–9% of cases every year. Finally, the network has created a momentum for better knowledge of rare tumours of the ovary for both patients and healthcare professionals. Thanks to this network, clinical trials have been developed at the national and international levels such as the randomised ALIENOR trial for relapsing granulosa tumours.

The next steps will be to increase the number of trials for these rare tumours which deserve specific treatments as they are biologically and clinically different from the typical epithelial ovarian cancer. These trials will be based on strong translational research that has been developed thanks to national and international cooperation.

7. Sarcoma (NETSarc and RePPS)

Since 2009, a network of 26 reference centres for sarcoma patients in France was designated by the French National Cancer Institute. The outcome of the 26,883 patients discussed in these 26 NETSARC multidisciplinary tumour boards (MTBs) was reported at ESMO 2016. The NetSarc database includes patient characteristics, treatment and diagnostic procedures, survival, and progression. Soft-tissue, visceral, and bone sarcomas represent 17,801 (66%), 4625 (17%), 4457 (17%) of the patients respectively [17]. Individual NETSARC centres managed a median of 404 patients (range 92–2974) in 5 years; 37% were presented to a NetSarc MTB prior to any initial treatment. Local relapse rates were significantly lower in patients discussed in NetSarc MTB prior to first treatment (22% versus 29% at 24 months, $P < 0.001$). In multivariate analysis, the lack of discussion in NetSarc MTB prior to initial treatment in a reference centre was an independent unfavourable prognostic factor for local, for metastatic, and for overall relapse (HR 1.9, 95% CI 1.6–2.2) along with age, grade, tumour size, depth, and tumour location (all P values < 0.001) and was associated with the highest hazard ratio along with grade 3. Finally, conclusions are to report relapse rates higher than previously published in this large real-life series of 26,883 sarcoma patients of the NETSARC network. Presentation in an MTB prior to first treatment is a major parameter associated with lower rates of relapse.

These two national experiences have highlighted the importance of a network including regional organisation to organise patient management care pathways to optimise the efforts for a majority of patients.

8. European expert cancer centres network

The European Commission is implementing the directive 2011/24/EU of the European Parliament and the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare; in principle, this directive is meant to grant EU patients the right to access safe and good-quality treatment across EU borders. A 'by-product' of all this is the creation of the European Reference Networks (ERNs) as a means to provide

highly specialised healthcare for rare or low-prevalence complex diseases.

The formal activation of ERNs will be a cornerstone in EU cooperation on rare cancers. Thus, it was decided that the Joint Action on Rare Cancers (JARC) of the European Public Health Programme should be instrumental in this. In fact, JARC aims at optimizing the process of creation of the ERNs by providing them with operational solutions and professional guidance in the areas of quality of care, epidemiology, research and innovation, education, and state-of-the-art definition on prevention, diagnosis and treatment of rare cancers. JARC was launched in October 2016 to support the cooperation between the Commission and the Member States concerning rare cancers. Coordinated by the Istituto Nazionale dei Tumori of Milan (Italy), JARC takes advantage of a strong partnership of 34 partners and 18 European Member States (MSs). JARC will focus on all the 12 'families' of rare cancers with the following specific objectives:

- to improve epidemiological surveillance of rare cancers in Europe;
- to identify standards of care for all 12 families of rare cancers (head-and-neck cancers, rare thoracic cancers, rare male genital and urogenital cancers, rare female genital cancers, neuroendocrine tumours, tumours of the endocrine organs, tumours of the central nervous system, sarcomas, rare digestive cancers, rare skin cancers and non-cutaneous melanoma, rare haematological malignancies, all paediatric cancers) to ensure the sharing of best practices and equality of care for rare cancers across Europe, particularly through clinical networking;
- to promote integration of translational research innovations into rare cancer care.

The objectives of JARC will be implemented through the creation of a platform for national authorities, institutions, scientific and professional societies, as well as patient organisations, to work out consensus-based recommendations, focussing on how to shape the new ERNs; this is viewed as a great opportunity for the improvement of rare cancer patient care and research in Europe.

In the course of their work on European centres of reference (ECRs), a working group of medical care and health services (comprising representatives from member states), has decided to seek advice from an expert group on centres of reference on several specific issues. The experimental phase of the work on ECR focussed on the field of rare diseases, which clearly needs an EU approach. European reference networks (ERNs) for rare diseases should serve as research and knowledge centres, updating and contributing to the latest scientific findings, treating patients from other member states and ensuring the availability of subsequent treatment facilities where necessary. In 2016, an EU call for rare cancer was set up, and several EU countries applied for an EU network dedicated to rare adult cancer. The EURACAN (Rare Adult CANcer) ERN will aim to establish a world-leading, patient-centric and sustainable network of multidisciplinary research-intensive clinical centres focussed on rare adult cancers (RACs) with the underlying vision to (1) standardise and improve the quality of care of all RAC European adult patients and (2) ensure an optimised access to clinical innovation in the field of RAC and across all member states.

9. Goals and missions

EURACAN is the ERN of rare solid tumours in adults, and as such brings together reference expert centres with a complete set of multidisciplinary expertise, endorsed by their countries to provide high-quality care in selected groups of patients with rare cancers (Fig. 1). EURACAN will specifically aim to (1) increase and accelerate access to pathological diagnosis and associated treatments across all EU MSs with a view to improving patients' quality of life and survival rates; (2) develop dedicated medical training programmes in order to improve and harmonise the quality of care; (3) involve patient advocacy groups (PAGs) and assist them in wide dissemination to enhance overall patient information and empowerment; (4) implement 'roadmaps' for referral and self-referral of patients to expert centres, to optimise the patients' care pathways and ultimately quality of care; (5) develop and continuously review clinical practice guidelines (CPGs) across the various domains, to spread and support best practices; (6) carry out a thorough socioeconomic assessment of the impact of RAC on patients' quality of life and healthcare systems and formulate recommendations to health authorities to lower the economic impact of rare diseases on health systems; (7) initiate and promote novel translational research programmes to maximise innovation transfer in the clinic; (8) interact with key national/international actors/networks and infrastructures involved in cancer care and research [e.g. the National Cancer Institute, under the National Institutes of Health, USA, (NCI), the International Agency for Research on cancer (IARC), under the World Health Organisation of the United Nations] and beyond, with other rare diseases stakeholders and ERNs [e.g. Patient Advocacy Groups (PAGs), European organisation for Rare Diseases (EURORDIS), EIC, the European Society for Medical Oncology (ESMO), European Organisation for Research and Treatment of Cancer (EORTC), the International Rare Cancers Initiative (IRCI), RD-CONNECT, a global infrastructure project initiated in November 2012 that links genomic data with registries, biobanks and clinical bioinformatics tools to produce a central research resource for rare diseases, the European clinical research infrastructures network

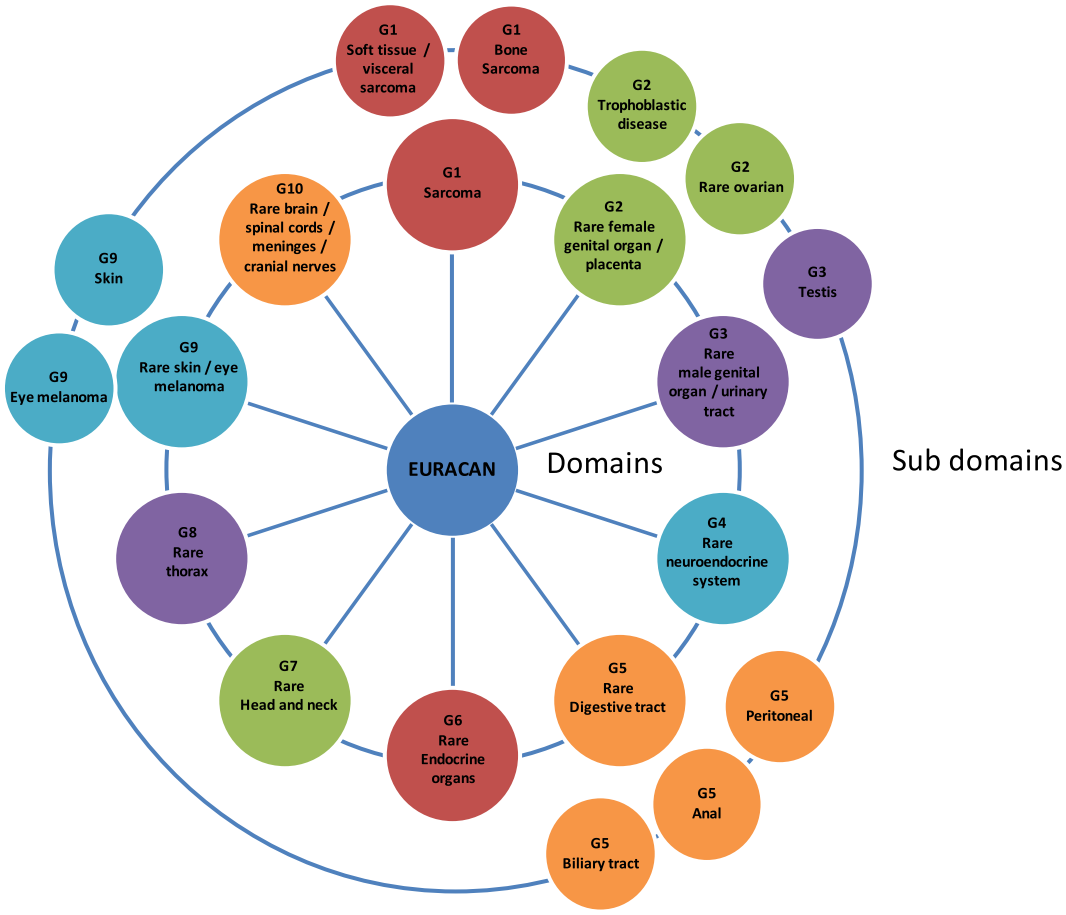

Fig. 1. EURACAN-targeted rare adult cancer (the governance). Rare adult solid cancers were grouped into ten domains corresponding to the RARECARE classification and the ICD10. These domains are also based on preexisting successful collaborations, in particular for clinical research and expert networks active in the last 10–20 years. The ten domains are the following: G1, sarcoma; G2, rare gynaecological cancers; G3, rare genitourinary cancers; G4, neuroendocrine tumours; G5, rare digestive tract tumours; G6, endocrine cancers; G7, rare head-and-neck cancers; G8, rare thoracic cancers; G9, rare skin cancers and eye melanoma; G10, rare brain cancers.

(ECRIN), a pan-European network, Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), Joint Action on Rare Diseases (JARD), Joint Action on Rare Cancers (JARC), scientific societies, research cooperative groups, etc.] to promote cross-fertilisation between activities and share/disseminate best practices through EURACAN communication platform.

10. Partners

Most centres in EURACAN cover a variety of domains, and therefore most countries have on their territory the required expertise for all domains of rare tumours. However, this may not be the case for all countries, in particular those with limited population sizes. Another limitation is the availability of large technological equipment: e.g. proton beam therapy, carbon ion therapy, isolated limb perfusions, etc. Cross-border pathways already exist within and between the potential centres. This overview already documents important activity in this field but also the diversity and complexity of modalities in place to enable a patient to get treated or to obtain a second opinion from an HCP in a country other than his/her own. So, the EU network will be organizing collaborations between HCPs, full members and affiliated centres (in general regional centres, members of the potential national network), to enable the European patient affected with a rare cancer to get optimal treatment in one of the centres involved in EURACAN collaboration.

11. EU added value and expected impact of the planned activities

Suboptimal treatment outcomes are common for RACs due to a lack of medical expertise in the management of rare cancers associated with poor referral rates from general practitioners. It will be a mission of EURACAN HCPs to communicate in their region of influence on the optimal management of RAC patients, and to provide guidance to the first care centres and reference centres not engaged in RAC. The expertise of the medical teams

and their awareness of rare tumours determine the extent and likelihood of mismanagement.

EURACAN healthcare providers have advanced knowledge of more than one type of rare malignancy, and together they will reach the critical level of expertise required to offer EU RAC patients access to better, safer therapeutic options which will be disseminated to all regions. The intention is to alleviate differences in relapse and mortality rates for the various types of RAC and to decrease the significant survival differences observed between the EU MS for the same types of RAC [6]. By organising this multitumour integrated multinational network, and by centralising knowledge and experience, medical research, training, and resources, EURACAN will enable this major improvement in the access to excellent diagnosis and treatment for European patients and unify practices across the EU. It will also enable the generation of a clearer picture on comparative incidences of RACs. EURACAN aims to deliver benefit to the whole patient pathway, to connect to the patients' healthcare centres in their country of origin, and to facilitate cross-border healthcare whenever needed. Dedicated work on patient pathways will therefore be implemented for all domains of EURACAN, specifically on initial diagnosis and consultations, first treatment, assessment, follow-up and education.

12. Conclusions

Patient with RAC more frequently experience delays in diagnosis and treatment than patients with frequent cancers, often resulting in an inadequate first treatment. This is a result of multiple factors, from lack of recognition of the nature of the disease by the primary care physician (general practitioner (GP), radiologist, surgeon) to an inaccurate diagnosis by the pathologist-dedicated networks. National experiences from reference networks have shown that providing information to the primary care physicians and a national coordination of diagnostic procedures enables improvements in adherence to clinical practice guidelines [18,19]. All these experiences are clearly favourable to patients with rare cancers.

High-quality management of rare cancers needs to be based on scientific evidence that should include international consensus guidelines, multidisciplinary managed care, and high-quality clinical trials. The organisation of management of rare cancer patients should take account of national and local structures and can be facilitated by having reference centres for rare cancer and/or reference networks share multidisciplinary expertise and access to clinical trials, so that information gathering and sharing results in a coordinated approach to the treatment of a large number of patients each year. Conducting trials in a small number of patients presents its own challenges: novel trial design, overcoming regulatory barriers for international collaboration, and funding of studies in rare tumours by academic bodies with little or no pharmaceutical support. Many of these difficulties can be overcome through the establishment of robust international/European collaborations that harmonise the approach to clinical trials and routine practices. However, there remain diseases for which clinical trials are virtually impossible to perform. For these we need reliable data collection by national registries that can be merged to form international data sets.

Conflict of interest statement

All authors except Dr. LeCesne have no conflict of interest to disclose, including any financial, personal or other relationships with other people or organisations that could inappropriately influence their work. Dr. Le Cesne reports personal fees from Pharmamar, personal fees from Pfizer, personal fees from Lilly, personal fees from Amgen, personal fees from Novartis-GSK, outside the submitted work.

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