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Editorial

Specialized teams or specialist networks for rare cancers?

Even when conservatively defined by an incidence lower than 6 cases/100.000/year, rare cancers are not rare at all,[1] accounting for more than 20% of all cancers and affecting more than 4 million people in the European Union, including those that are cured, those in clinical follow-up or receiving treatment for recurrences, and those that are suffering for the long term treatment sequelae. Every year, more than 500,000 people in the EU are diagnosed with a rare cancer.

The management of rare tumors is far from optimal; over 198 rare cancers have been identified and grouped into almost twelve 'families', thus posing problems in obtaining a correct pathological diagnosis. Surprisingly, since the 1986 report[2] on the value of second opinions for complex diagnoses of sarcomas (a significative subsetting of the rare tumors family), despite the introduction of new diagnostic tools and the development and spreading of educational workshops, disagreement between pathologists and expert panels are still present (i.e. unrepresentative samples, heterogeneous tumors, misdiagnosis or erroneous grading, etc…); this has left the percentage of discordance unchanged over the years. Even if molecular biology can facilitate diagnosis,[3] such techniques, presently not routinely available in every lab, are best utilized by expert pathologists with an experience in molecular biology. Given the multitude and complexity of rare tumors, non-specialized pathologists might be lacking experience, and such diagnostic uncertainties could result into inappropriate treatments and delays. Surgery is the most important treatment for solid rare cancers. About 2 out of 3 of patients receive surgery as the sole treatment modality, plus another 30% receiving surgery in combination with radio- or chemotherapy. Rare cancers are almost ubiquitous and affect every district of the human body: this explains why surgical oncologists will occasionally deal with only a small number of them, depending on the anatomical district they specialize in.

Surgery for rare cancers may not necessarily be more demanding than the standard practice, from a technical point of view; however, the lack of oncological understanding of the disease may often lead to mismanagement, even in the lack of any technical challenge. On the other hand, a multidisciplinary clinical approach at the very beginning of the patient's journey may not always be feasible: pulling together a panel of experts to stimulate a multidisciplinary discussion may be impractical, if not unfeasible. .

According to the project "Surveillance of Rare Cancers in Europe" (RARECARE),[4] survival differences between rare and common cancers are small at one year from diagnosis (68% vs. 80%), but they increase markedly thereafter (up to 48% vs. 64% at 5 years, respectively). This suggests that treatments for rare cancers are far less effective than those for common cancers.

EUROCARE-5, a recent population-based study on cancer survival in Europe [5] showed that some European countries have failed to develop a well needed organization to optimize the treatment for such infrequently seen conditions. EUROCARE-5 confirmed how national socio-economic factors are likely to influence outcomes of cancer patients. Limited access to expensive cancer drugs, delayed diagnosis and late presentation may have less influence on cancer survival than generally assumed, but diverse outcomes should challenge health care systems to re-evaluate existing strategies and upgrade them according epidemiological data.

A possible way forward is to promote adherence to guidelines, which was shown to improve outcomes in some rare cancers.

A continuous and repetitive referral to guidelines might have a highly valuable educational impact, enhancing awareness of a standardized work-up among unexperienced clinicians first treating such diseases. Appropriate referral as well as compliance to guidelines were found to be important in a French cohort-based study on a family of rare cancers, sarcomas[6] in terms of outcomes and survival. This study underlined that guidelines are even more effective if applied in referral centers.

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Unfortunately, guidelines covering the whole range of rare cancers families cannot be made available.

Should patients with rare cancers be treated by centers of reference from the very beginning of their clinical history? In the first instance we need to define what a referral center is; according to the European Cancer Institutes Accreditation and Designation Program, the main feature of a reference institution, besides surgical expertise, is to have a high enough "volume" to certify medical expertise, technical adequacy and access to clinical trials.[7] However, there is no evidence to support this statement. The pattern of referral of rare cancer patients, as well as their management, varies substantially across the EU; to what extent centralization is in place across the EU still needs to be clarified, where national or regional health systems differ substantially.

Establishing a network of expert Centers could be an interesting alternative. Cancer Networks have been viewed as a strategy to improve outcomes by centralizing patients and decreasing patients migration[8]: networking between centers of advanced treatment and surroundings hospitals is a key element to ensure that expertise travels, rather than patients.

The EU Reference Networks (EURN) offers a great opportunity to improve the quality of care for rare cancers: networking is foreseen by the EU Cross-border Health Care Directive, i.e. the EU instrument sanctioning the right of patients to be treated across EU countries. It is based on healthcare cooperation between member states following the development of a EU Health Policy in conditions requiring a concentration of resources or expertise (especially for those suffering from low prevalence and rare diseases where expertise is scarce). Albeit informal in most cases, several networks have been established. Some of them are supported through the EU public health and Research Programs, particularly for rare diseases, pediatric tumors and complex neurological diseases. Cancer outcomes will depend on how the EU Commission will wish to set up EURNs for rare cancers over the next years. Some ongoing European efforts might help the EU Commission to advance its actions: RARECAREnet[6] is a EU project which, by means of high resolution studies on European cancer registries, will describe the healthcare pathway for rare cancers. The ongoing pilot study involves cancer registries from 7 EU countries with the following aims: a) estimating indicators for the degree of centralization of rare cancers, b) mapping hospitals where rare cancers are most frequently treated and c) analyzing the association between hospital volume and outcomes.

Rare Cancers Europe is a multi-stakeholder effort between cooperating partners (including ESSO),[9] which works as think-tank for rare cancers. It is based on a set of 39 recommendations on rare cancers, paving the foundation of its current projects: a consensus on innovative methodologies for clinical research on rare cancers was recently published,[10] while a project on how to methodologically "adopt" five rare cancers is currently ongoing. A consensus event was organized in 2014 to improve the quality of pathologic diagnosis and a consensus document therefrom is currently under preparation. This vital opportunity for the new EURNs on rare cancers will have to address the challenges in the management of rare cancers: the real issue is not to offer single lead specialists but a reachable referral to appropriate therapeutic strategies which could be accomplished by:

1) Increasing awareness of rare cancers amongst first line physicians, surgeons and oncologists. Informing and educating pathologists is also crucial to ensure accurate diagnosis and grading, and to enhance a "second opinion" culture. Spreading knowledge and good practice guidelines on rare cancers is strategic. EU scientific Societies and referral centers must lead in creating awareness in the medical community about rare cancers to shorten the time to diagnosis and treatment.
2) Supporting patient associations and making sure their recognition as stakeholders in order to improve quality of care of rare cancer patients. Patient empowerment may finally determine those changes which otherwise would hardly happen, or would develop at a much slower pace. Evidence based guidelines and good service guidelines must be developed together with patients advocacy groups.
3) Developing collaborative healthcare networks. Participating into a cancer network can facilitate the involvement of pathologists and ensure exhaustiveness. However, sharing patients amongst different centers implies extra workload and higher expenses: Networks are unlikely to develop until financial implications are acknowledged and addressed.
4) Developing a multidisciplinary clinical approach and healthcare pathways supporting patients from diagnosis to rehabilitation, including psychological support. Personalizing cancer treatment should be a duty for surgical oncologists, not just by looking at technical issues, but also at patient values, quality of life, etc. Healthcare pathways must be developed nationally and across the border.
5) Developing alternative study designs and methodological approaches to clinical research, and improving accuracy and standardization of staging procedures and treatment plans for rare cancers.

The more realistic solution to rare cancers care uncertainties seem to rest on a quick and simplified referral system to specialized centres at any "critical" time, from diagnosis to complex surgery, from advanced radiation therapy to innovative medical treatment with new medications. This might not preclude that patients' care could take place "close to home" during most standard phases of the therapeutic pathway. Reference centres as well as regional centres are required to be open minded, willing to

collaborate and to share information, intelligence and knowledge, with the support of national health authorities. Favouring such an efficient network would prevent niches of high specialization vs areas of low quality care across EU Countries.

Conflict of interest

The authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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