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Histopathologic challenges: The second OPINION issue

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ABSTRACT

Classification and definition criteria for rare cancer is still an open issue in clinical practice due to several factors, which include the limited available molecular data to better defining specific tumor groups or "families" of interest. An important issue related to the proper management of these entities is the correct diagnosis and subtyping of a given entity. The high complexity associated with the histopathologic diagnosis and eventual molecular analysis may suggest the use of a histopathologic second opinion from a specialized pathologist. Diagnostic inaccuracies and difference between primary diagnosis and second opinion are expected at the population level: however, the magnitude of this difference is remarkably high and calls for implementation of second opinion in routine practice outside reference centers.

Background

Until few years ago there was no consensual worldwide definition of rare tumors, a fact that made them as an open issue. In the United Stated (US), rare tumors were defined as those with fewer than 15 new cases per 100,000 per year (incidence) [1] and in Europe they were included among rare diseases with a frequency of less than 50 cases per 100,000 (prevalence) [2]. The project Surveillance of Rare Cancers in Europe (RARECARE), 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, as prevalence rate is biased by cancers with a high life expectancy. The threshold for rarity was set at < 6/100,000/year. The list of rare cancers was based on the International Classification of Diseases for Oncology (ICD-O 3rd edition) [2]. The US, Japan and several European countries estimated the burden of rare cancers according to the RARECARE definition and list of malignancies [3–6].

Dimension of the problem

According to the last European estimation, rare cancers account for about 24% of all cancers and affect more than 5 million people at the European Union level. Annually, more than 630,000 people in the EU are diagnosed with a rare cancer [7].

A particular feature is seen, for instance, when looking at cancer incidence rates by age. The incidence of rare cancers significantly exceeds that of non-rare cancers in the pediatric population. Also, 5-year relative survival rates for rare cancers are lower than those for non-rare cancers — 48.5% versus 63.4% — making rare cancers a significant burden and a public health priority [7]. Following the last updating, in the EU there are 198 cancers that fulfill the criteria to be considered as rare [7], which show a variable life expectancy.

Currently, rare cancers are primarily classified by tumor location, although there is an emerging paradigm that would possibly group rare cancers into molecular "families" [8–11]. With advancements in genomics and the rising of precision medicine, it is now expected that a growing number of neoplasms traditionally not included in the category of rare tumors (particular less common molecular subtypes or tumors with associated specific mutations)

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will be categorized as rare cancers.

Value of histopathologic second opinion in diagnosis of cancer

Second opinion in histopathology is one mechanism for diagnostic error reduction by redundancy and should be considered as an integral part of the many aspects related to complete quality assessment program in a pathology service [12].

A second opinion may confirm or question the first diagnosis and treatment plan, give more information about the patient's disease or condition, and offer other treatment options [13].

Second opinion (SO) in diagnostic pathology has recently received considerable attention as a result of efforts to enhance institutional performance and reduce medical errors [14]. However, the mechanisms by which second opinion is obtained greatly influence the results [15]. Second opinions given by another institution or a specialty panel at the time of patient referral produce highly discordant results compared with analysis of cases referred to experts for review [16]. In the case of expert review, discrepancies are not viewed as 'misdiagnosis' but as an acknowledged need for assistance.

Second histopathology opinion can result in major therapeutic and prognostic modifications for patients sent to large referral hospitals. Although the overall percentage of affected cases may be not large [15,16], the consistent rate of discrepant diagnosis uncovered by second opinion histopathology have a relevant human and financial impact.

Obtaining a pathologic second opinion is useful for confirming and/or providing additional information regarding a primary diagnosis, and in some instances, offering a more explicit diagnosis. Second opinion can also be referred to as consultation cases or second review or just review cases.

The most common source for a pathologic second opinion is the request of patients who are seeking potentially different therapeutic options. But it is also common practice between pathologists of the same institutions (internal or intra-departmental second opinion) or from different institutions (inter-departmental second opinion), also, it is a common practice to review histologic materials prior to entry into a clinical-trial study [14]. Systematic second opinion histopathology is also the policy of several oncological institutions around the world.

As mentioned earlier, second opinions of pathology diagnoses may be routinely used intra-departmentally not only for immediate patient diagnostic accuracy, but also as a tool for peer review, quality assurance, and quality improvement. These may occur as consensus conferences or mandatory second opinions of initial diagnoses of cancers [17].

Additionally, directed peer review (topographic or disease selective) provides extra benefit through the identification of latent factors that may influence diagnostic error.

Extra-departmental second opinions are a logical extension of intradepartmental pathology reviews. A second opinion of outside cases prior to treatment remains the best method of ensuring the highest diagnostic accuracy for cancer patients and patients with other serious conditions who go to an institution for definitive treatment.

Rare tumors and histopathology: the second opinion issue

The management of rare tumors is far from optimal. They are often inadequately diagnosed and treated [18]. The relative length of time for patient referral is highly variable and appears to be longer in rare cancer patients than in patients with common cancers [16]. This may be due to non-specificity of symptoms, late presentation, but also to the lack (or limited) knowledge on how diagnose and guide these patients [19]. Concerning pathologic diagnosis of rare cancers, there is still considerable variability and disagreement between general pathologists or even expert panels, in spite of using novel diagnostic tools. For instance, molecular features of a given case are usually informative; in particular those needed to evaluate rare tumors are not routinely available in every pathology laboratory and, again, due to their complexity, are best handled by pathologists with experience in molecular biology [20].

In rare cancers, careful pretreatment evaluation is essential for accurate diagnosis and appropriate treatment decision making. The inexperience of non-specialized pathologists with the multitude and complexity of rare tumors is not the only most important factors accounting for diagnosis uncertainties. Fluorescence In Situ Hybridization (FISH) and molecular biology can facilitate diagnosis [20,21], but their use requires experienced pathologists with expertise in molecular biology. The central question that arises is whether all rare cancer cases should be reviewed in a specialized center.

In the literature, the proportion of diagnostic errors in patients with soft tissue sarcoma ranges between 25% and 40% [22–24]. Non concordance between first diagnosis and review seems very frequent for PNET tumors [25], sarcomas [26,27], GISTs [28], penile cancer [29] and dermatofibrosarcoma protuberans [30] for which specific markers are available. Similar results were reported by Harris et al. [31], with a high degree of agreement for osteosarcoma and chondrosarcoma and low agreement for leiomyosarcoma and malignant fibrous histiocytoma.

Surprisingly, since the first published reports on second opinion for sarcoma tumors in 1986 [23], despite the introduction of new tools (immunochemistry, molecular biology etc.) and the development of educational workshops, the percentage of concordance has remained unchanged [26]. Disagreements between diagnostic pathologists and expert panel members seems to be inescapable (unrepresentative samples, heterogeneous tumors, misdiagnosis of grading, etc). however guidelines with rule of conduct should be advisable.

A prospective study involving the systematic comparison of initial histological diagnosis of sarcoma by a first ('non-expert') pathologist and second opinion (SO) from regional and/or national experts of the disease in a comprehensive population of patients diagnosed in a precise geographical region over a one-year period reported full concordance for only 54% of cases. [27], Discrepancy in a pathologic diagnosis can be the result of several factors, including operational errors, tumor heterogeneity, poorly stated criteria, ambiguous qualitative terms, imprecise qualitative terms, cognitive mistakes, or difficult diagnoses; all these parameters largely apply to the diagnosis of rare cancer since these tumors are by definition not so common and frequently display a morphologic heterogeneity resulting in unfamiliar microscopic picture for most non-specialized pathologists [16]. The sources on which diagnostic error may occur are therefore quite heterogeneous.

Concordance seems independent from the type of laboratory providing the primary diagnosis, the nature of the tumor samples or the tissue affected (bone, soft tissue, viscera). The most frequent discrepancies identified were related to tumor grade and histological type. Although the tumor grade must be included in the histological report generated at the time of diagnosis, this information is not always given, as confirmed in other studies demonstrating that the reproducibility of grade is very difficult to achieve [32]. On the other hand, when non expert pathologists participating in the study did grade a tumor, their evaluation was generally correct. Exact determination of the tumor type and grade is crucial for making individual treatment decisions and subsequently improving patient outcome [33].

With the introduction of targeted treatments and the proliferation of clinical studies, patients whose grade has not been correctly evaluated may be excluded from trials [34,35]. In addition to that, the result of diagnostic uncertainties implies an important limitation in applying proper therapeutic protocols: in the epidemiological studies both incidence and survival evaluation can be strongly influenced by the imprecise definition of the neoplasm and outcome.

In cases where the original pathologist has a low level of confidence in the diagnosis, second pathology opinion should be mandatory with inclusion of additional studies useful to strength the final diagnostic reports. Electron microscopy, histochemistry, immunohistochemistry, and molecular biology studies have a variable role in delineating the type of tumor actually present [36]. Second opinion pathology consultation occurs in a variety of different clinical settings and with different driving factors. Ideally, second opinions should be performed prospectively and in real-time before treatment is undertaken.

There is a large need to gain recognition for the process of second opinion. This has been standard practice in the UK since 2006 [37]. In other countries some institutions entirely support second opinion, particularly when patients firstly present with a rare tumor diagnosed elsewhere and are listed for having treatment for their primary tumor. However, in many national and regional health care systems this process is not part of the common clinical pathway and patients are charged for cost of second opinion.

To achieve a successful recruitment for second opinions requests, many requirements must be met. In particular, there must be a key opinion leader and expert pathologist with recognized expertise in the field. Financial support to the pathologists participating also seems essential. Finally, it is important to keep the pathologists informed through regular meetings and newsletters. They must be involved and get feedback about the final diagnosis of their patient as well as about the advancement of ongoing studies. Cancer network participation can facilitate the involvement of pathologists and ensure exhaustiveness. It is well established in sarcoma pathology that “expert” opinion is not always absolutely convergent, though often different conceptualizations of a tumor do not necessarily generate different treatment implications.

A centralized pathological review, a rapid and efficient help with access to molecular biology analysis seem of vital importance in these rare tumors. More efficient information and education of the pathologists also seems essential to ensure accurate diagnosis and grading.

In general practice, second opinion surgical pathology can result in major therapeutic and prognostic modifications for patients sent to large referral hospitals. Although the overall percentage of affected cases is not large, the consistent rate of discrepant diagnosis uncovered by second opinion histopathology may have an enormous human and financial impact. This is particularly true in uncommon and rare tumors.

Conclusion and future directions

Rare cancers are an increasingly important issue in clinical practice. To avoid misclassification, it is recommended that the cases being the subject of histopathology second opinion, most probably in centralized centers of excellence across the European Union but whose characteristics still need to be define by the active players including the medical associations, health authorities at EU and national levels, and patients’ associations.

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