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Original article

Exploring real-world practices and challenges of sarcoma diagnosis in Morocco: a survey-based study among 144 pathologists

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Abstract. *Background and aim:* Sarcoma diagnosis is a challenge for laboratories of cytopathology and anatomic pathology. We conducted this survey-based study to better elucidate real-world practices and challenges of sarcoma diagnosis. *Methods:* This was a cross-sectional study using an anonymous questionnaire. The survey was distributed among pathologists using snowball sampling. Descriptive statistics were used to report the finding of this survey. *Results:* A total of 144 Moroccan pathologists were surveyed. Most respondents were from academic institutions (41.7%) and those with a specialization in sarcoma diagnosis represented 57%, through training using post-graduate fellowships followed by internships abroad and inter-university diplomas. Remarkably, 36.8% of participants reported no training on sarcoma pathology during their career. Regarding frequency of sarcoma diagnosis, 64.6% of pathologists reported having received less than one case of sarcoma per week and more than 70% did not receive sufficient information from referring clinicians. The majority of pathologists reported their nonattendance in multidisciplinary meetings. Morphology and immunohistochemistry were the most frequently used diagnostic tools, while fluorescence in situ hybridization and other molecular biology techniques were accessible for only 27% and 20.1% of pathologists, respectively. Response time during pathological diagnosis of sarcoma was 14 days according to 52.8% of surveyed participants. In addition, a second opinion was needed for 66% of pathologists. *Conclusions:* Specialized training on sarcoma pathology in Morocco is lacking. A national working group on sarcoma pathology is needed to provide second opinions, and therefore, improve the management of this malignancy of poor prognosis. (www actabiomedica.it)

Key words: sarcoma, molecular biology, immuno-histochemistry, anatomic pathology, Morocco, survey

Introduction

Sarcomas are rare malignancies developed from soft or bone tissues and can affect all anatomical sites of the human body, and more frequently the extremities (1). Each sarcoma histotype has individualized hallmarks based on its clinical presentation, epidemiological characteristics, diversity of risk of progression and local recurrence, metastatic potential, and sensitivity to chemoradiation. Sarcomas are very heterogeneous in terms of histological subtypes, and thus, the difficulty of their diagnosis and therapeutic management (2). The current management of sarcomas is one of the most challenging areas of pathology and oncology (1,2). In Morocco and based on Casablanca cancer registry, bone and soft tissue sarcomas represent

10.1% and 5.3% of childhood and adolescent cancers, respectively. The complete diagnosis of sarcomas is a major issue in laboratories of cytology and anatomical pathology. Indeed, a very precise and accurate diagnosis of sarcomas requires immunohistochemistry (IHC) and molecular biology techniques which are the cornerstone of an optimal diagnosis. In addition, the histopathological analysis of sarcomas involves a pathologist with specialized training. In cases where expert review is not available, a second opinion is often recommended (3). Since sarcomas are rare tumors, their diagnosis is difficult and diagnostic delays are habitually lengthy which may further worsen prognostic outcomes in young patients (4).

During the last decade, major diagnostic advances have been made in this field, particularly with the arrival of new IHC-based and also novel molecular biology techniques (5-8). This has enabled the diagnosis of new sarcoma entities with specific alterations in an important number of soft tissue and visceral sarcomas which may have prognostic and predictive values (9-11). On the other hand, therapeutic approaches were also improved with the advent of targeted agents. An illustrative example is the kinase inhibitors for gastrointestinal stromal tumors (GISTs) that have changed the prognosis of this entity based on the use of the concept of predictive biomarkers (12,13).

In Morocco, research on sarcoma is considerably neglected and there are few original publications covering this aggressive malignancy. To this end and in order to explore real-world practices and challenges with the diagnosis of sarcoma, we conducted a cross-sectional survey study among Moroccan pathologists. This may promisingly identify strategies to improve the national efforts toward cancer control through the diagnosis of challenges in the pathology area. To the best of our knowledge, this is the first Moroccan and North-African study to report diagnostic challenges of sarcoma viewed by pathologists.

Materials et methods

To conduct this survey, a semi-structured questionnaire was designed in French on the freely available Google Forms® platform. Data collection were performed based on an anonymous self-administered form distributed to Moroccan pathologists practicing in academic institutions, public hospitals, and private laboratories of anatomic pathology using snowball sampling. The online survey was left open for inclusion for two months, from 01 May 2022 to 01 July 2022. No ethical committee approval was needed for this research as per the Moroccan law and all participants provided their consents in the online survey to use their data for research. Participants' information was collected anonymously and stored with complete respect of personal data protection. Descriptive statistics based on Excel (Microsoft ® Office) were used for the analyses as appropriate.

Results

Global overview of study population

A total number of 144 pathologists encompassing 72.2% of females practicing in Morocco were surveyed. This included 41.7% of them practicing in university hospitals, 24.3% in public institutions, and 34% in the private sector (Table 1).

Table 1. General overview of demographic characteristics on study population (N = 144).

Demographic features	%
Age groups	
<30 years	12.5 %
30-39 years	34 %
40-49 years	31.9 %
50-59 years	12.5 %
≥60 years	9 %
Gender	
Female	72.2 %
Male	27.8 %
Experience	
<5 years	31.3 %
5-9 years	22.9 %
10-19 years	25.7 %
≥20 years	20.1 %
Practice sector	
Public institutions	24.3 %
University hospital	41.7 %
Private sector	34 %

Training of participants and research activities on sarcoma pathology

Mainly 57.6% of respondents had specialized training on sarcoma pathology based on post-graduation fellowships,14.6% were enrolled in internships abroad, 4.9% completed a training using inter-university diploma, and 36.8% had no specialized training during their career (Figure 1). A specific education on sarcoma pathology was achieved primarily in Morocco (60.4%) and abroad for 39.6% of surveeyes. Importantly, 81.9% of pathologists stated that they have never conducted or participated in research on sarcoma.

Overview of pre-analytical phase

Regarding sarcoma cases received in laboratories of anatomical pathology per week, 64.6% of respondents stated to have received less than one case of sarcoma, 33.3% received between 1 and 10 cases, and only 2.1 received more than 10 cases. When surveyed on the quality of tissue samples received from clinicians, 70.8% of pathologists believed to have received samples of adequate size, 29.2% considered the size of samples not sufficient to validate sarcoma diagnosis. In this regard, the entire samples were not frequently received from clinicians. In fact, 54.2% stated having rarely received the whole specimens and 17.4% have never received whole tissues, probably because they were sent in parallel to other laboratories. Respondents also revealed that in most cases (74.3%), clinical and imaging information were not complete in the request reports provided by clinicians.

Access to diagnostic techniques and expert panel meetings

The diagnostic tools available to the participants were mainly morphology (100%) and IHC (82.6%), while the FISH and other molecular biology techniques were available only in 27.1% and 20.1% of pathologists' settings, respectively. Of note, molecular biology analyses were performed at external national or international levels in the majority of cases. Only 17.4% had access to genetic testing in their local setting. The majority of Moroccan pathologists (81.3%) did not participate in multidisciplinary meetings specialized in sarcoma management. Pathologists who had the opportunity of participating in these meetings were mainly from cities where they are located (93.5%) and those from other settings participated rarely in these board consultations (6.5%).

Diagnostic time and requirement of second review opinions for sarcoma

Based on the results of this survey, the response time for cases of sarcomas was heterogeneous ranging from 7 to 21 days or more. Indeed, most pathologists

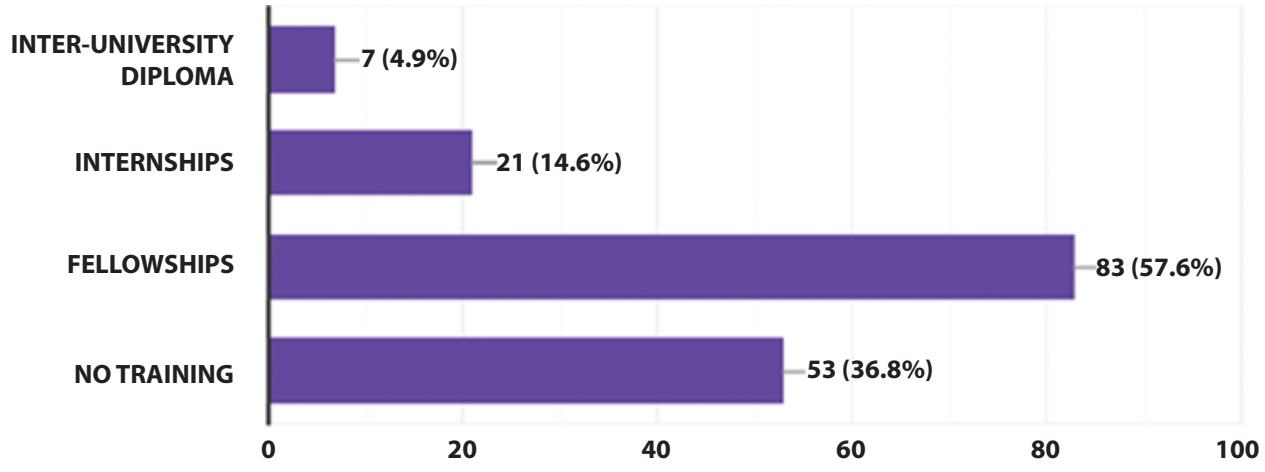

Figure 1. Training of participants on sarcoma pathology.

stated to have performed the whole process of sarcoma diagnosis from the pre-analytical phase to reporting in 14 working days followed by 29.9% in one week, 11.8% in three weeks, and finally only 5.5% in more than three weeks. Regarding second review opinions, 66% stated the need of a second expert opinion for all sarcoma cases. This request was frequent according to 66% of surveyees. Regarding re-reviews of diagnosed cases, 56.9% of pathologists received less than 10% of the requests. 27.1% of surveyed pathologists received re-review requests of 20% cases and 13.2% acknowledged to have received re-reviews in 50% of cases. Remarkably, 2.8% of Moroccan pathologists claimed to have systematically received re-reviews for all sarcoma cases diagnosed in their setting. The final diagnosis retained after re-review was in line with the first result of the histopathological analysis according to 38.2% of surveyed pathologists and it was different according to 2.1 of them. Finally, our survey results had also shed light on the urgent need to build a national expert working group. Indeed, 97.2% of Moroccan pathologists recommended the requirement of an essential national sarcoma review network to support pathologists in diagnosing this rare malignancy.

Discussion

Sarcomas are rare malignancies of mesenchymal origins accounting for 0.5-1% of tumors in adults. Their rarity as well as their heterogeneity make their correct diagnosis a real challenge for pathologists around the globe. The impact of a pathological review of sarcoma is not limited to the determination of histotypes, but also in providing its degree of aggressiveness, prognostic biomarkers, as well as the assessment of therapy response (14). In fact, these elements are essential when selecting the best therapeutic approach including the adequate chemotherapy protocols and targeted therapies as per international recommendations (14).

According to the results of our survey, it is obvious that the pathology management of sarcomas represents a great challenge for pathologists in Morocco and it is affected by several factors. The first part concerned the availability of a specialized training on sarcoma pathology which is still insufficient. In fact, an important number of the surveyed pathologists have not received any specialized training in this field. Moreover, the pathological management of sarcomas in Morocco is most often performed by general pathologists who do not have enough experience in terms of sarcoma. Another factor that may had negatively affected training on sarcoma pathology in Morocco is the lack of research activities in this area. The current practice of these pathologists is governed by morphology and IHC which are affordable and accessible techniques in the context of low- and middle-income countries such as Morocco. Morphological analysis undoubtedly represents a fundamental step in the pathological diagnostic reasoning in combination with other complementary techniques to establish the diagnosis of sarcoma such as IHC, which is an essential part of sarcoma pathology review. IHC allows the determination of several types of antigens on sarcomatous cells using antigen-antibody reactions (14). Indeed, some markers can identify the line of cell differentiation. This includes cytokeratin markers of epithelial differentiation, and markers of muscle differentiation such as actin, desmin and myogenin in addition to CD31 and CD34 markers of vascular differentiation as well as cell proliferation markers such as Ki-67 (14). The use of IHC can also provide additional information on the mutational status of some oncogenes such as TP53.

The routine use of FISH and molecular biology techniques are rarely available in laboratories of anatomic pathology in Morocco. As demonstrated in our survey, these methods can be requested from external laboratories. FISH is particularly suitable during sarcoma diagnosis as it can detect amplifications or deletions of chromosomal parts (14). These alterations are of high importance as they confirm the diagnosis of certain types of sarcomas. Moreover, polymerase chain reaction (PCR) can also be used to support the analysis of DNA to identify oncogenic mutations associated with some sarcomas, such as mutations in the KIT and PDGFRA genes in GISTs (14). The reverse transcriptase (RT)-PCR is performed and it is also helpful when the specimen is an RNA after reverse transcription of RNA into DNA. It can detect fusion transcripts resulting from reciprocal translocations (14).

Unfortunately, the unavailability of all of these techniques necessary for the diagnosis of sarcomas results in an extension of the response time.

An optimal patient care requires enhanced collaboration between various stakeholders encompassing pathologists, surgeons, radiologists, and oncologists in order to accurately diagnose sarcoma, define the best therapeutic strategy, and propose the appropriate treatment (14). Multidisciplinary sarcoma meetings are crucial to define personalized approaches for each patient. In our context, the majority of surveyed Moroccan pathologists were not involved in these meetings which is a major challenge to be resolved in the future. Also, the incomplete anatomopathological examination request forms with insufficient information are also limiting the optimal management of sarcomas in our setting. This has a negative impact on the quality of diagnosis and it is associated with a lack of collaboration between pathologists and other clinicians. The latter category is unfortunately not sufficiently aware of the positive aspect of communicating clinical and radiological information, in addition to the appropriate sampling for the pathologist. Another issue reported by Moroccan pathologists is the fact that they do not always receive the entire sample, probably parts of collected specimens are sent in parallel to another laboratory; so, the clinician can compare the results of two laboratories. This attitude alters the quality of the diagnostic approach, since the sample arrives in insufficient size, in addition to the unethical pattern of this attitude.

Moroccan pathologists receive requests commonly for re-reviewing sarcoma cases from surgeons or clinicians. This is an attitude that is in accordance with international recommendations which require the need for a re-reading by a pathologist with expertise in sarcoma pathology. Unfortunately, Moroccan pathologists stated to have no feedback on the final diagnosis because of lacking communication and coordination between involved stakeholders (15). Promisingly, almost all Moroccan pathologists support the creation of a national sarcoma review working group. This network may promisingly provide second opinions as sarcoma diagnosis is rare, and therefore difficult to diagnose by pathologists with no former training in this area. Accordingly, before deciding on a therapeutic strategy, the histological diagnosis must first be confirmed within the framework of the sarcoma network. This working group can have three intervention levels. Pathologists must systematically address all new cases of soft tissue sarcomas of the limbs, viscera, or bone sarcomas to referring pathologists in the sarcoma network. The referring pathologists of the national sarcoma network must ensure a re-review of any new diagnosed case, according to the WHO recommendations and those established by the national sarcoma network. Then they must write a final report which must be returned as soon as possible to the pathologists so the report can be transmitted and shared on a database for each sarcoma diagnosis. For cases the diagnosis was not supported after the second reading, a third review can be requested for an in-depth level of analysis.

In France, a great initiative was established since the 1980s, by a group of pathologists from cancer centers to study cases of sarcomas and other connective soft tissue tumors in adults. This group meets once a month around a multi-head microscope to review all the cases of soft tissue sarcomas treated in the centers involved in the group. This working group has led to the creation of a histoprognostic grading system (16), which until now constitutes the international reference in soft tissue sarcomas, named later as the French Sarcomas Group (17). The Reference Network for Sarcoma Pathology (RRePS) was then created to better diagnose and treat soft tissue and visceral sarcomas. Based on this approach of scientific networking, another working group was created to combine the pathological review and the clinical management this time for bone tumors (ResOs). The main objective of this network of pathologists is to improve the anatomopathological management of sarcomas, GISTs and desmoid tumors, by ensuring a systematic and free review of any new case of these malignancies, while developing specific recommendations (13). After its establishment, the outcomes of the first two years have clearly shown the interest of such a network for patients, as well as for pathologists. After five years of its foundation, an important increase in the number of patients who have benefited from a re-review as well as a reduction of duration time to access this service was noticed. In fact, this organization of pathologists has

demonstrated its effectiveness and constitutes a real progress in the pathological management of sarcomas in France (19,20). In addition, the network was also an optimal strategy to optimize and standardize genetic techniques and the foundation of biobanks for training and research purposes (21).

The quality of sarcoma patients' care was considerably improved, particularly with the advent of molecular pathology that has enabled accurate diagnosis of specific alterations. This can be enhanced by the involvement of all health care professionals including pathologists in multidisciplinary review meetings to promote personalized medicine in sarcoma.

Conclusions

Sarcomas are rare and very heterogeneous tumors at the histological level. This explains the frequent diagnostic difficulties with major therapeutic consequences that can alter survival outcomes of sarcoma patients across the globe, and especially in under-resourced settings in Morocco. Our survey-based study provided the rationale to build training programs and actionable approaches to enhance this area of pathology. The French experience, in this perspective, is very attractive and leaves us very enthusiastic about the foundation of a national anatomopathological sarcoma network in Morocco.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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