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Ultra-rare sarcomas: a consensus paper from the Connective Tissue Oncology Society community of experts on the incidence threshold and the list of entities

Running title: Ultra-rare sarcomas: incidence cut-off & list

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The list of ultra-rare sarcomas, defined as those sarcomas with an incidence =/<1/1,000,000, comprises 56 soft tissue and 21 bone sarcoma types. The incidence of ultra-rare sarcomas account for roughly 20% of all soft tissue and bone sarcomas, confirming that challenges inherent ultra-rare sarcomas impact a large number of patients

Abstract

Background: Among sarcomas, which are rare cancers, many types are exceedingly rare; however, a definition of “ultra-rare” cancers is not established yet. The problem of ultra-rare sarcomas is particularly relevant since they represent unique diseases and their rarity poses major challenges for diagnosis, understanding disease biology, generating clinical

evidence to support new drug development and achieve formal authorization of novel therapies.

Methods: The Connective Tissue Oncology Society (CTOS) promoted a consensus effort in November 2019 to establish on how to define ultra-rare sarcomas through expert consensus and epidemiological data, and to work out a comprehensive list of these diseases. The list of ultra-rare sarcomas was based on the 2020 WHO classification, The incidence rates were estimated using the information network on rare cancers (RARECAREnet) database and the NETSARC registry, the French Sarcoma Network's clinical-pathological registry. Incidence rates were further validated in collaboration with the Asian cancer registries of Japan, Korea, Taiwan.

Results: It was agreed that the best criterion for a definition of ultra-rare sarcomas is incidence. Ultra-rare sarcomas were defined as those sarcomas with an incidence around =/<1/1,000,000, to include those entities whose rarity makes it extremely difficult to conduct well-powered prospective clinical studies. Based on this threshold, a list of ultra-rare sarcomas was defined, which comprises 56 soft tissue and 21 bone sarcoma types.

Conclusions: Altogether, the incidence of ultra-rare sarcomas account for roughly 20% of all soft tissue and bone sarcomas. This confirms that the challenges inherent in ultra-rare sarcomas affect a large number of patients.

Key words: sarcoma; incidence; ultra-rare; registry; rarity; drug development.

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Introduction

Rare cancers are defined as malignancies with an incidence of <6/100,000/year[1-5]. This definition is the result of a consensus effort within the European oncology community that

took place in the context of a project funded by the European Union (EU), entitled Surveillance of Rare Cancers in Europe (RARECARE).

The definition of rare cancers is based on incidence, and not on prevalence as it is in rare non-neoplastic diseases[1,6]. The incidence-based criterion for defining rare cancers has been internationally recognised and is currently used in Europe, USA and Eastern Asian countries[7-9]. In Europe, 12 families of rare cancers were identified with a wide consensus in the context of the *Joint Action on Rare Cancers* (JARC), launched by the EU[6]. Sarcomas are one of the rare cancer families with an incidence <6/100,000[6].

Among sarcomas, many types are exceedingly rare. They could be labelled as "ultra-rare", as in the *EU Clinical Trials Regulation (European Parliament and Council of the European Union, 2014)*. This regulation identifies ultra-rare diseases as having a prevalence below 2/100,000. However, a definition of ultra-rare cancers has yet to be established.

Within the sarcoma community, the problem of ultra-rare types is particularly relevant. The 2020 WHO classification of bone (BS) and soft tissue sarcoma (STS) listed approximately 100 different sarcomas and mesenchymal tumours of intermediate malignancy[10]. Most of these entities, representing unique diseases, are ultra-rare. Rarity poses major challenges for diagnosis, with approximately 20% of all sarcomas being misclassified when diagnosed outside reference centres[11], understanding disease biology, generating clinical evidence to support new drug discovery and development. This also leads to a specific problem in the regulatory setting, as formal authorization of novel therapies by regulatory agencies is difficult to achieve. Consequently, off-label use of medication, when affordable, is frequently the only way to access active treatments for those patients.

With this background, a representative, multidisciplinary group of experts from the global sarcoma community convened at the 2019 Annual Meeting of the *Connective Tissue Oncology Society (CTOS)* and initiated a process to reach a definition and a list of ultra-rare sarcomas. This list was intended to increase awareness of the wide variety of histologic types with limited incidence in the sarcoma family of tumours, to direct efforts to describe their natural history and develop novel ways to evaluate therapies in these malignancies, thus paving the way for discussion with academia, pharma and regulatory

bodies regarding the optimal method to facilitate the correct development and approval of novel therapeutics for ultra-rare sarcoma patients.

Here we provide a summary of the consensus process that led to the definition of ultra-rare sarcomas and, accordingly, the list of ultra-rare sarcomas.

Material and Methods

A consensus meeting was organised under the umbrella of CTOS (Tokyo, November 13th, 2019). Representatives from 30 sarcoma reference centres in the EU, USA, Canada, Asia and Australia, covering all disciplines involved in the research and care of sarcoma patients (epidemiology, pathology, molecular biology, radiology, surgery, radiation therapy, medical oncology) attended the meeting.

Prior to the meeting, a list of GIST/ STS and BS entities was circulated, taking the 2013 WHO classification of soft tissue and bone tumours as a backbone[12]. Mesenchymal neoplasms included in the WHO classification of breast[13], head and neck[14], female genital organ[15], central nervous system[16] and tumours of haematopoietic and lymphoid tissues were added[17]. Only histologies with metastatic potential were included.

In the identification and definition of each specific entity, it was decided not to take into account criteria beyond the WHO classification, such as molecular subtypes within each histology, specific anatomic locations, disease extent, age, or atypical presentations.

For those entities with data already available in population-based cancer registries (CRs), incidence rates were estimated through the RARECAREnet project database (www.rarecarenet.eu). This database is drawn from EUROCARE-5, the widest collaborative study on the survival of cancer patients in Europe (www.eurocare.it). Data on incidence (years of diagnosis 2000-2007) estimated through RARECAREnet were subsequently compared to those extracted by the NETSARC registry, the clinical-pathological registry of the French Sarcoma Network[18]. Given the centralized histological review of all cases performed within NETSARC, the risk of misclassification inevitably implicit in CRs, which are constructed on community-based pathological diagnoses, was minimized. Second, it allowed for the inclusion of diagnoses described in the 2013 WHO

classification, for which CR data are not yet available. Incidence rates were further validated in collaboration with the Asian CRs of Japan, Korea, Taiwan (years of diagnosis 2011-2015), all of which contribute to the RARACAREnet Asia project[9]. Appendix 1 and 2 summarize the list of entities for which the estimation of incidence was possible.

The CTOS panel of experts was provided with the incidence data for all STS and BS and was asked to 1) agree about the best indicator for defining ultra-rare sarcomas, 2) identify those sarcomas for which undertaking prospective large clinical studies (e.g. statistically powered randomized trials) is a major challenge, and 3) agree on the incidence cut-off to distinguish ultra-rare sarcomas (i.e. the entities for which undertaking large prospective studies is a major challenge) from other sarcomas,.

Once the 5th edition of the WHO soft tissue and bone classification[6] became available in 2020, the list of ultra-rare sarcomas already agreed by the authors on the basis of incidence was enriched with some of the newest entities introduced for the first time in the last WHO book, but whose incidence could not be estimated by either RARECAREnet (data refer to 2000-2007) nor NETSARC (2013-2016). The selection of the entities to be added to the ultra-rare group was made based on expert opinions. Through the same process, new entities introduced in the latest edition of WHO classification of female genital organs[15] and head and neck[14] tumours were added, if they met criteria for classification as ultra-rare.

The final list of ultra-rare sarcomas (Table 1 and 2) was shared also with all CTOS ultra-rare sarcoma consensus effort members that could not attend the consensus meeting.

Results

An agreement was confirmed to base the definition of ultra-rare sarcomas on incidence. It is notable that the precise incidence of ultra-rare cancers is often difficult to estimate, owing to both rarity and in some cases, recency of definition.

Appendix 1 and 2 present the incidence rate of GIST, STS and BS, respectively, ranked by declining incidence rate.

Looking to the listed entities and their incidence, the group reached a consensus about an incidence threshold of around ≤1/1,000,000/year as cut-off for identifying ultra-rare sarcomas.

The CTOS panel of experts perceived that conventional approaches to clinical studies are feasible for STS with an annual incidence >1/1,000,000 (i.e. GIST, undifferentiated pleomorphic sarcoma, well-differentiated/dedifferentiated liposarcoma, leiomyosarcoma, dermatofibrosarcoma protuberans, solitary fibrous tumour, angiosarcoma, myxofibrosarcoma, synovial sarcoma, myxoid liposarcoma), which account for about 80% of all STS (Fig.1A; Fig.1B). The remaining 20% represent the group of ultra-rare STS (Fig.1A; Fig.1B). Table 1 lists the ultra-rare STS identified by consensus on the basis of incidence together with the ultra-rare STS identified by consensus only. Overall ultra-rare STS include 56 different types.

Table 2 shows the list of ultra-rare BS identified by consensus on the basis of incidence together with the ultra-rare BS identified by consensus only. Osteosarcoma, conventional chondrosarcoma, Ewing sarcoma each have an annual incidence >1/1,000,000, accounting for 80% of all BS. The remaining 20% of BS consists of ultra-rare BS (Figure 2A and B). Of all BS, the ultra-rare diagnoses comprise 22 different types.

Discussion

BS and STS include roughly 100 different pathologic entities, as described in the 2020 WHO sarcoma classification[10], many of them being ultra-rare. Each of these entities is marked by a specific morphology, biology, natural history, sensitivity to medical agents and prognosis[19]. Their number increases every year, as new molecular markers are identified. Research and care in ultra-rare tumours is a major challenge, with major consequences for patients. To overcome these hurdles, there is an urgent need to improve patient centralisation as well as the interactions of researchers and patients, on one side, and regulators, on the other. With this background, a representative group of the global sarcoma community, under the umbrella of the CTOS, met together to agree on how to define ultra-rare sarcomas through expert consensus and epidemiological data, and to work out a comprehensive list of these diseases.

By consensus, it was agreed that the best criterion for a definition of rare cancers and therefore ultra-rare cancers is incidence, rather than prevalence. Ultra-rare sarcomas were

defined as those sarcomas with an incidence around =/<1/1,000,000, to include those sarcoma entities whose rarity makes it extremely difficult to conduct well-powered prospective clinical studies. Based on this threshold, it was found that ultra-rare sarcomas comprise 56 soft tissue and 21 bone sarcoma types, respectively, each of which deserves to be investigated and treated specifically. Altogether, the incidence of ultra-rare sarcomas account for roughly 20% of all STS and BS, respectively. This demonstrates that challenges inherent to being a patient who develops an ultra-rare sarcoma impact a large number of patients, in total. The consensus group eventually agreed that this list needs to be revised on a regular basis, as new sarcoma entities will be identified, and updated incidence data will become available.

The incidence of the various ultra-rare sarcomas was consistently low across Asia and Europe. The only two exceptions were phyllodes tumour and low-grade endometrial stromal sarcoma the incidence of which in Europe/RARECAREnet as well as in Asia, was slightly more than 1/1,000,000. However, these two entities had a much lower incidence in the NETSARC database, most probably due to diagnostic quality issues. On this basis, by expert consensus, phyllodes tumour and low-grade endometrial stromal sarcoma were included among the ultra-rare sarcoma.

Similarly to the process used for the development of the list of rare cancers by EUROCARE, we agreed to base the list of ultra-rare sarcomas on the WHO classification, which in turn utilizes a combination of anatomy and histology and molecular biological features to distinguish sarcoma types. Histopathologic features are just one of the attributes that singles out any clinical presentation. In addition to being affected by a given histologic sarcoma type, a patient obviously presents with a spectrum of clinical features, which may be rare and ultra-rare as well, such as a rare anatomic location or an unusual age, sex, etc. Although clinical presentations can impact prognosis and dictate treatment, the WHO classification was chosen because it is the list of cancer entities currently used to define and stratify diseases. Obviously, any clinical decision will be based on several factors, i.e. clinical characteristics of the individual presentation as well as molecular features (namely, when a treatment may be molecularly targeted, a molecular marker is relevant from the prognostic point of view, etc.).

The proposal of a threshold for ultra-rare sarcomas was also intended to help regulatory agencies to single out specific entities which are particularly challenging from the research standpoint. Ultimately, this means preventing ultra-rare sarcoma patients from missing opportunities for the identification and approval of effective therapies. Compared to more common entities, ultra-rare sarcomas are often poorly characterized with regard to their epidemiology, biology, natural history, prognostic and predictive factors, and sensitivity to standard treatments. Currently, there is no mechanism for bidirectional communication between the clinicians, researchers and regulatory bodies. We suggest that this could be achieved through regular mutual updates between the ultra-rare disease communities and regulators. In ultra-rare sarcomas, large studies are only possible with either long study durations and/or the involvement of a very large number of study sites (with corresponding quality control issues). This invariably decreases the interests of a pharmaceutical company to invest in and develop new agents in these tumours, even when an agent may be available for other indications. Thus, methodological issues add to the typical challenge of "orphan" drugs, i.e. the limited market. Large randomised clinical studies have not been undertaken for most ultra-rare sarcomas[20]. Exceptions include two randomized trials in alveolar soft part sarcoma, an ultra-rare STS. One of these studies was launched by the NCI in 2011 (*ClinicalTrials.gov Identifier: NCT01391962*) and is still open to recruitment. The second trial (*ClinicalTrials.gov Identifier: NCT01337401*) took five years to enrol 48 patients in three countries and met the primary endpoint, but there was no submission for regulatory approval. Another recent example was a novel agent with positive outcomes for epithelioid sarcoma, requiring a confirmatory randomised trial versus placebo in Europe before any approval and in the US for anything beyond conditional approval.

Currently, there is only one drug specifically approved in one of the 56 ultra-rare STS in the list, and it is only approved by the FDA, namely tazemetostat in epithelioid sarcoma[21]. By contrast, while pexidartinb could be investigated in a randomized study in localized tenosynovial giant cell tumour (TGCT) leading to its approval by FDA in 2019, this is not feasible in the ultra-rare malignant TGCT subtype[22].

Most potentially active new and old drugs in ultra-rare sarcomas are often used as off-label treatments. Interestingly, off-label agents in ultra-rare sarcomas are often suggested, even as first-line therapy, by US, EU and Japanese clinical practice guidelines[23-26]. The main barrier to label extension for drugs already on the market is the fact that the initiative to file

for approval can only be taken by pharmaceutical companies, whose interest is usually low when a drug is almost off patent or already available as a generic agent. Clearly, this results in discrepancies across countries and discrimination against patients affected by ultra-rare sarcomas.

In order to improve this situation, new study designs need to be conceived, adopted and endorsed particularly from the regulatory standpoint. In the area of ultra-rare sarcomas, disease-based discussions with regulatory agencies need to be planned on a regular basis, before embarking on the assessment of specific agents, including the incorporation of expert scientific advice, which affects the type of study protocol proposed for development. If an internal control arm is not feasible, optimising the collection of external high-quality data by clinical registries should be encouraged. In the EU, an opportunity not to miss is the involvement of the European Reference Networks (ERNs), i.e. networks of cancer centres appointed by their governments to treat and research rare cancers. When label extension is not feasible, centralizing the use of selected off-label agents in sarcoma networks would be a way to guarantee appropriateness. Current patients would benefit from new treatments likely to be effective and future patients would benefit from additional knowledge gathered by expert centres. Adaptive regulatory pathways could be instrumental in this regard.

All this requires a sustainable global collaborative effort. Thus, the sarcoma research community should be able to collaborate on a global scale. Pharmaceutical companies should value partnerships with academia. Regulatory bodies should listen to the disease-based communities, involving researchers and patient advocates. Ultimately, this will involve close scrutiny and knowledge of each type of ultra-rare sarcoma. This is easy when dealing with common cancers. It may be exceedingly difficult when dealing with rare cancers. It may be almost impossible, unless a concerted effort is made, when dealing with ultra-rare cancers, such as the one fifth of sarcoma patients belonging to the rare family of sarcomas.

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Tables

Table 1. List of ultra-rare soft tissue sarcomas (STS) identified based (first column) on incidence and of ultra-rare STS identified (second column) on expert consensus only (i.e. including STS histologic types not found in the population registries) according to the 2020 WHO classifications of soft tissue and bone tumours.

Incidence-based in population based registries *(RARECARENet EU, Asia, Net-Sarc)*	**WHO** *(Soft tissue and bone tumours, Gynecological, Head and Neck, Haematological)*
Adult fibrosarcoma	
Alveolar rhabdomyosarcoma	
Alveolar soft part sarcoma	
Angiomatoid fibrous histiocytoma	
Clear cell sarcoma	
Desmoplastic small round cell tumor	
Ectomesenchymoma	
Embryonal rhabdomyosarcoma	
Embryonal sarcoma of the liver	
Endometrial stromal sarcoma	High-grade *BCOR*-rearranged endometrial stromal sarcoma
	High-grade *YWHAE*-rearranged endometrial stromal sarcoma
Endometrial stromal sarcoma, low grade	
Epithelioid sarcoma	

Extra-renal malignant rhabdoid tumor	
Extra-skeletal Ewing sarcoma	
Extra-skeletal myxoid chondrosarcoma	
Extra-skeletal osteosarcoma	
Fibroblastic reticular cell tumour	
Follicular dendritic cell sarcoma	
Giant cell tumour of soft tissues	
Haemangioendothelioma, composite	
Haemangioendothelioma, epithelioid	
Haemangioendothelioma, pseudomyogenic	
Haemangioendothelioma, retiform	
Histiocytic sarcoma	
Infantile fibrosarcoma	
Inflammatory myofibroblastic tumour	
Interdigitating dendritic cell sarcoma	Indeterminate dendritic cell tumour
	Interdigitating dendritic cell sarcoma
Intimal sarcoma	
Langerhans cell sarcoma	
Low-grade fibromyxoid sarcoma	
Low-grade myofibroblastic sarcoma	
Malignant glomus tumor	
Malignant granular cell tumor	
Malignant myoepithelioma/myoepithelial carcinoma	
Malignant tenosynovial giant cell tumor	
Myxoinflammatory fibroblastic sarcoma	
Ossifying fibromyxoid tumour, malignant	
Papillary intralymphatic angioendothelioma	
PEComa, excluding non-epithelioid angiomyolipoma	
Phyllodes tumour, malignant	
Phosphaturic mesenchymal tumour, malignant	
Pleomorphic liposarcoma	

Pleomorphic rhabdomyosarcoma	
Round cell sarcoma/Ewing-like sarcoma	*CIC*-rearranged sarcoma
	Round cell sarcoma with *EWSR1*-non-*ETS* fusions
	Sarcoma with *BCOR* genetic alterations
Sclerosing epithelioid fibrosarcoma	
Spindle cell / sclerosing rhabdomyosarcoma	
	Biphenotypic sinonasal sarcoma
	Inflammatory leiomyosarcoma
	Malignant melanotic nerve sheath tumour
	Metastasizing leiomyoma
	Myxoid pleomorphic liposarcoma
	NTRK-rearranged spindle cell sarcoma (emerging)

Abbreviations:
RARECARENet: Surveillance of Rare Cancers in Europe network;
EU: European Union

Table 2. List of ultra-rare bone sarcoma (BS) identified based (first column) on incidence and of ultra-rare BS identified (second column) based on expert consensus only (i.e. including BS histologic types not found in the population registries) according to the 2020 WHO classifications of soft tissue and bone tumours.

Incidence-based in population based registries *(RARECARENet EU, Asia, NETSARC)*	**WHO**
Adamantinoma	
Angiosarcoma of bone	
Chondrosarcoma, clear cell	
Chondrosarcoma, dedifferentiated	
	Chondrosarcoma, periosteal
Chordoma, conventional	
Chordoma, dedifferentiated	

	Chordoma, poorly-differentiated
Epithelioid haemangioendothelioma of bone	
Fibrosarcoma of bone	
Leiomyosarcoma of bone	
Low-grade central osteosarcoma	
Malignancy in giant cell tumor of bone/giant cell tumor of bone, malignant	
Mesenchymal chondrosarcoma	
Osteosarcoma, parosteal	
Osteosarcoma, periosteal	
Osteosarcoma, high-grade surface	
Undifferentiated high-grade pleomorphic sarcoma of the bone	
	Rhabdomyosarcoma of the bone
	CIC-rearranged sarcoma
	Round cell sarcoma with *EWSR1*-non-*ETS* fusions
	Sarcoma with *BCOR* genetic alterations

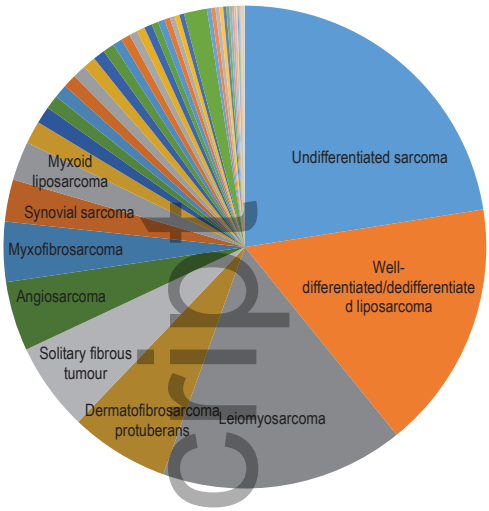
Abbreviations:
RARECARENet: Surveillance of Rare Cancers in Europe network;
EU: European Union

Legends

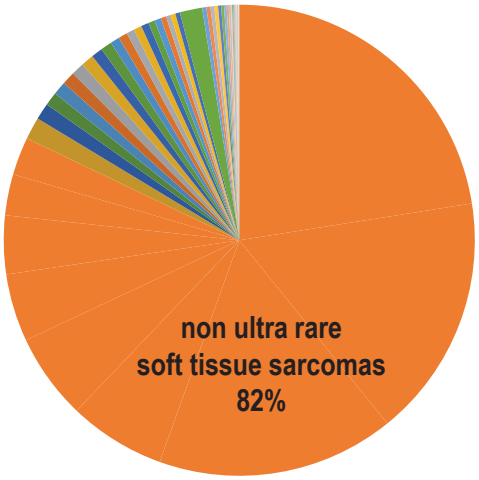
Figure 1. Ultra-rare vs. non ultra-rare STS. Labels of non-ultra-rare STS subgroups are provided in Figure 1A; the % of non-ultra-rare STS of all STS is provided in Figure 1B.

Figure 2. Ultra-rare vs non-ultra-rare BS. Labels of non-ultra-rare BS subgroups are provided in Figure 2A; the % of non-ultra-rare BS of all sarcoma is provided in Figure 2B.

A



B



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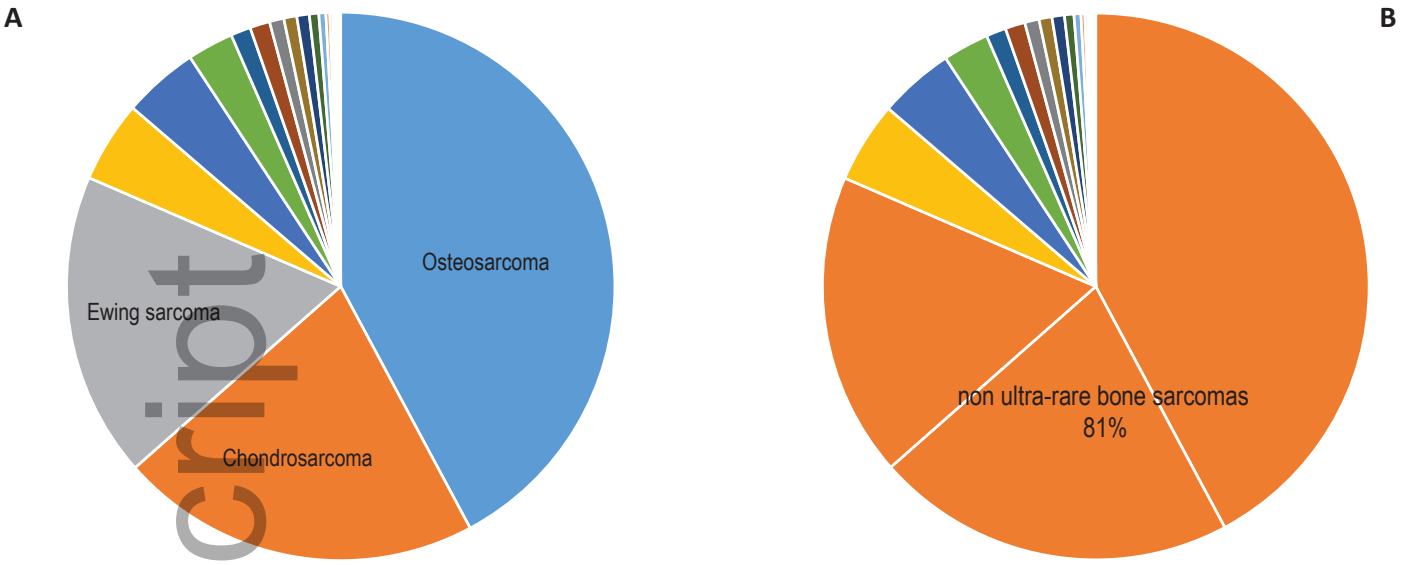

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