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INVITED COMMENTARY

The diagnostic landscape of bone and soft tissue sarcoma: the pan-sarcoma era and AI-driven classification

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Abstract

Bone and soft tissue sarcomas are a diagnostic challenge due to their histological complexity, variety, and mutational heterogeneity. This has led to continued refinements in classification and diagnostic criteria, presented and soon to be updated by the WHO. This commentary features articles published in this journal and elsewhere that have ultilised pan-sarcoma datasets and artificial intelligence-based classifiers. A notable entry is the DKFZ Sarcoma Classifier, which is based on methylation profiles and available for use *via* a commercial platform. This work has created hope that one day a comprehensive sarcoma classifier will be available, though it is also a reminder of the many challenges apparent in studying rare cancer types.

Keywords: sarcoma; bone cancer; soft-tissue sarcoma; pan-cancer; genomics; machine learning

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Introduction

This commentary relates to a validation study of the 'DKFZ Sarcoma Classifier' published in JPCR on 7 July 2021 and authored by Lyskjær *et al* [1].

Sarcomas were recognised as a pathological entity over 1,000 years ago, with Hippocrates (460–375 BC) having recorded observations of tumours in the bone and soft tissues of his patients, and practitioners in ancient Rome having identified distinct types that include lipomas [2]. The move from gross to microscopic observations became common practice following the publication of Etmullerus' tome *Description of All Diseases* in 1712 [3], and from there the study of bone and soft tissue sarcomas became distinct fields of research.

Although all sarcomas are believed to share mesenchymal cell origin, histological observations demonstrate unprecedented variation, even within a specific type. For example, chondrosarcoma is a type of bone tumour that is defined by the presence of cartilage expressing lineages [4]. This type can be subdivided into at least six distinct subtypes including central conventional, periosteal, extraskeletal myxoid, mesenchymal, clear cell, and dedifferentiated chondrosarcoma [5]. Given the sheer number of types and subtypes, it has been difficult to formulate accurate classification systems that can be used for the differential diagnosis of sarcomas. During the 20th century, many systems have been proposed, but these tended to be based on the resemblance of sarcomas to normal tissues and cell lineages, as noted in the famous book on the subject by Maximilian Borst (1869–1946) [6]. In modern times, following the incorporation of techniques such as karyotyping and fluorescence *in situ* hybridization, the comprehensive WHO guidelines have become the gold standard, in which over 100 types of sarcoma and their mimics, and many more subtypes, are defined to the best of current knowledge. With each edition, there have been notable amendments. A recent example from the 2020 edition is the redefinition of undifferentiated round cell tumours as distinct from Ewing sarcoma, BCOR and CIC-rearranged sarcomas [7]. These constant changes come from the irreconcilable problem of histological ambiguity, along with the emergence of new molecular evidence. For this reason, modern

research has focused on molecular markers [8] and augmentations to classification and diagnosis now involve some molecular diagnostic tests [7]. Increasingly, researchers are training artificial intelligence (AI) algorithms to help classify sarcomas and build diagnostic tools.

The move to molecular diagnosis in bone and soft tissue tumours

With the appreciation that mutational patterns can improve sarcoma diagnoses, tests for specific drivers instigated through nucleotide aberrations (e.g. *TP53* in osteosarcoma [9,10]), or gene fusions [11] (e.g. the EWSR1::FLI1 fusion in Ewing Sarcoma [12]), have become diagnostically useful. That said, the WHO guidelines cite only a small number of mutational tests as critical to the diagnosis of sarcomas, with histological interpretation remaining the primary methodology. The key issue is that only a fraction of diseases can be classified by single, unique driver events. Modern examinations of driver distributions show that the majority of drivers exist at less than 5% frequency and that there are potentially hundreds of unknown drivers underlying rarer subtypes [13].

The multi-omics era and pan-sarcoma studies

As the costs of DNA sequencing dropped, researchers have broadened the focus from specific mutations and biochemical pathways to sarcoma genomics. The techniques employed include large mutation 'panel sequencing', whole exome and whole genome sequencing (WGS), along with transcriptional and methylation analyses. In effect, these pan-sarcoma studies aim to derive a new classification system by contrasting the many sarcoma types and subtypes within one statistical framework. Success has been achieved in explorations of relatively simple panel tests, covering only a few hundred genes. In a pan-sarcoma study that deployed a panel of 465 genes and some additional informed targets, many diagnostic refinements were reported [14]. Interestingly, this study found that 137 liposarcomas diagnosed as non-specified could be re-diagnosed as either well- or dedifferentiated liposarcoma. More generally, around 10% of diagnoses could be redefined using this targeted panel alone.

In terms of WGS pan-sarcoma studies, Genomics England Ltd, a UK Government-funded company, has sequenced more than 1,600 sarcomas [15] as part of the 100,000 Genomes Project [16]. The primary report, published in 2024, states that 34% of 1,617 sarcomas have actionable mutations derived from the whole genome data [17], which led to the commissioning of diagnostic WGS for patients with sarcoma receiving treatment in NHS England centres. This marks the beginning of the sarcoma multi-omics era with WGS becoming a standard research resource.

Classification studies have extended beyond DNA sequencing for quite some time; an expression study on Ewing Sarcoma was published in this Journal in 2015 [18]. A novel pan-sarcoma expression profiling was published in 2005 [19], which featured 181 tumours across 16 types of bone sarcoma. Multi-omics studies have now become more common and, in 2024, a large study incorporating immune profiling of 1,340 sarcomas [13] revealed five cross-sarcoma immunotypes, with immune depletion detrimentally affecting overall survival. The hope in multi-omics studies such as these is that new diagnostic markers can be discovered in complex data patterns and eventually incorporated into guidelines. An apparent problem is extracting classifications from such large volumes of data. The complexity of sarcoma biology often makes simple clustering methodologies ineffective. Indeed, despite the increasing number of classification studies, the WHO guidelines have included only very few new molecular tests.

Artificial intelligence and the classification of sarcomas

As of the 2010s, AI algorithms have been available across multiple computer platforms and coding languages, which has encouraged their use in the analysis of big data [20]. As pointed out in an Editorial published by this journal in 2024, the machine learning (ML) branch of AI has become a particularly vibrant area of cancer research and diagnostic pathology [21], though this is not without challenges [22].

The advantage of ML over standard statistical analyses is that complex, abstracted patterns can be derived from data that would otherwise be invisible to standard statistical models. For classification tasks, the random forest method [23], one type of machine learning, is highly suited because it can learn classifications based on decisions (features) such as the presence or absence of a given mutation. This allows feature

extraction and therefore the potential to design laboratory tests based on tangible genetic, transcriptomic, or healthcare input data.

A stand-out attempt to use machine learning/random forest in the classification of sarcomas has been the DKFZ Classifier (English expansion: 'German Cancer Research Center classifier'), which was created in 2021 by groups working at this centre within the Heidelberg University Hospital [24]. The underlying method was based on an already published application of methylation array-based classification of central nervous system tumours [25], which is a comparable challenge to sarcoma classification. With some modifications, the sarcoma DKFZ Classifier has an error accuracy of 0.65%, which was based on a training set of 1,077 sarcomas across 65 types and subtypes. Upon real-world validation on a smaller number of cases ($n = 428$), the diagnosis match between classifier and institutional diagnosis was 61%, noting that revisions were performed in 29 cases after the discrepancy was highlighted, and cases followed up. The classifier has been developed since and is available from its new commercial owner, Epignostix, at https://app.epignostix.com/#/classifiers.

In 2021 this journal published a validation study by Lyskjær *et al* [1] that aimed to assess the accuracy of the DKFZ Classifier in UK patient data, and point to variations in subtype performance. The complete dataset comprised 986 sarcomas, including subtypes that were not included in the original training set. The diagnostic match was lower, with 55% receiving a diagnostic prediction and 450 (45%) having a diagnosis match. Limiting the validation to subtypes for which the classifier was trained demonstrated a surprising level of consistency with predictions for 61% of cases and, of those, 88% having a diagnostic match. As before, there were a small number of re-diagnoses following the identification of mismatches and follow-up.

Classification challenges in rare sarcoma subtypes

The validation of the DKFZ Classifier by Lyskjær *et al* [1] points to a fundamental challenge of building machine learning classifiers: although it is possible to gain accuracies in the region of 90% for some sarcoma subtypes such as mesenchymal chondrosarcoma and chordoma. In the rarer diseases, where few available datapoints are available for algorithm training, we end up with undesirable results (e.g. malignant peripheral nerve sheath tumours, 24% diagnostic match). As this study points out, around 25% of the institutionally diagnosed subtypes (including 19 subtypes of soft tissue sarcoma) were not included in the original training set, which leaves a considerable gap that needs to be filled in the next steps of development.

Concluding remarks

The DKFZ Classifier is a notable entry among pan-sarcoma and classification studies, and it highlights both the potential and challenges. Methylation is a known hallmark of many sarcomas [24] and has great potential to differentiate diseases more efficiently and accurately than histology alone. Methylation arrays are also cost-effective and bioinformatically lightweight compared to WGS, meaning they are deployable in many healthcare settings. The challenge is to improve accuracy in the setting of very rare sarcoma subtypes. In the AI world, desirable training sets typically include thousands of entries for each label [23], meaning that our sarcoma datasets fall very short. One solution is to compile or federate the larger datasets available today, as a single training resource of more sufficient size. Another idea is to focus away from all-encompassing pan-sarcoma studies and train specific algorithms to differentiate sarcoma diagnoses that are often confused, thus relating machine learning tasks more closely to the issues found clinically. The next decade will determine whether AI-driven classifiers can move from research tools into routine clinical diagnostics, especially for rare sarcoma subtypes where histology alone is insufficient.

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Author contributions statement

WCHC drafted and edited the manuscript.

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