Primary bone sarcomas
what's hot and what's not

INTRODUCTION

This paper is the second in a series discussing current approaches and future developments in the management of patients diagnosed with sarcoma. While this article will focus on primary bone sarcomas – namely osteosarcoma, Ewing's sarcoma, and chondrosarcoma – brief consideration will also be given to chordoma and giant cell tumours of bone, due to recent changes in the management of these lesions. The paper begins by providing an overview of accepted diagnostic and therapeutic algorithms. This will be followed by a summary of important advances in the surgical and nonsurgical management of these patients. Finally, we will examine current research trends and consider discoveries that promise to impact the treatment of primary bone sarcomas in years to come.

Primary bone sarcomas are rare, and overall represent less than 1% of new cancer diagnoses in the United Kingdom annually.[1] Considered together, these tumours have a bimodal distribution, with the first peak occurring between 15 to 19 years of age and the second in adults over the age of 75.[1] However, each tumour subtype has a specific age predilection. Ewing's sarcoma and osteosarcoma are diseases of the young, with the former most commonly seen in children under the age of nine years and the latter in those between ten and 29 years of age. Contrastingly, chondrosarcoma rarely occurs in young adults. Instead, its incidence increases linearly after the age of approximately 30 years.[2] Despite these established patterns, each sarcoma subtype can occur at any age, particularly in a vulnerable population. Secondary osteosarcomas can arise years after radiation exposure, for example, following radiotherapy treatment for a carcinoma, or in pre-existing lesions, such as Pagetoid bone. These tumours are typically associated with a more aggressive disease course and have significantly poorer outcomes than osteosarcomas that arise *de novo*. Chondrosarcomas can be seen in patients in their mid-to-late 20s, often due to malignant transformation of an enchondroma or an osteochondroma. For instance, in patients with hereditary multiple exostoses, the lifetime risk of developing a secondary, usually low-grade, chondrosarcoma is on the order of 2.5% to 5%.[3,4]

DIAGNOSIS

The rarity of primary bone sarcomas can render diagnosis challenging. A high index of suspicion is required for patients that present with low-energy fractures, abnormal radiological findings, or atypical pain and swelling. A particularly concerning complaint is bone pain at night and even in the setting of 'normal' radiographs; this presentation mandates additional imaging. Possible confounders include a history of trauma and lack of constitutional symptoms. Report of an injury and absence of fever, night sweats, and weight loss may be taken by clinicians to wrongly indicate that malignancy is unlikely. Radiological features that should prompt suspicion include new bone lysis or deposition, periosteal reaction, and soft-tissue swelling. The National Institute for Health and Care Excellence (NICE) guidelines state that clinicians should have a low threshold for referring these patients for review in a recognized sarcoma centre.[5] All patients with a suspected primary bone tumour require biplanar radiographs of the affected bone and cross-sectional imaging, preferably in the form of an MRI. These studies should image the full length of the bone in question to both characterize the primary lesion and identify any skip metastases. For patients over the age of 40 years, bony lesions are most commonly caused by myeloma, lymphoma, and metastasis. Work-up of these patients should therefore be more extensive to either diagnose or rule out these causes. An isolated bony lesion in a patient with a known history of cancer cannot be assumed to be related to the previous carcinoma, and must be fully investigated to exclude a primary

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Table I. Bone biopsy principles

Principle
Tract should be located such that it can be excised *en bloc* with the tumour at the time of definitive surgery
Avoid neurovascular structures
Stay within a single, involved anatomical compartment
Have an experienced sarcoma pathologist available
Ensure lesional tissue is obtained (most aggressive component)
Avoid contamination (minimize haematoma, do not cause pathological fracture)

Table II. Standard management for patients with osteosarcoma, Ewing's sarcoma, and chondrosarcoma

Diagnosis	Standard treatment	Chemotherapeutic agents
Ewing's sarcoma	Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	Combination of four to six of: doxorubicin, cyclophosphamide, ifosfamide, vincristine, dactinomycin, etoposide
	As above + neoadjuvant or adjuvant radiotherapy	
	Chemotherapy + definitive radiotherapy	
Osteosarcoma	Neoadjuvant chemotherapy + surgery + adjuvant chemotherapy	High-dose methotrexate, doxorubicin, cisplatin with/without mifamurtide
Chondrosarcoma	Surgery only	None

bone sarcoma. A CT scan of the thorax, abdomen, and pelvis is required to exclude an occult primary malignancy. Suspicious bone lesions require biopsy, most commonly a core needle biopsy performed by a member of the sarcoma diagnostic service. Biopsy principles are listed in Table I and must be strictly adhered to so that future limb-salvage surgery is not compromised. Patients should be referred for biopsy to a recognized sarcoma service.

Once a diagnosis is confirmed, systemic staging is performed. The majority of patients with bone sarcoma are nonmetastatic at presentation, but between 15% and 30% of patients unfortunately have synchronous metastatic disease at diagnosis.[6,7] The most common sites of distant disease are the lung followed by bone and, consequently, all patients require a CT scan of their chest, along with either a whole-body isotope bone scan or positron emission tomography-CT (PET-CT) scan. Whole body MRI is being investigated by some centres as part of their staging protocols.[6]

TREATMENT

While the diagnostic algorithm is similar for all primary bone sarcomas, treatment varies by tumour type. An overview of the standard management for patients with osteosarcoma, Ewing's sarcoma, and chondrosarcoma is included in Table II. The approach and outcomes have not changed significantly since multiagent chemotherapy was introduced in the late 1970s.[8] One commonality between all bone sarcomas is the goal of limb salvage surgery. While the diagnosis of a limb sarcoma historically necessitated amputation, limb salvage surgery has been the treatment of choice over the last 30 years. Retrospective clinical studies have demonstrated the safety of limb preservation from an oncological perspective.[9] While limb salvage surgery was previously viewed as having superior functional and psychological outcomes compared with amputation, this perspective may be changing, as studies both supporting and refuting any difference have recently been published.[9-11]

Osteosarcoma

Patients diagnosed with high-grade localized osteosarcoma are treated with chemotherapy and surgery. The typical chemotherapy regimen involves doxorubicin, cisplatin, and high-dose methotrexate. Certain patients (high-grade, complete resection, children, and young adult) also receive the immune modulator mifamurtide. While chemotherapy may shrink the primary tumour, its primary role is to prevent the development of metastatic deposits and its use significantly increases overall survival compared with surgery alone.[12] Five-year survival rates are in the range of 55% to 65% with this combined therapy.[13,14] Good prognostic factors include chemotherapy-induced necrosis rates of > 90%, appendicular location, low-grade, localized disease, and age less than 18 years.[12,15,16]

Ewing's sarcoma

The mainstay of treatment for patients with Ewing's sarcoma is also chemotherapy and surgery. The chemotherapy regimen differs slightly from that of osteosarcoma, and is subject to regional variation. Protocols consist of a combination of four to six of the following agents: doxorubicin, cyclophosphamide, ifosfamide, vincristine, dactinomycin, and etoposide.[8] While surgical resection is the best method of achieving local disease control, Ewing's sarcoma tumours are radiosensitive and radiation can be used either as an adjunct to improve margins or as definitive treatment in certain situations. Scenarios where radiotherapy may be considered include in the neoadjuvant setting when the tumour involves critical neurovascular structures and limb-salvage is to be performed, for palliation if the patient presents with metastatic disease, or as definitive treatment for axial lesions where wide excision is associated with unacceptable morbidity. Overall survival rates and factors associated with improved prognosis are similar to those for osteosarcoma.[6,17]

Chondrosarcoma

Unfortunately, conventional chondrosarcoma does not respond to either chemotherapy or standard doses of photon radiation, leaving surgical resection as the only reliable treatment option. Tumour grade can be difficult to determine on biopsy, particularly in the pelvis, for which concordance between biopsy and final pathology may be as low as 30% to 40%.[18,19] Consequently, it is suggested that a minimum 4 mm margin should be achieved for all tumours, regardless of grade on biopsy, to minimize the chance of local recurrence.[20] An exception to this approach may be in the setting of low-grade intramedullary chondrosarcomas of long bones, as studies suggest that intralesional curettage does not compromise oncological outcomes while preserving function.[21] Prognosis is highly dependent on grade and location. For example, a recent systematic review found that the five-year survival for grade 1 chondrosarcoma ranged from 82% to 99%, while for patients with dedifferentiated tumours this was 18%.[22]

WHAT'S HOT AND WHAT'S NOT

Successful treatment of a patient with a bone sarcoma involves not only eradicating their cancer but also maximizing postoperative function. While overall survival rates have not improved, important steps forward have been made to enhance patients' quality of life following their diagnosis. This next section will cover developments in endoprosthesis design and surgical adjuvants that have changed the care of sarcoma patients for the better.

Hot: advances in endoprosthesis design

As sarcomas are often juxta-articular, the ability to perform limb salvage surgery is predicated upon having an endoprosthesis with good long-term survival. Due to the nature of the resection required to safely remove the tumour, as well as the young age of most patients, different demands are placed on a tumour prosthesis compared with an implant used for degenerative disease. Tumour prostheses involve long segments with often little bone available for fixation, and are covered by an impaired soft-tissue envelope. Implantation often involves a compromised field due to radiotherapy and/or a compromised host due to chemotherapy. Lastly, and perhaps most importantly, endoprostheses are often being used in young patients and future growth needs to be accommodated. Consequently, a successful implant should maximize long-term fixation, minimize the risk of infection, and take into consideration eventual leg-length discrepancy. Advances in these three areas will be discussed in turn.

Not: aseptic loosening

Reported risk factors for aseptic loosening following tumour surgery include longer resection length, younger age, smaller intramedullary canal, and a distal *versus* proximal location for the femur.[23] Many strategies have been attempted to improve fixation, particularly for tumours around the knee. Three design changes that have been shown to reduce loosening in mid-to-long-term studies are replacement of a fixed with a rotating hinge articulation, addition of a hydroxyapatite (HA) coating to the implant, and incorporation of an extracortical plate to short intramedullary stems. Myers et al[24] presented ten-year follow-up data for a cohort of 192 patients that received endoprosthetic reconstruction following resection of a bone tumour in either the distal femur or proximal tibia. At this timepoint, 35% of fixed-hinge prostheses required revision for aseptic loosening. This compared with only 24% of rotating hinge implants without HA collar and 0% with HA collar ($p < 0.0001$). The authors postulate that this significant difference may be related to reduced bushing wear with the rotating hinge design.[24] Bus et al[25] reported similar findings with regards to the advantages conferred by addition of HA. In a retrospective review of 110 MUTARS modular endoprostheses, the HA coating reduced loosening from 31% to 5% ($p = 0.06$).[25] The role of HA has been studied extensively and appears to be related to improved osseointegration. This is supported by the finding on histological analysis of mature lamellar bone integration with HA-coated collars compared with a lack of bone-implant bonding with non-collared designs[26] (Fig. 1a,b). In the scenario when extensive bone resection is required, a short intramedullary stem (< 100 mm) can be the only reconstructive option. Typically associated with an increased likelihood of aseptic loosening, Stevenson et al[27] showed that addition of an extracortical plate to short-stemmed endoprostheses results in comparable implant survival to standard-length controls. Despite resection of > 70% of the length of the bone, the authors report no loosening at a mean of 8.5 years (2 to 16) if extracortical plate osseointegration took place (Fig. 1c).[27]

Not: infection

Along with aseptic loosening, infection is a major reason for revision of tumour prostheses.[23] One promising strategy to reduce infection rates is the addition of a silver coating to the prosthesis. Silver ions in solution have long been known to have antimicrobial properties via bactericidal effects.[28] Early and midterm outcome data indicates that a silver coating not only reduces overall infection rates, but may also facilitate eradication of infection, should it occur.[29,30] Wafa et al[30] conducted a case-control study to investigate the impact of Agluna-treated (silver-treated) tumour implants on infection rates both in primary reconstruction and revision for infection settings. At one-year follow-up, they report an overall postoperative infection rate of 11.8% for the silver-treated group *versus* 22.4% for the control group ($p = 0.033$). When analyzing the group of patients that experienced infection, they also found that having a silver-treated implant translated into a higher rate of success following both two-stage revision and debridement and implant retention (DAIR) compared with traditional implants.[30]

Not: leg-length discrepancy

As sarcomas most commonly occur in the metaphysis of long bones and often involve the adjacent physis, managing leg-length discrepancy is a major challenge when treating paediatric patients. For estimated differences of greater than 5 cm, options include a growing endoprosthesis or secondary lengthening procedures.[31] Most extendible prosthesis designs require additional surgical procedures to achieve incremental lengthening, either through a worm-gear mechanism or insertion of increasingly large collars.[31] While effective, this strategy is associated with the need for multiple general anaesthetics, increased risk of infection, and more time away from school and friends. A recent systematic review found that children with femoral replacements required a mean of 6.9 lengthenings following the index procedure, to achieve a mean growth of 84.8 mm.[32] Consequently, one important advance for paediatric sarcoma patients with juxta-articular

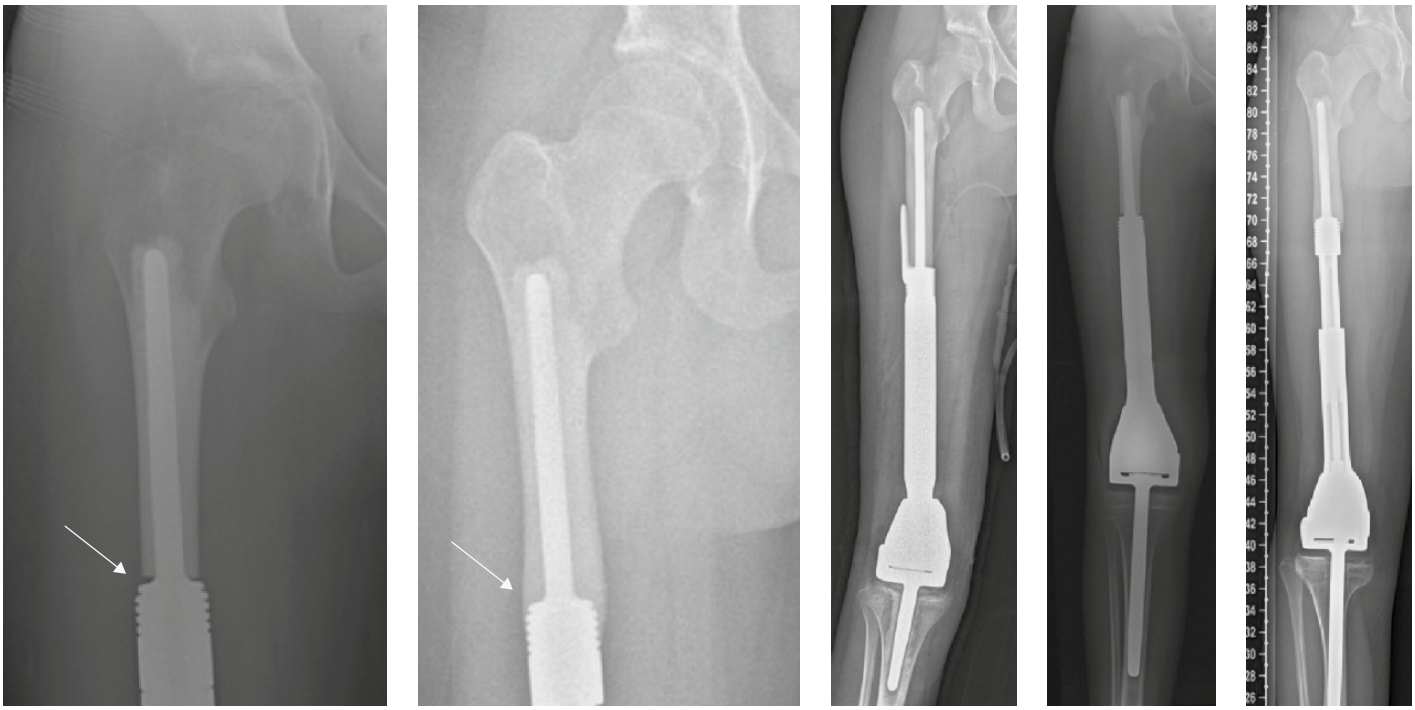

Fig. 1a Fig. 1b Fig. 1c Fig. 1d Fig. 1e

Fig. 1 Radiographs demonstrating advances in endoprosthesis design. a) and b) Progressive bony ongrowth onto the hydroxyapatite collar of a distal femoral endoprosthesis. The collar is shown a) immediately postoperatively and b) after six years. c) A well-fixed distal femoral endoprosthetic replacement with a short-stem and extra-cortical plate. The patient is a 13-year-old girl treated for a large distal femoral metadiaphyseal osteoblastic osteosarcoma. d) and e) A noninvasive growing endoprosthesis, shown d) prior to and e) following serial lengthening.

disease is the development of noninvasive extendible endoprostheses. These endoprostheses utilize an external electromagnetic field to activate an internal magnet-driven gearbox and therefore serial lengthenings can be performed in the clinic without anaesthesia (Fig. 1d,e). As these implants are relatively new, only midterm data are available for discussion.[31,33,34] Gilg et al[34] reported on their five-year results for 50 children who were reconstructed with the Stanmore noninvasive extendible Juvenile Tumour System prosthesis (Stryker Implants). The authors reported a revision-free survival of 81.7% at three years and 61.6% at five years with good functional outcomes and effective correction of leg-length differences. Paradoxically, infection rates were high at 19.6%, occurring at a mean of 12.5 months postoperatively. Although concerning, the authors rationalize that this surprisingly high infection rate may be skewed by the subset of patients with tumours in the proximal tibia, as all of these children experienced wound complications and four of six developed a deep infection.[34] Larger series and longer follow-up are required to fully assess the suitability of this promising prosthesis.

ADVANCES IN ADJUVANT TREATMENTS

Hot: proton beam radiotherapy

While radiotherapy plays an important role in the management of Ewing's sarcoma, traditional photon radiation has not been effective in more radioresistant tumours such as chondrosarcoma, osteosarcoma, and chordoma.[35] This is particularly unfortunate in axially based tumours, where *en bloc* resection is often excessively morbid and a nonsurgical method of achieving local control is desirable. To achieve any therapeutic benefit in these tumour types, high radiation doses are required (> 70 Gy);[35] however, these doses are often not achievable in the spine or pelvis due to the proximity of radiation-sensitive structures such as the spinal cord, bowel, and great vessels. There has consequently been much interest in the use of proton beam therapy for unresectable bone sarcomas, as these heavier particles reduce the amount of scatter, limiting off-target effects. Studies to date have consisted of small, heterogeneous patient cohorts and must be interpreted with care; however, they have shown promise in otherwise difficult-to-treat tumours. For example, Indelicato et al[36] reported on their results with proton beam therapy (median dose of 70.2 Gy) for chordomas and chondrosarcomas of the spine. In a cohort of 39 patients, they were able to achieve a local control rate of 71% and overall survival rate of 76% at four years post-treatment with less than 15% experiencing serious side effects.[36] While no randomized controlled trials exist comparing proton beam therapy with either photon-based radiation or surgical resection, local cure rates appear better than the former[37] and comparable to the latter.[38]

Hot: targeted therapies

Improved understanding of tumour biology has led to the discovery of targeted therapies that have revolutionized the treatment of some cancers. While clinical effectiveness of targeted therapies in bone sarcoma has yet to be demonstrated, success in the management of giant cell tumours with denosumab, a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, is a promising first step. Giant cell tumours of bone (GCTB) are benign but locally aggressive tumours that classically occur in the epiphyseal-metaphyseal region of long

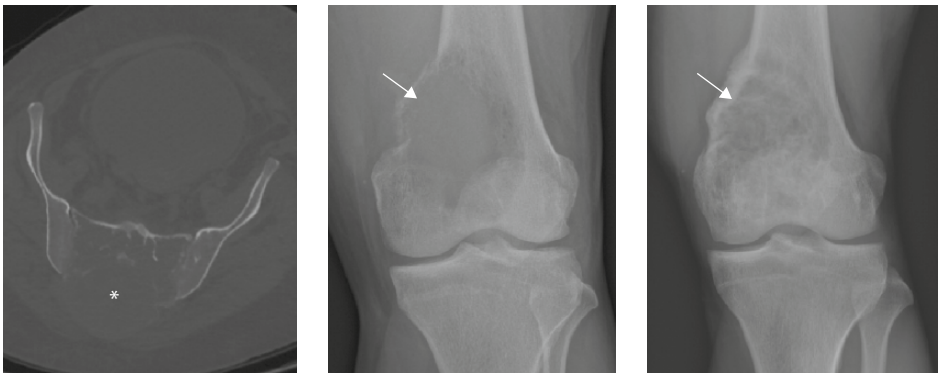

Fig. 2a Fig. 2b Fig. 2c

Fig. 2 Use of denosumab in giant cell tumour of bone (GCTB). a) An example of a difficult-to-treat lesion in the sacrum. b) and c) Images of a distal femoral GCTB: b) on presentation; and c) following four months of denosumab treatment. The patient subsequently underwent successful extended curettage and cementation.

bones and affect patients between 20 and 50 years of age.[39] While smaller, intraosseous tumours are treated with extended intralesional curettage, large juxta-articular and axially located GCTBs can be very difficult to manage. As shown in Figure 2, these tumours can occur in anatomical regions associated with significant surgical morbidity (Fig. 2a) and can be joint-threatening (Fig. 2b). It is thought that the pathological cells in GCTB are mesenchymal stromal cells. These cells secrete high levels of RANKL, which in turn induce the osteolytic behaviour of osteoclast-like giant cells.[39] Denosumab, a monoclonal antibody that binds to RANKL, was initially developed as a treatment for osteoporosis and a decade ago was found to be effective in eliminating giant cells and halting tumour progression in GCTB.[40] Traub et al[41] reported on a prospective nonrandomized study of 20 'high-risk' GCTB patients that received neoadjuvant denosumab. These patients were gauged high-risk due to the presence of joint-threatening lesions, as they had one or more of extensive periarticular bone loss, pathological fracture, and large soft-tissue mass on presentation. The authors found improved subchondral and cortical bone in all cases that then permitted joint preservation surgery in 90% of patients[41] (Figs 2b and 2c). This study and others have, however, raised the concern that local recurrence rates are not improved and remain between 15% and 30%, regardless of denosumab administration.[39,41-43] Current indications for use of denosumab in GCTB include lesions that are recurrent or deemed to be unresectable,[39] and there is good evidence that it is beneficial in large Campanacci grade 3 tumours to facilitate complete surgical excision.[43] Several controversies remain with regards to duration of treatment, dosing schedule, and the long-term effects in this young patient population. Short-term serious adverse events appear rare and include osteonecrosis of the jaw, atypical femoral fractures, and rebound hypercalcemia.[44] As denosumab was initially studied in the older osteoporotic population, the long-term consequences of chronic use are unclear, particularly in young women of child-bearing age.[39] Clearly, as with any new promising agent, additional research and objective scrutiny of clinical outcomes are required to identify the ideal patient and clinical scenario for the use of denosumab in the treatment of GCTB.

LOOKING TO THE FUTURE

Research into the pathogenesis of sarcomas has a rich history; investigations into families with high rates of bone and soft-tissue tumours led to the discovery of the oncogene p53 by Li et al[45] in the 1960s. However, given its low incidence, sarcoma research has been overshadowed in recent decades by interest in more common cancers, such as breast cancer and haematological malignancies. Regardless, over the last five years, important strides have been made in understanding the cascade of events that lead to the development, progression, and metastasis of primary bone sarcomas. Areas of interest include identification of circulating biomarkers, elucidation of the genetic landscape, and characterization of the tumour microenvironment, with the end goal of improving diagnosis and treatment of patients. Key findings in each area will be summarized here.

Potentially hot: circulating biomarkers

Treatment of a bone sarcoma has many phases – diagnosis, neoadjuvant chemotherapy, surgery, adjuvant chemotherapy, and finally surveillance for local and distant recurrence. Patients are followed closely, in early stages to determine how the tumour is responding to chemotherapy, and in later stages to monitor for disease recurrence. Detection methods are either noninvasive, namely physical examination and imaging studies, or invasive, in the form of biopsy. Noninvasive methods may not detect subtle changes or early recurrence, and biopsy is expensive for the healthcare system and painful for the patient. There has consequently been a push to develop alternative techniques of monitoring disease course. One promising avenue is detection of tumour biomarkers in peripheral blood. Detectable moieties include circulating tumour cells, DNA, and microRNA. For example, based on the knowledge that isocitrate dehydrogenese type 1 (IDH1) is a mutation present in 60% of chondrosarcomas, Gutteridge et al[46] demonstrated that this mutant DNA could be detected in patient plasma and that levels correlated with tumour grade and treatment stage. Similarly, Shulman et al[47] recently published on their success detecting circulating DNA from Ewing's sarcoma and osteosarcoma patients using next-generation sequencing assays. Interestingly, they also showed that among patients with newly diagnosed Ewing's sarcoma, detectable circulating DNA was associated with a worse three-year overall survival compared with patients without detectable levels (79.8% *vs* 92.6%; $p = 0.01$).[47] This area of investigation promises not only to shed light on tumour behaviour but, with further work, should also improve disease surveillance and prognostication in a meaningful way.

Potentially hot: elucidating the genomic landscape

The widespread availability of rapid genetic sequencing technologies has led to enormous interest in characterizing the genetic and epigenetic alterations that lead to different tumour types, including primary bone sarcomas. In recent years, much focus has been placed on the role of microRNAs in disease initiation, progression, and metastasis. MicroRNAs (miRNA) control gene expression by binding to messenger RNA, leading to repression of translation. For instance, overexpression of an miRNA that downregulates a tumour suppressor gene will have an oncogenic effect. It is hoped that identification of causative miRNAs in sarcoma will not only allow insight into tumour biology, but also contribute to diagnosis and treatment. Such avenues of investigation are arguably most important in diseases such as osteosarcoma and chondrosarcoma that do not possess a common mutational profile. While most Ewing's sarcomas carry the EWS-FLI1 translocation, osteosarcoma and chondrosarcoma are characterized by genomic instability with both intra- and inter-tumoural heterogeneity.[48] In the last few years, there has been an spike in studies investigating miRNA in bone sarcomas. In one study, Andersen et al[49] profiled the expression level of 752 miRNAs in a total of 101 osteosarcoma patients. The authors identified 29 deregulated miRNAs and focused on two (miR-221 and miR-222) that were significantly associated with time to development of metastasis.[49] One specific diagnostic challenge that miRNA detection may address is distinction of benign cartilage tumours (namely enchondroma) from low-grade chondrosarcoma. Currently, this remains a radiological and clinical diagnosis, as biopsy does not always correlate with final pathological analysis from the resection specimen.[18] To this end, Zhang et al[50] performed an miRNA microarray comparison of normal cartilage with enchondroma and chondrosarcoma specimens. They identified two miRNAs (miR-181a and miR-138) that were consistently and significantly increased in low-grade chondrosarcoma compared with the other two sample types.[50] Next steps will be to determine whether these two miRNAs can be used prospectively to diagnose low-grade chondrosarcoma in biopsy specimens.

Potentially hot: manipulating the tumour immune microenvironment

Characterization of the tumour microenvironment, particularly the immune infiltrate, has translated into large gains in the treatment of haematological malignancies and certain carcinomas.[51] Given the lack of current genomic targets in bone sarcomas, modulating the tumour microenvironment is particularly appealing. Furthermore, the potential for immune regulation is reflected in the success of mifamurtide (liposomal muramyl tripeptide), an agent that selectively induces macrophage cytotoxicity, in osteosarcoma. A decade ago, the Children's Oncology Group demonstrated that the addition of mifamurtide to the standard chemotherapy regimen improved six-year overall survival from 70% to 78% ($p = 0.03$).[52] This drug is now approved in the United Kingdom and Europe for patients under the age of 30 years with localized osteosarcoma.[8] Unfortunately, mifamurtide is currently the exception, as other immune modulators have thus far failed to translate success in preclinical models into improved outcomes in human clinical trials.[53] Despite some setbacks, research continues, and one area of promise is inhibition of the programmed cell death 1 receptor/ligand (PD-1/PD-L1) pathway in chondrosarcoma. The PD-1/PD-L1 pathway is an immune checkpoint that in normal circumstances promotes self-tolerance by down-regulating T cell activity. It has also been identified as a mechanism for tumours to evade the immune system.[54] Recently, Kostine et al[55] examined PD-L1 expression in chondrosarcoma subtypes and found that while it was absent in conventional tumours, positivity was displayed in 41% of dedifferentiated chondrosarcomas. While anti-PD-1 therapy has not yet been successful in sarcoma,[56] studies such as these may identify suitable tumour types for this approach.

CONCLUSION

Primary bone sarcomas are a rare entity that require a high index of suspicion to diagnose and early referral to specialty centres for diagnostic work-up and management. While overall survival in Ewing's sarcoma, osteosarcoma, and chondrosarcoma has not changed appreciably since the 1970s, quality of care and outcomes has improved significantly. Advances in endoprosthesis design and radiation technology have led to better patient functional outcomes and more options in difficult-to-treat cases. Promising research in targeted therapies and tumour biology portend well for the future, as early evidence suggests that great strides in how we diagnose and treat bone sarcoma patients are to come.

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