■ ANNOTATION

Controversies in orthopaedic oncology

ATTEMPTING INTERNATIONAL CONSENSUS

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Chondrosarcoma is the second most common surgically treated primary bone sarcoma. Despite a large number of scientific papers in the literature, there is still significant controversy about diagnostics, treatment of the primary tumour, subtypes, and complications. Therefore, consensus on its day-to-day treatment decisions is needed. In January 2024, the Birmingham Orthopaedic Oncology Meeting (BOOM) attempted to gain global consensus from 300 delegates from over 50 countries. The meeting focused on these critical areas and aimed to generate consensus statements based on evidence amalgamation and expert opinion from diverse geographical regions. In parallel, periprosthetic joint infection (PJI) in oncological reconstructions poses unique challenges due to factors such as adjuvant treatments, large exposures, and the complexity of surgery. The meeting debated two-stage revisions, antibiotic prophylaxis, managing acute PJI in patients undergoing chemotherapy, and defining the best strategies for wound management and allograft reconstruction. The objectives of the meeting extended beyond resolving immediate controversies. It sought to foster global collaboration among specialists attending the meeting, and to encourage future research projects to address unsolved dilemmas. By highlighting areas of disagreement and promoting collaborative research endeavours, this initiative aims to enhance treatment standards and potentially improve outcomes for patients globally. This paper sets out some of the controversies and questions that were debated in the meeting.

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Introduction

Orthopaedic oncology has been a subspeciality of orthopaedic surgery since the 1800s, gaining ground since the adoption of neoadjuvant chemotherapy for osteosarcoma in the 1980s.[1] Primary bone sarcomas are rare, with approximately 550 new cases per year in the UK. This represents less than 1% of all new cancers.[2] The degree of centralization of treatment for sarcomas varies around the globe, but many are now treated in specialist centres, while local, national, and international societies have emerged. Their purpose has been to build expertise through education and collaboration in an active, interconnected global community of orthopaedic oncologists.

With the vast available range of resources such as academic journals, PubMed, Google Scholar, and more, clinicians can find themselves overwhelmed by differing opinions and evidence when attempting to answer everyday questions about the treatment of sarcomas. Global meetings often concentrate on presenting new research, while typical day-to-day treatment decisions often remain controversial. The general level of evidence on which we base decisions has been evaluated as low, and is dominated by observational series.[3]

The need for answers to key clinical questions in sarcoma care has never been greater. The first author presented a lecture entitled ‘Controversies in Chondrosarcoma’ at the International Society of Limb Salvage (ISOLS) in 2022, and this spawned a debate about how best to provide some clarity from the array of available literature.

Consensus meetings

Consensus meetings in medicine were initially popularized by the National Institutes of Health (NIH) in 1976 as a modification of the “science court concept”, which held that scientific fact could emerge in a court-like procedure, where expert scientists used the adversarial approach to resolve controversial issues.[4]

The Delphi method was originally conceived in the 1950s. The name refers to the Oracle of Delphi, a priestess at a temple of Apollo in ancient Greece known for her prophecies. The Delphi method allows experts to work toward a mutual agreement by conducting a circulating series of questionnaires and releasing related feedback to further the discussion with each subsequent round. The Delphi method has been adopted by the medical community, and many consensus

meeting guidelines have been published as a result. The method has its admirers and detractors, but remains a valuable tool if undertaken honestly and with clarity, and allows participation by a large section of the community. The Delphi method is an accepted approach in orthopaedic oncology and has been used before to determine priorities.[5,6]

In January 2024, the Royal Orthopaedic Hospital organized a global consensus meeting (Birmingham Orthopaedic Oncology Meeting; BOOM) with the aim of generating consensus statements on two areas of controversy: chondrosarcoma and periprosthetic joint infection (PJI) after reconstruction for sarcoma.[7] The process started with the development of a local organizing committee, a group of regional leads (one for each continent) and an invited scientific committee of a representative from 150 specialist units from 47 countries. The meeting was endorsed by all major orthopaedic oncology organizations, ISOLS, Musculoskeletal Tumour Society, European Musculoskeletal Oncology Society, Asia Pacific Musculoskeletal Tumour Society, and Sociedad Latinoamericana De Tumours Musculoesqueléticos.

A series of online questionnaires were used to develop a panel of 120 questions, which were ranked in terms of priority by the scientific committee. The highest-priority questions were then grouped into 20 themes (ten for chondrosarcoma and ten for PJI) with two questions for each theme. Each theme was then allocated to two different units from different continents to compile a narrative review of the evidence, grade the strength of the evidence,[8] give a personal view on the question, and develop a consensus statement on the subject of the question.

The organizing committee conducted a pre-meeting anonymous poll after the evidence had been amalgamated, to gain an understanding of the level of controversy for each question, and then allocated appropriate time for debate at the meeting. This formed the basis for research into whether the influence of attendance at such a meeting shifts opinion. The final list of questions posed at the meeting is described in Supplementary Table i.

Areas of controversy in chondrosarcoma

Chondrosarcoma is the second most common surgically treated primary sarcoma of bone but remains rare, with an age-standardized incidence of approximately 3.4 to 4.1 per million people per year. It presents in three main forms: conventional central chondrosarcoma, peripheral chondrosarcoma, and dedifferentiated forms of both of these subtypes. Rarer subtypes, including myxoid, clear cell, and mesenchymal chondrosarcoma, represent less than 5% of chondrosarcomas.[9] Chondrosarcoma is considered radio- and chemoresistant and it is therefore predominantly treated surgically. A diagnostic dilemma exists for differentiating between benign enchondromas, atypical cartilaginous tumours, and malignant chondrosarcomas, and subsequently balancing the morbidity of treatment with the requirement for oncological safety.

The most controversial areas as deemed by the scientific committee are detailed below, in order of priority, with a brief synopsis of the problems.

De-differentiated chondrosarcoma. This rare subtype is extremely aggressive, with a high rate of pathological fracture, local recurrence (LR), and poor survival: five-year survival ranges from 7% to 24% in the literature.[10,11] Given these poor survival rates, questions remain as to how aggressively they should be treated. How extensive should the surgical margin be to secure oncological control, and is amputation justified if indicated in the face of limited survival? Some units advocate using chemotherapy to improve survival rates, but the results of studies range from not showing any benefit to finding promising results.[12]

Radiology of chondrosarcoma. Central cartilage tumours (CCTs) are found incidentally on up to 3% of routine MRI scans of the hip, knee, or shoulder. Atypical cartilage tumours (ACTs) were defined in the 2020 by the World Health Organization as larger CCTs (> 5 cm) of limbs and replaced the term grade 1 chondrosarcoma, to reflect their indolent nature.[13] Subsequently, some studies have shown a huge 'increase' in the incidence of ACTs without a corresponding increase in high-grade tumours.[14,15] Differentiating ACTs from higher grade chondrosarcomas can be difficult, and knowing when or how to treat ACTs even more so. Some units advocate intralesional treatment, others a wide resection. Other groups take the view that radiological surveillance is oncologically safe.[16] Recently, several studies have described predictive classification systems based on MRI with high sensitivity and specificity, though these are not yet in routine practice.[17,18]

Pathological fractures. Pathological fractures occur in approximately 15% of cases and are more common in higher-grade tumours. It is accepted that the outcomes for patients with pathological fractures are worse, but studies have suggested that pathological fracture per se does not influence the overall survival of the patient, as the grade and subtype are more important.[19] A common belief is that pathological fractures result in higher rates of LR, but the literature is unclear.[20] This quandary leaves clinicians debating when limb salvage surgery is safe in the presence of a pathological fracture, or whether amputation offers any survival benefit.

Management of ACTs. Management of ACTs is possibly the most controversial area. A recent publication has shown evidence that the risk of metastatic disease from ACTs confined to bone is negligible.[21] Many clinicians advocate intralesional curettage of symptomatic or large low-grade lesions, but given the evidence that preoperative biopsy is poor at predicting the highest grade of the tumour, other clinicians prefer wide en bloc excision, with an increase in surgical morbidity. Several units have now published evidence that radiological surveillance of intraosseous ACTs is safe, but the interval of scans and when to intervene remain unclear.[16] The role of preoperative biopsy in chondrosarcoma, and particularly ACT, is also hotly debated. Several studies have shown that predicting the biological behaviour of chondrosarcoma by biopsy is highly inaccurate, adds little to the treatment decisions, and may be misleading, while radiological classifications are more accurate.[22,23] Units in countries where litigation rates are high suggest that biopsy is of medicolegal importance and mandatory in all cases prior to treatment decisions.

Pelvic chondrosarcomas. The pelvis has been reported to be the most common site for chondrosarcoma. The literature suggests that the outcomes for pelvic tumours are worse than those in the limbs. However, some reports suggest that the biological

behaviour of chondrosarcoma of the pelvis is similar to that of other sites but often present later, larger, and with a greater soft-tissue component.[24]

Surgical margins. Surgical margins are known to be vital to reduce LR and improve disease-specific survival (DSS). A 'wide' margin is needed for high-grade sarcomas, but what is a wide margin? The international definition of 'wide' varies significantly. Some regions use a tumour-free margin as their definition, while others have attempted to define a wide margin in millimetres, and varied the definition by grade and subtype of chondrosarcoma as predicted by risk of LR or DSS at different measurements. Until surgeons can agree on a definition of what margin we are aiming for in specific grades and subtypes of tumour, the language we use is ambiguous and open to individual interpretation.[25]

Locally recurrent disease. Surgeons often feel guilty if a patient presents with LR, but the interplay between width of surgical margin achieved, histological grade of tumour, and biological behaviour of chondrosarcoma subtypes is complex. It has been questioned whether LR is a function of the natural aggressiveness of the tumour, but there is convincing evidence that the width of surgical margins is crucial in reducing the risk of LR, and that LR independently reduces DSS. If LR does occur, the clinician is faced with the question of how aggressive they should be in treating it, and whether amputation is justifiable.[25]

Inadvertent intralesional margins for high-grade chondrosarcoma. All surgeons accept that wide margins for high-grade chondrosarcoma are preferred; however, intralesional margins occur in 5% to 10% of cases.[26] Intralesional margins can be micro- or macroscopic, and their consequences are intensely debated. Evidence exists that they have a negative impact on both LR and DSS.[25] However, whether the surgeon should immediately reoperate to achieve clear margins, amputate the affected limb, or observe the patient and intervene if isolated LR occurs is controversial. Since only 40% of patients will actually develop LR, it is appropriate to ask whether immediate surgery represents over-treatment, or if the effect on survival is so significant that it should be undertaken regardless.[25]

Surveillance of chondrosarcoma. Once a chondrosarcoma has been excised, the optimal follow-up interval and preferred imaging technique remains debated and varies significantly around the world. The cost of protracted regular follow-up for ten years with MRI or CT scans is enormous, and in low-economy countries this is felt the hardest. The impact of surveillance on patients' lives is huge in terms of time, economic burden, and anxiety in the build-up to surveillance appointments (termed "scanxiety"). The effectiveness of surveillance should be measured by how frequently an intervention has to be made to treat a detected LR or metastasis, and if it improves the patient's outcome. In the days of personalized medicine, whether surveillance can be tailored to the patient's predicted outcome based on known risk factors also remains controversial.

Adjuvant therapies. Chondrosarcoma remains a disease principally treated by surgery, but the emergence of new forms of radiation therapy, particularly proton and carbon ion therapy, as well as chemotherapy, is gaining evidence of effectiveness. Indications for heavy ion therapy are skull base or sacral locations, and those tumours are deemed unresectable. However, many countries do not have access to these technologies. Chemotherapy targeting isocitrate dehydrogenase mutations, however, shows very early promising results in current clinical trials, with a median progression free-survival of six months.[27] Chemotherapy is most commonly given for de-differentiated chondrosarcoma, though the evidence for this is also contradictory. Defining the current role of adjuvant therapies in chondrosarcoma is important.[11]

Areas of controversy in PJI for oncology reconstructions

Following excision of a tumour, reconstruction is often needed to restore function: the use of endoprostheses is a mainstay. In this situation, PJI is a greater risk than after routine primary or revision arthroplasty.[6] The International Consensus Meetings have gone a long way to harmonize and define preventative and treatment measures to reduce PJI, but how applicable some of these measures are to the unique nature of oncological patients is debatable. The incidence of PJI after endoprosthetic or allograft reconstruction is approximately 10%.[28,29] Many of the controversial areas of PJI in oncology patients are similar to those affecting arthroplasty patients but with the added context of adjuvant chemo- and/or radiotherapy with wider exposures, larger prostheses, higher blood loss, and greater complexity. The expected oncological prognosis is also important in decision-making. If patients have metastatic disease with a limited life expectancy, protracted procedures should be avoided.

The most controversial areas as deemed by the scientific committee are detailed below, in order of priority, with a brief synopsis of the problems.

Two-stage revision. Two-stage revision is the gold-standard treatment of PJI in oncology, but this is not uniformly defined. Given the challenge of bone loss after resection, some groups have suggested that the extra morbidity associated with removing a well fixed stem may not be justified in two-stage revision. Evidence suggests that amputation rates are approximately 35% in patients after PJI. Knowing when it is safe to proceed with a second stage is a concern.[30–32]

Antibiotic prophylaxis. Prophylactic Antibiotic Regimens In Tumor Surgery (PARITY) was the first randomized controlled trial in sarcoma surgery, and studied the effect on PJI of one-day rather than five-day prophylaxis with cephalosporin. It showed non-inferiority in the rate of PJI between groups, but higher levels of antibiotic-related complications in the five-day group. The choice of antibiotic was not tested, and whether extended prophylaxis is justified after high-risk reconstructions, such as those of the pelvis and proximal tibia, remains a concern.[33]

Acute PJI during chemotherapy. Unlike arthroplasty patients, many oncology patients need to restart myelosuppressive chemotherapy two weeks after reconstruction. When a patient presents with an acute PJI, a knowledge of when they can resume therapy, balanced against a consideration of which operation is most likely to salvage the limb, is critical.[34,35]

Debridement, antibiotics, and implant retention. Debridement, antibiotics, and implant retention (DAIR) is very attractive in oncology procedures, but how effective it is with large reconstructions, whether modular implants should be exchanged at considerable expense, and whether the large

periprosthetic space warrants use of local antibiotic carriers remain to be established.[34,36]

Single-stage revision. For the same factors as question 14 (DAIR), single-stage revision is also attractive. Evidence suggests this is less effective than two-stage revision, so defining when it should be considered and for how long antibiotics should be given are further matters for debate.[32,34]

Antibiotic suppression. Given the reduced efficacy of two-stage revision in an oncology setting (approximately 70% success), when to consider extended antibiotics after revision or long-term antibiotic suppression is controversial.[32,34]

Risk factors for PJI. Many reports have described individual risk factors for PJI in oncology patients, but whether any of these can be addressed remains unclear. There are global differences in the availability of coated implants (silver/iodine); it is also unclear whether they have a prophylactic or treatment effect, and whether the expense is justified.[37,38]

Wounds. Oncology patients have large wounds and receive anticoagulant prophylaxis because of an increased risk of deep vein thrombosis. Consequently, they often have persistent wound drainage. How aggressive a surgeon should be in managing this problem, and a coherent strategy to manage wound complications, need to be clearer.[34,37]

Allograft reconstructions. Reconstructive options vary globally, with surgeons preferring endoprostheses or allografts depending on the basis of availability, expense, and tradition. Debate continues about whether the rate of PJI differs between the two, and its optimal treatment strategy.[39,40]

Organisms. Due to adjuvant treatment, significant previous exposure to antibiotics (in neutropenic sepsis) and tumours of the pelvis mean that the organisms that cause PJI in oncology patients are often more unusual and drug-resistant compared to those complicaing routine arthroplasty. Defining the effectiveness of different treatment strategies on different groups of organisms would be welcome.[34]

Future research opportunities and collaboration

One of the major aims of the consensus meeting was to highlight areas of disagreement and allow global collaborative projects to address these areas with colleagues attending the meeting. It is hoped that the meeting will be repeated in two years' time, when the results of the projects can be shared and voted upon.

Conclusions

There is a famous quote: "the more I learn, the more I realize how much I don't know". In a small but crucial speciality, where decisions about treatment can affect patients' survival, this is pertinent. Many problems faced in our field are the same across the globe, but there are also subtle differences. The harmonization of answers to day-to-day problems by consensus will potentially help millions of patients across the globe and highlight areas of difference and lack of evidence for future research collaborations.

Take home message

- The Birmingham Orthopaedic Oncology Meeting (BOOM) attempted to gain global consensus on chondrosarcoma and periprosthetic joint infection.
- By highlighting areas of disagreement and promoting collaborative research endeavours, this initiative aims to enhance treatment standards and potentially improve outcomes for patients globally.

Supplementary material

The BOOM Consensus Meeting Committee member list, along with the full list of questions that were voted upon.

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