Denosumab: does it have a role in operable giant cell tumours of bone?

Although uncommonly associated with mortality, giant cell tumours of bone (GCTB) are an aggressive, metastasizing pathology that have the potential to cause local destruction of bone. It is generally accepted that no single treatment is superior to another in managing this condition; however, efforts continue to be made in assessing the impact of chemotherapy, radiological, and surgical modalities. In this study from **Mumbai (India)**, the authors examined the role of denosumab in improving local recurrence free survival (LRFS) and the overall likelihood of achieving successful surgical treatment of operable GCTB in adult patients.[1] This study benefits from a reasonably sized cohort of 44 patients, all of whom were undergoing surgery for an operable isolated GCTB and received preoperative denosumab prior to surgical excision. A total of 22 patients subsequently underwent curettage, 16 underwent tumour resection, and six had surgery with a change of intraoperative plan converting resection to curettage. In terms of medical treatment, this cohort of patients received a mean of five cycles (2 to 7) of denosumab treatments. In 42 of 44 patients, denosumab was found by the team to have improved the successes of the planned surgical treatment. Within the 41 patients who were available for follow-up (mean 34 months), there were 12 local recurrences in 11 patients who had undergone curettage and in one patient who had undergone resection of the lesion. The mean time to local recurrence was found to be 16 months. The local recurrence free survival was calculated as 94% for patients who underwent lesion resection and 64% for cases treated with curettage alone. In this series, the local recurrence rate was found to be high; however, those patients who received denosumab suffer from a noticeable selection bias. Most had extensive periarticular bone loss with minimal subchondral bone with or without a cortical break and an associated soft-tissue extension, which are accepted as risk factors for increased local recurrence. No malignant transformation of GCTB occurred during denosumab therapy but the exposure to denosumab was considerably lower than in other published series. Local control rates do not seem to improve with the administration of denosumab, but it may be that a short preoperative course could contribute to converting a lesion requiring resection into one in which curettage may suffice.

Survival with the 2000 patients in the EURAMOS-1 (European and American Osteosarcoma Study) cohort X-ref

High-grade osteosarcoma is a devastating diagnosis for young patients and children. As part of tackling this rare disease, the work of the European and American Osteosarcoma Study (EURAMOS) group has been perhaps the most significant step forwards in both aiding research collaborations and delivering randomized controlled trials investigating treatment strategies. The other major output from these collaborations has been very large cohort studies, which are able to answer demographic and survival questions that have not been possible before. A prime example of these massive cohort studies is the recently published EURAMOS-1 study, the largest osteosarcoma trial performed to date. Based in a number of centres around **Europe and North America**, this collaboration of four study groups recruited 2260 patients between April 2005 and June 2011 with Mo or M1 high-grade osteosarcoma treated with surgical resection and a combination of methotrexate, doxorubicin, and cisplatin.[2] The survival outcomes and prognostic factors were analyzed and reported in this large cohort study. Patients were followed up as part of the cohort for a median of 54 months from biopsy. Treatments, recurrence, and outcomes were recorded. At their three-year follow-up timepoint, event-free survival was found to be 59%, and at the five-year mark, event-free survival was 54%. The authors showed that the most adverse factors at diagnosis were metastases or a tumour affecting the axial skeleton. Both telangiectatic and unspecified conventional histological subtypes were associated with a favourable prognosis when compared with the chondroblastic subtype. Overall, the three-year and five-year survival following biopsy was 79% and 71%, respectively. Furthermore, in patients undergoing radical resection, data failed to support the hypothesis that axial tumour site was associated with a worse outcome. In conclusion, nearly four out of every five patients with non-metastatic osteosarcoma who have all disease resected are alive five years later, and the risk of relapse appears to decrease over time. The report of this large cohort reinforces the impact of known prognostic factors.

Localized synovial sarcoma: the survivors at five years

Synovial sarcoma is a pathology that receives much attention from our oncological colleagues, and this interesting paper from **Birmingham (UK)** adds to the profusion of studies in this field.[3] The authors investigated the long-term outcome in patients with synovial sarcoma, treated with surgical excision at a single specialist centre, who survive to the five-year follow-up point. In this large retrospective review, the authors report on the 31-year period following 1980 and the outcomes of patients with synovial sarcoma treated in this timeframe. This single tertiary referral centre treated 191 patients over those three decades with excision of the osteosarcoma, each of which have been followed up for at least five years. The mean overall disease-free survival at five years was found to be 76.4%, with the corresponding value of 60.4% at ten years. Unsurprisingly in this aggressive diagnosis, metastases occurred in 73 patients at a median interval of 20 months, and recurrence was reported in 23 patients at a median interval of 33 months. Those patients with a grade 3 tumour larger than 5 cm showed a significantly worse survival, and ten patients developed a metastasis at over five years following definitive surgical treatment. Interestingly, although 76% of patients had limb salvage, only 55% received radiotherapy and 30% received chemotherapy, despite the ongoing debate regarding the chemoresponsiveness of synovial sarcomas. This study updates the evidence for prognosis of this diagnosis and, with the caveats above, shows that at five and ten years, patients with resectable tumours are more likely to have survived than not, which is slightly more positive than was previously thought.

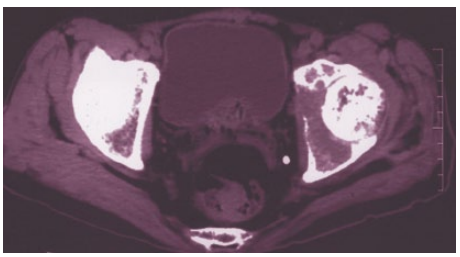
Should surgical treatment be repeated for local recurrence of soft-tissue sarcomas?

Soft-tissue sarcomas represent a common but complex diagnosis, often requiring both soft-tissue and bony reconstruction in combined orthopaedic and plastic surgical procedures. For this and other reasons, the successful treatment of primary soft-tissue sarcomas is challenging to deliver, and establishing a likely accurate prognosis is difficult. This is made even more demanding when managing local recurrence after initial surgical treatment, an area for which there is little evidence to guide treatment. This study from **Nagoya (Japan)** examines the clinical outcomes and factors associated with survival and local re-recurrence in patients who presented with local recurrence after initial surgical treatment, and who underwent another resection

with a goal of negative margins.[4] The group report their experience of treating 530 patients with soft-tissue sarcoma without metastasis with surgical resection. Of these patients, 26 (5%) were lost before three years of follow-up, but the team state that these patients were not suspected to have died in the interim. Of the remaining 504, 59 showed local recurrence. Of these 59 patients, 34 (58%) were treated with revision wide resection and 25 (42%) were treated with nonsurgical treatment. In all, 30 patients treated with surgery were available for follow up for a median of five years (1 to 12). Five- and ten-year survival rates after resection of the recurrence were 70% and 44%, respectively. Unfortunately, 12 patients went on to develop distant metastases after their second operation and ten patients showed additional local recurrences. Overall five- and ten-year local re-recurrence free rates were found to be 66% and 50%, respectively. The team found that a positive margin at surgery was associated with further recurrence, and that survival rates were better in patients with recurrence developing after two years. The overall five- and ten-year amputation-free rates were 86% and 81%, respectively. However, with the numbers of patients included in the study, the authors could not show that the use of adjuvants had an effect on local re-recurrence or survival.

Malnutrition and complications: do they interact in patients with bone sarcomas?

■ This study from **Boston, Massachusetts (USA)** explored the influence of malnutrition on the incidence of complications following the excision of primary bone sarcomas.[5] It is important to realize that more patients are malnourished than one might initially think. In terms of a balanced diet, as well as adequate vitamins and minerals, the majority of obese patients are in fact malnourished. In the setting of oncology, there is a complex interaction between nutritional status and body composition. These factors are independent of body mass index. In this retrospective cohort study, the authors studied the outcomes of a group of 275 patients who had undergone surgery for primary bone sarcomas with a preoperative albumin measured within four weeks prior to surgery. Complications were defined as patients suffering infections, consequential haematomas, the need for additional surgery, or wound complications. The team established a multivariable model containing potential covariates in an attempt to establish if malnutrition itself was associated with complications. The authors found that age and neoadjuvant radiotherapy were independently associated with postoperative complications, but that albumin did not appear to be meaningfully associated with complications. In contrast, a subanalysis of patients without a pelvic tumour who did not receive radiotherapy revealed that albumin less than 2.8 g/dl was independently associated with postoperative complications. Nutritional status is a modifiable risk factor that can be optimized to improve the outcome of surgery not just for primary bone sarcomas, but for all surgery. It seems sensible that nutritional status is evaluated in all patients prior to surgery, but this study shows that the correlation is more complicated than one might first hypothesize. We would comment, here at *360*, that this study uses a somewhat simplistic view of malnutrition, as albumin is only one of the factors associated with malnutrition. This is a first look at the problem – and a more refined analysis with measures of body composition and micronutrients would certainly be appropriate here.



Locally recurrent chondrosarcoma of the pelvis and limbs can only be controlled by wide local excision

■ This study from **Birmingham (UK)** benefits from the astute observations of a regional bone tumour unit.[6] The authors sought to investigate the relevant factors in achieving local and systemic control of a locally recurrent chondrosarcoma of the bone. Chondrosarcomas are somewhat location-dependent and, in general, deep chondrosarcomas (such as those in the pelvis) do not present until much further progressed. The Birmingham team here set out to evaluate the issues with locally recurrent tumours. A total of 126 patients, each of whom showed locally recurrent chondrosarcoma in the pelvis or limbs between 1990 and 2015, were identified from the local tumour registry and form the population for this study. This is a subgroup representing 24.3% of patients presenting with primary chondrosarcoma over this interval, and each patient had a minimum of two years' follow-up accompanied by full histopathology records. These authors show that in patients without metastases before or at the time of recurrence, disease-free survival is 62.5% at one year and 45.5% at five years. Furthermore, they showed that the significant factors influencing disease-free survival were the tumour grade and surgical margins, increasing age at time of diagnosis or recurrence, and a longer interval between primary surgery and recurrence. Secondary local recurrences occurred in 26% of patients. This study probably reveals no surprises to most readers; it supports the use of wide margins to reduce recurrence, and reports that prognosis is worse if local recurrence is a higher grade than the primary tumour.

Are limb-sparing surgical resections comparable to amputation for patients with pelvic chondrosarcoma?

■ Commonly occurring in the pelvis, chondrosarcoma is typically treated with a surgical plan following one of two strategies: limb salvage or amputation. In recent times, there has been a growing trend towards limb salvage, and a team in **Cleveland, Ohio (USA)** has investigated the success of this strategy when compared with amputation in pelvic chondrosarcoma.[7] The authors took advantage of data from the National Cancer Database recorded between 2004 and 2014 for patients diagnosed with pelvic chondrosarcoma who had undergone either limb-sparing surgery or amputation. Propensity score-matched cohorts were generated using patient demographics, tumour attributes, and treatment characteristics. This is a good way of allowing for selection biases in large data sets; however, it is not without its problems. A total of 385 patients (75%) whose records were available on the data set underwent limb-sparing surgery, and 131 (25%) underwent amputation. Propensity score matching resulted in two balanced cohorts of 131 patients. It is reasonable to assume that in a diagnosis such as this, where survival is extensively studied, the cohorts were relatively well matched. However, the authors were not able to show a difference in overall survival between limb-sparing and amputation procedures. Close analysis of the data showed a five-year survivorship of 70% in patients undergoing either limb-sparing surgery or amputation. The ten-year survivorship was 60% and 59%, respectively. Older age, higher Charlson/Deyo Comorbidity Index, higher grade, and positive surgical margins were associated with decreased survival. This is a useful study that shows similar outcomes for pelvic chondrosarcoma treated by limb salvage or amputation. Although this is not a randomized study and there will be many confounding factors, it confirms that the only thing the surgeon can affect (the surgical margins) does affect outcome. Chondrosarcoma is a surgical disease and the operating surgeon must achieve clear margins – ideally the first time, but definitely the second.

Dose escalation and proton therapy in chondrosarcoma and chordoma

Chondromas and chondrosarcoma are rare malignancies that are challenging to treat, and both surgical and non-surgical treatments form the mainstay of management strategies. Recent studies have suggested that proton beam therapy may be efficacious in treating these lesions, and this retrospective study from **Tampa, Florida (USA)** not only compares the patient outcomes affected by conventional and particle therapy, but also looks at the role of high doses (⩾ 70 Gy) of definitive radiotherapy (DRT) and preoperative radiotherapy in both pathologies.[8] Records from the National Cancer Database collected between 2004 and 2014 were used to identify 863 patients with chondrosarcoma and 715 patients with chordoma who were treated with curative proton beam or conventional radiation therapy, with a dose range between 20 Gy and 80 Gy, and who were followed up for at least 15 months. The authors show that patients receiving DRT were older and showed advanced disease. For patients with chondrosarcoma, high-dose DRT and proton therapy were associated with improved rates of overall survival at five years. In those patients receiving treatment for chordoma, proton therapy brought improved overall survival at five years, and a high dose of conventional radiotherapy improved overall survival when delivered both definitively and preoperatively. This useful paper shows that high-dose radiotherapy and proton beam therapy may well be useful for chordoma and chondrosarcoma, despite the conventional thinking that these are both radioresistant lesions.

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Children's orthopaedics

X-ref ***For other Roundups in this issue that cross-reference with Children's orthopaedics see: Sports Roundup 2; Wrist & Hand Roundup 1; Oncology Roundup 2.***

Closed reduction for DDH: worth a thought?

Developmental dysplasia of the hip (DDH) is one of the leading causes of early osteoarthritis and the subsequent need for hip arthroplasty. A spectrum of disease exists, from mild dysplasia to frank dislocation; the treatment goal is to obtain a concentric and stable reduction to allow normal acetabular growth and remodelling. The driver for DDH also varies considerably with moulding deformities, genetic, and neuromuscular causes. The role of closed reduction (CR) and hip spica casting is being increasingly questioned due to the mixed results following failure of reduction, and the risk of iatrogenic avascular necrosis of the femoral head (AVN). Researchers from the International Hip Dysplasia Institute (IHDI) in **Orlando, Florida (USA)** have, therefore, established and enrolled patients into a multicentre and multinational cohort of patients to examine the long-term outcomes following this procedure, but here they report the short-term results of the study.[1] Data were prospectively collected for patients with infantile DDH treated between 2010 and 2014. In all, 87 hips in 78 patients were evaluated with a median age at initial reduction of eight months; most also underwent adductor tenotomy at that time. Overall, 79 hips were initially successfully treated with CR and, at the most recent follow-up at a median of 22 months, 72 remained stable giving an overall failure rate of 9%. Likelihood of failure of treatment was not affected by initial reducibility, age at initial CR, or previous brace treatment. More concerningly, 25% developed radiological evidence of AVN. Yet, the risk of AVN was unaffected by the presence of an ossific nucleus, by previous brace treatment, age at CR, or pre-reduction reducibility. Duration of brace treatment was, however, predictive of AVN with a mean period of 15 weeks in those who developed AVN *versus* 12 weeks in those who did not. The acetabular index and IHDI grade were recorded to measure residual dysplasia. The mean acetabular index at latest follow-up was 25° (SD 6°). Indeed, eight of the 72 hips that were initially successfully reduced subsequently closed and were treated for residual dysplasia with femoral and/or acetabular osteotomies. Moreover, an older age at initial CR was predictive of this. Overall, this is a really interesting study that removes a lot of the methodological issues of previous work.

Intermediate to long-term results of femoral neck lengthening (Morscher osteotomy)

Coxa brevis or short femoral neck, in association with overgrowth of the greater trochanter, are thought to be caused by an ischaemic event in the proximal femoral epiphysis. This may be caused by a number of pathologies such as Perthes disease, developmental dysplasia of the hip, or following infection. The condition is, in itself, not common, but when it does occur the biomechanical consequences are relatively predictable, with the reduced lever arm causing abductor insufficiency and Trendelenburg gait, as well as a mild leg-length discrepancy and impingement of the trochanters on surrounding structures. Given the mechanical nature of the problem and predictable biomechanical consequences, there ought to be a simple solution with an appropriate osteotomy. In the early 1980s, Morscher developed a femoral neck lengthening osteotomy consisting of a double osteotomy of the shaft and greater trochanter, lateralizing the femur along the line of the neck and restoring the abductor tension. This paper from **Atlit (Israel)** was performed by surgeons in three centres who followed what is probably the largest series of patients treated using this technique.[2]