Denosumab: what we know and what we don't X-ref

Denosumab was touted as the cure-all drug for giant cell tumours (GCT) and fast-tracked by regulators given its impressive early results. It is a monoclonal antibody to the RANK-Ligand, a key step in cell-to-cell mediation between osteoclasts and osteoblasts, resulting in bone resorption. This pathway has been implicated in oncological osteolysis and also in aseptic loosening. Denosumab is particularly effective against GCT of bone and has been shown to be clinically useful to downstage tumours with a large soft-tissue extension which can allow for less morbid surgery. The role of denosumab in conventional limb GCT of bone is, however, yet to be defined. This review from various centres[1] highlights the current strengths in the literature, and what is and isn't known about denosumab use. The recurrence rates when therapy is stopped, along with the concerns over long-term use and unclear clinical toxicity, are clearly and succinctly reviewed. A must-read for any clinician treating bone sarcomas or those involved in the long-term aftercare of these patients.

Patient or clinician functional results?

In a very interesting article that piqued our interest, here at *360*, surgeons in **Boston, Massachusetts (USA)**[2] have reported the outcomes of tumour surgery, from both the patient and the clinician perspectives. The current vogue is to report patient-reported outcomes for healthcare interventions, however, there are some concerns that these outcome measures are 'contaminated'. There has been research to suggest that extrinsic factors such as ease of parking, quality of hospital food and others are specifically associated with the reporting of outcome scores. In an interesting and cunningly designed study, these surgeons set out to establish if there is a difference between patient- and clinician-reported functional outcomes using the MSTS score. They report the outcomes of 128 patients, all presenting with bone metastasis of the lower limb. The authors report patient and clinician outcomes as determined by the MSTS extremity score. Perhaps not surprisingly, the clinicians' MSTS score resulted in an overestimation of the function as compared with the patient-perceived score, with an overestimate on average by 8 points. Interestingly, despite the discrepancies, clinicians' estimates did correlate reasonably well with patient scores for the overall MSTS score and domain score, except for emotional acceptance and lifting ability. It appears that clinicians are able to grade functional outcomes reliably, however, there are differences in the baseline and overall functional outcomes assessments, with clinicians overestimating functional outcomes when compared with patients.

Can sarcoma metastasis be treated effectively with intramedullary nailing? X-ref

Intramedullary nailing has been the standard of care for patients suffering with long bone metastasis for over two decades. Interlocked intramedullary nails provide stable fixation along the length of the long bone and have become an accepted form of palliative treatment for patients presenting with metastatic disease. There are, however, some concerns including spread of tumour, risk of systemic embolisation, pulmonary embolus and contamination of surgical sites. There has been a recent move towards excision for solitary metastasis, especially if the primary carcinoma is amenable to treatment. Treatment of sarcomatous spread is essentially extrapolated from evidence supporting carcinomatous spread. The orthopaedic group in **Houston, Texas (USA)**[3] have shared their experience of 40 intramedullary nailing procedures performed in 34 patients, all presenting with multifocal metastases from sarcomas. Surgery was indicated for patients who showed signs or symptoms of an impending fracture or presented primarily with a pathologic fracture. The study was reported to a mean of 13 months' follow-up, during which 88% (n = 30) of patients died. Survival was to a median of five months after surgery and was definitive (i.e. no further surgery was required) in 85% of patients. This study serves to underline the effectiveness of intramedullary stabilisation for patients with an impending or pathologic fracture from multifocal metastatic sarcoma. The paper also highlights the dismal prognosis for these patients, essentially meaning that a single intramedullary nail is the definitive treatment for the majority of patients.

CT for identification of metastatic spread

In the age of limb-preserving surgery, the use of CT to plan resection and undertake limb salvage has become commonplace. This paper from **New York, New York (USA)**[4] may sound a warning bell for surgeons relying on CT scanning in entirety, particularly in cases of local metastasis. The group evaluated their experience of pulmonary CT scanning for metastatic spread of osteosarcoma and compared them with the findings at thoracotomy to establish the accuracy of CT scanning in detecting metastasis from bony sarcoma. The study team collated data on patients who underwent a pre-operative CT scan and subsequent thoracotomy for resection of metastatic disease. Over the 19 years of the study there were 88 patients who underwent 161 thoracotomies. Perhaps surprisingly, given the general perception of sensitivity of CT scanning for metastatic disease, the authors of this study established that in 56 (35%) cases there were more visible metastatic deposits on surgery than on CT scanning. This study really is interesting in that it quantifies the number of potentially missed metastases following staging CT scan, with 1 in 3 patients having more metastasis than previously thought on surgical intervention, and 1 in 5 of these having viable tumour cells at the time of surgical intervention.

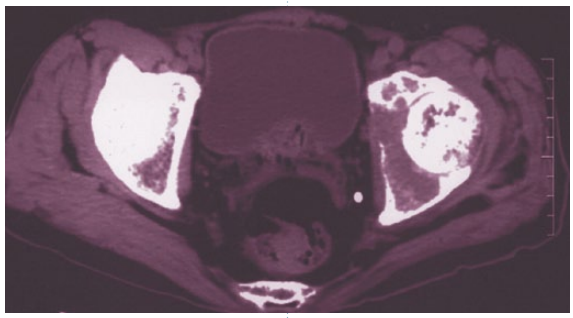
Resection of renal metastasis gold standard

There are a number of different options for treating metastatic disease, and bone metastases are being treated more and more aggressively as the years progress. The choice of simple stabilisation to symptomatically treat and avoid fracture is in many centres no longer considered gold standard treatment for solitary metastasis where patients are now more frequently being offered either intralesional curettage or complete excision to improve longer-term tumour-related and local control outcomes. Investigators in **Boston, Massachusetts (USA)**[5] have set out to answer the pertinent question in renal cell carcinoma: which strategy is likely to offer the best outcomes? They report a series of 183 patients, all with renal carcinoma and metastasis to the appendicular skeleton. In common with all retrospective series of patients, the treatments were subject to selection bias. However, allowing for this there were reasonable comparison groups of 48% metastasectomy, 30% intralesional curettage and 22% stabilisation only. The recurrence rates were significantly different in each group, with 39% suffering recurrent

disease in the stabilisation group, 22% in the intralesional curettage group and 12% in the metastasectomy group. This nicely executed paper gives the simple message that complete resection of renal metastases really does offer the best outcome. If patients have a good life expectancy, this should be the prime consideration, which necessitates, of course, management in a specialist tumour centre.

Survival with spinal metastatic disease X-ref

Perhaps one of the more difficult decisions to make in orthopaedic oncology is the management of metastatic spinal disease. Often with poor results from a neurological perspective, there have been a number of studies investigating the outcomes in particular following presentation with metastatic compressive spinal disease. One of the most difficult things to balance is life expectancy as very few prognostic tools exist, and those that do are complex to implement. A research team in **Boston, Massachusetts (USA)**[6] have set out to evaluate three methods for construction of a prognostic score. The authors used a cohort of 649 patients and used a multivariate Cox model to identify factors independently associated with survival and then produced three scoring systems; a classic; a nomogram-based; and a boosting (machine learning) algorithm. The authors then went on to establish which of the scoring systems was most discriminatory using a ROC analysis. The traditional scoring system was the worst of the methods, while the nomogram and 'boosted' algorithm performed equivalently, with the nomogram performing better on the test dataset and the boosted analysis performing better on the teaching dataset. The authors sensibly conclude that with accuracies of around 0.75 at 30 days, 90 days and a year, the nomogram method performed extremely well, is easy to apply and clearly could be used to furnish surgeons with an acceptably accurate estimate of survival for metastatic disease. As trauma orthopaedic surgeons and orthopaedic oncological surgeons are facing more and more metastatic disease (in part due to an ageing population and in part due to the improved survivals offered by chemotherapy and radiotherapy to primary carcinomas), we are going to rely more and more on tools like this. Clearly, in the future prognostic tools will be used as a key part of the decision making process. Orthopaedics is desperately in need of a large-scale cancer registry, not just to evaluate the likely survival of patients presenting with metastatic disease, but also to help guide decision making which can be complex and is often made in the midst of difficult and busy outpatients clinics without the usual benefits of an MDT process.



Osseointegration in amputation X-ref

The outcomes following amputation are prejudiced by the prosthesis socket. There are few patients who do well with a poorly formed residium or poor stump. A recent development has been the use of osseointegrating prostheses to facilitate bone weight bearing through a protruding bone-anchored prosthesis. This promising technology has been steadily evolving over the past decade or so, and found application in combat veterans and amputees following trauma or tumour. The bone-anchored prosthesis offers the potential to improve gait kinematics and potentially even for the adoption of more advanced prostheses as the socket is more firmly fixed to the residual limb. Surgeons in **Gothenburg (Sweden)**[7] have reported their own experiences of bone-anchored prostheses, paying particular attention to the infectious complications at the skin-bone barrier. The authors report a series of 30 patients, all scheduled for abutment exchange or removal. They took the opportunity to characterise the microbiological environment within the local environment and they present plenty of food for basic science and clinical thought. The vast majority of patients (n = 27/30) had bacterial genetic material detectable in cells adjacent to the abutment, and commonly within the actual bone canal. A range of cocci were responsible, with *Staphylococcus aureus*, Coagulase-negative Staphylococci, Streptococci and *Enterococcus faecalis* most commonly isolated. The authors also established that shorter, well fixed prostheses were more likely to demonstrate larger bacterial loads, and loosening itself was associated with IL-10 and osteocalcin expression. It seems that length isn't everything in osseointegrative prostheses, and as osseointegration will almost certainly become the standard attachment method for patients with amputations, it is essential to resolve these problems with infection. This series is another step along the way and suggests that improvements in technology and a better understanding of the surgery could lead to longer-term improved outcomes with these systems.

Modular distal femoral reconstruction X-ref

Distal femoral reconstruction is now a mature technology for patients with significant destruction of the distal femur due to tumour, osteolysis or trauma, and this technique has an established track record. The fundamental choice is between fixed and rotating hinge designs, with the majority of surgeons and prostheses now offering the latter. This large series from **Bologna (Italy)**[8] is essentially a design surgeon series and charts the progress of 687 patients, all undergoing distal femoral reconstruction of the Rizzoli megaprosthesis. The majority of these (n = 491) were fixed hinge, with the more recent being rotating hinge (n = 196). In what is an honest series, the surgical team report a 27% failure rate with a ten-year survival of 70%. Perhaps most interesting was the observation that in contrast to traditional revision arthroplasty in this group of patients, there was no difference between fixed and rotating hinge prostheses for outcomes in terms of aseptic loosening and infection. However, all implant fractures were in the fixed hinge group and there were significantly improved functional outcomes in the rotating hinge prosthesis. Whilst there is nothing new here, it is one of the largest series in existence and sets a benchmark of approximately a 3% per year failure with megaprosthesis around the knee. This is in line with other published series.

REFERENCES

1. **Gaston CL, Grimer RJ, Parry M, et al.** Current status and unanswered questions on the use of Denosumab in giant cell tumor of bone. *Clin Sarcoma Res* 2016;6:15.
2. **Janssen SJ, van Rein EA, Paulino Pereira NR, et al.** The discrepancy between patient and clinician reported function in extremity bone metastases. *Sarcoma* 2016 (Epub ahead of print) PMID: 27725792.
3. **Moon BS, Dunbar DJ, Lin PP, et al.** Is it appropriate to treat sarcoma metastases with intramedullary nailing? *Clin Orthop Relat Res* 2017;475:212-217.
4. **Heaton TE, Hammond WJ, Farber BA, et al.** A 20-year retrospective analysis of CT-based preoperative identification of pulmonary metastases

in patients with osteosarcoma: A single-center review. *J Pediatr Surg* 2016 (Epub ahead of print) PMID: 27836366.

5. Langerhuizen DW, Janssen SJ, van der Vliet QM, et al. Metastasectomy, intralesional resection, or stabilization only in the treatment of bone metastases from renal cell carcinoma. *J Surg Oncol* 2016;114:237-245.

6. Paulino Pereira NR, Janssen SJ, van Dijk E, et al. Development of a Prognostic Survival Algorithm for Patients with Metastatic Spine Disease. *J Bone Joint Surg [Am]* 2016;98:1767-1776.

7. Lennerås M, Tsikandylakis G, Trobos M, et al. The clinical, radiological, microbiological, and molecular profile of the skin-penetration site of transfemoral amputees treated with bone-anchored prostheses. *J Biomed Mater Res A* 2016;105:578-589.

8. Pala E, Trovarelli G, Angelini A, Ruggieri P. Distal femur reconstruction with modular tumour prostheses: a single Institution analysis of implant survival comparing fixed versus rotating hinge knee prostheses. *Int Orthop* 2016;40:2171-2180.

Children's orthopaedics

X-ref ***For other Roundups in this issue that cross-reference with Children's orthopaedics see: Knee Roundup 7; Trauma Roundups 3 and 7.***

Supracondylar fractures and lateral wires X-ref

Two worthwhile papers take another look at the topic of lateral wire fixation compared with the more traditional 'crossed' wire configuration in supracondylar fractures. In the first of this brace of reports, clinical results from **Cairo (Egypt)**[1] are reported of an investigation into wire configuration and stability in supracondylar fractures. This original paper reports a randomised (allocation concealed), unblinded, controlled trial with six months' follow-up at a Level I trauma centre. It involved 60 children (mean age 5.1 years; 70% boys) and was designed to establish if there is a difference between dual lateral and crossed wires. Patients were assessed six months after closed reduction and K-wiring, and the main outcome measures were radiological evidence of fracture stability, range of motion, ulnar nerve injury, and pin-track infection. Undisplaced Gartland type I fractures, open fractures and fractures associated with vascular injury, compartment syndrome, or pre-operative ulnar nerve injury were excluded from this study. The initial findings of this paper suggest that a medial and lateral pin configuration improved stability of supracondylar humeral fractures when compared with two lateral-entry pins in children managed with closed reduction and percutaneous pinning by junior trainees. The commentary suggests that things aren't always as they seem. To the casual reader, the original paper legitimises the use of medial wires, and superficial analysis of the data tends to support this prejudice. However, there are some significant methodological deficiencies which are ably discussed in the commentary.[2] There is a particular criticism about the role of junior trainees assisting junior trainees, and important confounding factors including time to procedure, swelling, and time of procedure were not mentioned in the initial paper. We would tend to agree with the commentary in that the original paper lacks a clear definition of outcome and the findings of this trial have limited implications for the treatment of supracondylar humeral fractures in the general clinical setting. This paper does, however, make a start in terms of subjecting what is an increasingly divergent view between surgeons to the rigours of randomised methodology – we look forwards to the inevitable larger trial with perhaps more tightly defined outcome measures.

Femoral head revascularisation can be monitored with perfusion MRI

Monitoring the clinical outcome of patients with Legg-Calvé-Perthes disease can be somewhat difficult, with patients generally monitored based on their symptoms and serial radiographs. Investigators in **Dallas, Texas (USA)**[3] have put the relatively new modality of perfusion MRI scanning to the test in the evaluation of disease progression in Legg-Calvé-Perthes. Perfusion MRI scanning was performed on 29 patients (30 hips) with a mean age of 8.4 years, all presenting with Waldenström stage I/II of the disease. The scanning was undertaken as part of a prospective study and, as such, all patients had two or more scans and 21 patients (22 hips) had three or more. Perfusion percentages of the femoral epiphyses were measured by two independent observers and perfusion on initial scan ranged from 5% to 70%. Serial assessment demonstrated a pattern of revascularisation from the periphery of the posterior, lateral and medial aspects of the femoral epiphysis and converging towards the anterocentral region. The average rate of revascularisation was 4.9% per month (± 2.3) within a wide range (0.6% to 10.4%). This paper introduces the tantalising concept of perfusion MRI as a useful imaging modality in the assessment of revascularisation in Legg-Calvé-Perthes. Use of this method will likely become the benchmark for evaluation of this condition and is therefore important from a methodological perspective, as further studies are undertaken.

Microfracture an option for osteochondritis dissecans of the capitellum X-ref

Osteochondritis dissecans of the capitellum can be a tricky condition to treat. It is not always self-limiting and in more severe cases it can be functionally limiting. Perhaps clouding decision making further, it is relatively poorly studied and occurs in active adolescents, thus decision making is often difficult. Loose body removal with drilling or microfracture is a viable treatment option in the young athlete. The majority of patients with grade IV elbow osteochondritis dissecans had resolution of pain and capitellar tenderness, improved movement and elbow function and improvement of radiographic abnormalities at two-year follow-up. The authors from **Boston, Massachusetts (USA)**[4] were able to report the results of an impressive 21 adolescents, all with grade IV elbow osteochondritis dissecans. The surgical team undertook loose body removal and microfracture of the denuded capitellar cartilage. This study reported clinical and MRI follow-up at over two years following this procedure. Patients with additional elbow pathology, prior elbow surgery, or shorter follow-up were excluded. Fifteen of the patients (71.4%) had either clinical or radiographic resolution at the most recent follow-up, and perhaps most impressively, nine (50%) had complete resolution on MRI, with 13 reporting no clinical tenderness at final follow-up. Functionally, the majority (18/21) of patients had returned to sport. The authors also attempted to identify predictors of clinical outcome and it appears that a shorter duration of symptoms correlated with smaller lesions and with improved clinical or radiographic outcome. Clearly, for the more significant grades of osteochondritis the use of foreign body removal and microfracture yields a more than acceptable clinical result, and it is heartening not only to see some research in what can be a