Oncology

Nerve sheath tumours not as bad as we thought?

Even by the standards of orthopaedic oncology, nerve sheath tumours are rare, usually arising as the result of radiotherapy or neurofibromatosis type 1 (NF1). They remain a bit of an enigma. Reaching the diagnosis and decision on optimal management can be tricky, and there remains some significant uncertainty as to whether neurofibromatosis-related nerve sheath tumours vary in prognosis away from the sporadic forms. Oncologists at the **IUCT-Oncopole, Toulouse (France)** conducted a large study of 353 patients (37% with NF1 and 59% with sporadic tumours), presenting over a 23-year period with histologically proven malignant peripheral nerve sheath tumours (MPNST).[1] Review included a multivariate analysis, and demonstrated the perhaps not surprising poor prognostic factors which included high grade, deep location, locally advanced stage at diagnosis, and macroscopically incomplete resection. Interestingly, those patients with NF1 did not experience a negative prognostic effect, except for those suffering recurrence or metastasis. In this setting, where NF1-related MPNST patients were treated with palliative chemotherapy, survival was poorer than in patients with sporadic forms. This study queries the conventional belief that NF1 is a poor prognostic indicator for patients with MPNST. It is one of the largest studies of what is a poorly understood diagnosis, mostly due to its rarity. While this study does have its shortcomings, we would urge readers to re-evaluate their preconceptions in patients with neurofibromatosis and malignant nerve sheath tumours.

Ewing's sarcoma in the pelvis

Tumours seen in the pelvis generally suffer from later diagnosis and poorer prognosis than their appendicular skeleton cousins. The combination of inaccessibility, proximity to vital structures and delayed diagnosis can make the outlook rather bleak for patients presenting with primary tumours of the pelvis, and especially so with Ewing's sarcoma. In an interesting paper from the Scandinavian group at the **Karolinska University Hospital, Solna (Sweden)**, the authors sought to tease out any differences between sacral and non-sacral tumours.[2] The study team were able to report on the outcomes of 117 patients with Ewing's sarcoma of the pelvic ring; 88 had tumours in the innominate bones and 29 in the sacrum. As would perhaps be expected in a mixed bag of presentations such as this, treatment was with a combination of radiotherapy and surgery. Radiotherapy was the sole local treatment for 40% of the innominate bone tumours, in contrast to 79% of the sacral tumours. The five-year disease-free survival rate in the sacral tumour group was significantly better than in those with innominate bone tumours (66% *vs* 40%). This paper has two interesting messages: disease-free survival among patients with Ewing's sarcoma was improved in tumours localised to the sacrum compared with the innominate bones; and local radiation therapy alone appears to result in acceptable local tumour control, and may be the treatment of choice for sacral tumours. This study should, however, be taken in context; the absence of documentation of systemic therapy is a major limitation, and is of utmost importance in Ewing's sarcoma. Should there be any unreported differences here, then the findings of this study are completely invalidated. The authors hypothesise that the difference in behaviour between sacral tumours and non-sacral tumours may be due to a different 'biologic microenvironment', possibly the close proximity to the presacral venous plexus, although this does seem to be an assertion without evidence.

Bone grafting in polyostotic fibrous dysplasia

Polyostotic fibrous dysplasia (PFD) is a genetic disease (GNAS mutation) that results in the replacement of normal marrow cells with immature osteoprogenitor cells, producing fibro-osseous tissue in place of normal marrow. One of the widely accepted treatments for PFD is bone grafting following excision of the fibrous tissue. Researchers at the **National Institutes of Health, Bethesda (USA)** have attempted to shed some light on the role of grafting in the treatment of this tricky condition. Their clinical paper reports the outcomes of 23 subjects undergoing 52 bone-grafting procedures and reported to an average follow-up of 20 years.[3] The investigators attempted to establish if graft material (autograft *vs* allograft) and type (structural *vs* non-structural) of grafting had any influence on outcomes. The authors were unable to show any advantage in their series of graft types or materials. The authors conclude that bone grafting, including both allograft and autograft, is of limited value in ablating the lesions of fibrous dysplasia.

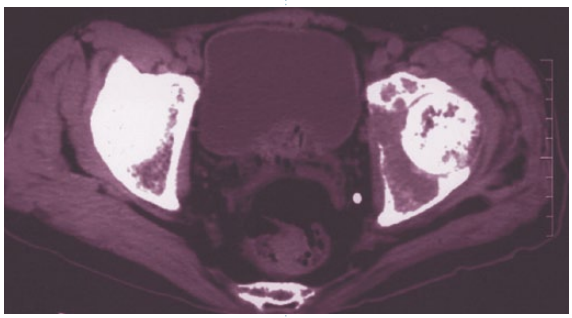
Radiation and non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma (NHL) of bone is traditionally treated with chemotherapy and radiation therapy, but the role of radiotherapy in disease management, and particularly in terms of patient functional outcomes and survival after treatment, has not been extensively studied. These authors from **Rush University, Chicago (USA)** have investigated the survival advantage of radiotherapy in a large cohort of 70 patients, all with NHL of bone and assessed at a minimum follow-up of six months for associated complications of radiotherapy.[4] All patients included in this retrospective analysis had biopsy-proven NHL of bone. One group of patients were treated with systemic therapy alone (n = 46 patients), and the other with combined modality therapy (n = 24 patients). In all cases, rituximab was the sole chemotherapy agent utilised. There were no differences in Kaplan-Meier survivorship in patients treated with and without radiation at five years. Patients who were treated with radiation were more likely to experience problems with fracture healing, and were at a higher risk for fracture in the post-treatment period. While the results of this study are fairly clear-cut with regard to the disadvantages of radiation therapy, there are certainly also some difficulties with the power of this study. A *post hoc* analysis suggested that this study was only powered to establish a 30% difference in survival. The jury is still out on any survival benefit of radiation therapy, however, the downsides in terms of orthopaedic complications are quite clear.

A new approach for desmoid tumours?

Magnetic resonance-guided, high-intensity focused ultrasound (MRgFUS) is a relatively new non-invasive therapeutic modality that may be useful to treat extremity tumours, especially in situations in which standard treatments would be associated with unacceptable morbidity or are ineffective, as is the case with desmoid fibromatosis. Researchers at **Stanford (USA)** are amongst the first investigators to report the use of MRgFUS in a clinical setting,[5] and here at *360* we are quite excited about the potential applications of this technology in the future. This small experimental and clinical study reports the outcomes of nine patients with extremity desmoid tumours in a cadaver study, demonstrating the ability of the technique to ablate a predetermined target volume in the cadaveric tissue. The nine patients who underwent treatment

all had refractory tumours that had either failed to respond to traditional treatment or had tumour-related symptoms. There were five patients available for interval scan follow-up and, of these, tumour regression was seen in four. This study provides early evidence that MRgFUS may be useful as a novel treatment modality for desmoid tumours, and is certainly worth further investigation in this as well as other types of tumours.



Meta-analysis not quite right? X-ref

There is an age-old adage - 'rubbish in, rubbish out' - that can be applied to most things in life, but particularly to medical statistics. Noting the findings of a number of recently published meta-analyses, all of which concluded that pathologic fracture is a negative prognostic factor in osteosarcoma, an author from **Vanderbilt University, Nashville (USA)** has questioned this conclusion – are meta-analyses always correct?[6] Arguing (eloquently) that the methodology of meta-analysis is to use composite outcome measures, the author emphasises that meta-analysis can generate false conclusions if important confounding variables were not accounted for in the index studies, thereby compromising internal validity. In his study, a multivariable survival analysis of a retrospective cohort of 131 patients (21 patients who suffered pathologic fracture, and 110 patients who did not), with conventional, high-grade osteosarcoma of the extremity long bones treated with neoadjuvant chemotherapy and surgical resection, was performed. Pathologic fracture did not significantly affect patient outcome or disease-free survival after controlling for confounding factors not accounted for in prior meta-analyses, such as tumour size, chemotherapy response and proximal tumour location. The author makes the point that uniformity of reporting and the sharing of individual study data would allow for adjusted meta-analysis to be performed, enabling greater accuracy in meta-analysis outcomes reporting. The counterargument, of course, is that use of multivariable outcomes in studies with limited events (this case has just 21) is in itself invalid, because although an adjusted analysis is likely to describe the small data set well, it perhaps may not be applicable to larger data sets. We wouldn't discard the meta-analyses results just yet, however, there is enough here to get us thinking.

Grafting in giant cell tumours

The treatment of the giant cell tumour consumes perhaps more words in orthopaedic literature than any other diagnosis in orthopaedic oncology. The pages of this journal are full of discussion surrounding bone grafting or polymethylmethacrylate (PMMA) support, with a range of studies on the topic. A small study from **New Jersey Medical School, New Jersey (USA)**, however, has something to add on the topic. Although describing the outcomes of just 43 patients, the series reports one of the most homogeneous patient groups reported in the literature. All of the patients had a similar lesion treated in the epiphysis of a long bone.[7] All patients underwent intralesional curettage and then treatment with either PMMA alone or graft (with or without PMMA supplementation). Outcomes were assessed to a mean of 59 months with measures of joint degeneration and functional outcome scores. Though a small study, this well conducted, careful trial demonstrated clearly that when compared with PMMA alone, the use of peri-articular bone graft constructs reduce post-operative complications (fractures and arthritis), and apparently without increasing the likelihood of tumour recurrence. The hypothesis suggested is that thermal damage from PMMA is decreased because bone graft increases the distance between the exothermic reaction of PMMA and the articular cartilage. The authors also hypothesise that the PMMA modulus mismatch between cortical bone and cancellous bone results in it acting as a rigid surface, concentrating pressure on the already thin cartilage and subchondral plate tissue. This may result in cartilage damage, fracture, and arthrosis.

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