ROUNDUP360

Oncology

Unpicking the causes of primary bone tumours

Primary bone tumours are challenging in every way. Initial diagnosis is often delayed and difficult, and successful treatment and rehabilitation is often equally demanding. For such a severe and debilitating disease, surprisingly little is known about the aetiology and natural histories. A small enclosed population like that in the British Isles provides the perfect study population for such a condition. We were delighted at *360* to come across this paper that sheds genuine light on a poorly understood problem. Researchers from **Newcastle (UK)** have attempted to describe the aetiology of bone tumours with a small-area analysis of primary bone cancer diagnoses in the UK. They investigated all new diagnoses of primary bone tumours by examining geographical patterning by linking diagnoses of primary bone tumours between 1980 and 2005 with deprivation indices and population density. The researchers used 2566 osteosarcoma and 1650 Ewing's sarcoma diagnoses, and national data on Townsend deprivation indices and population density. There was a significantly higher risk of osteosarcoma development in females from deprived areas (relative risk (RR) = 0.969). Ewing's sarcoma demonstrated a slightly different pattern, and appeared to be associated with rural environments. Ewing's sarcoma is more common with decreased population density and higher levels of car ownership (RR = 0.98 and RR = 0.99, respectively). The authors surmise that there is substantial evidence associating Ewing's sarcoma risk with rural environments and hence agricultural exposures, such as pesticides and zoonotic agents.[1]

Adjuvant chemotherapy in the longer term

The single biggest change in the management of primary, isolated osteosarcomas was the addition of adjuvant chemotherapy. This change in treatment was supported at the time by a number of randomised controlled trials. Here at *360* we were particularly delighted to see an extended follow-up of one of these trials nearly 25 years after it was originally published, as so rarely are these valuable trials reported with such extended follow-up. The research team at **Los Angeles (USA)** present a 25-year follow-up of a previously reported landmark randomised controlled trial. The original study was adjuvant chemo/radiotherapy *versus* observation for high grade localised osteosarcoma. The original study demonstrated improved survival for patients receiving the adjuvant chemotherapy. In the new study the results of the original 59 patients are presented. The authors have investigated the value of percent of necrosis after one adjuvant cycle as a predictor of disease-free survival. The investigators reviewed the long-term outcomes, follow-up visits and initial histological sections again for this new report of a Level I evidence paper. The authors identified a significantly better disease-free survival of 28% in the adjuvant chemotherapy group *versus* 15% at 25 years' follow-up. This result is also reflected in the survival at 25 years of 38% *versus* 15%. Initial tumour necrosis of > 90% was a predictor of disease-free and overall survival in this cohort of patients. The study clearly demonstrates the benefit of adjuvant chemotherapy in terms of disease-free and overall survival at over 25 years' follow-up.[2] At *360* we extend our hearty congratulations to the authors for what is an almost unique report of a landmark randomised controlled trial with valuable new data at 25 years of follow-up. We give the investigators the *360* thumbs up.

Vascularised fibular grafts may salvage massive femoral allografts

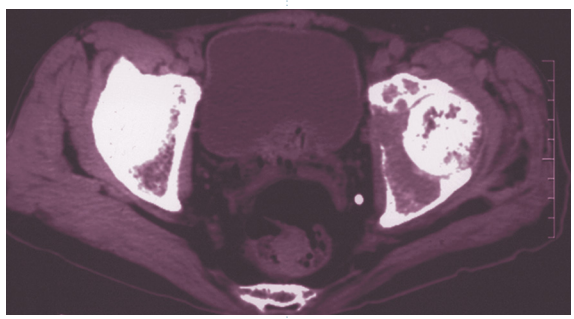
A real difficulty in the management of aggressive femoral tumours is reconstituting large sections of excised bone. Allograft can be successful but failure rates are high with rejection, nonunion and failure of fixation common. These problems are overcome by use of adjuvant fixation, or even massive prostheses. Most complications from massive allografts are because of a failure to integrate. We were interested here at *360* to read a report of a large number of cases looking at factors predicting success. Researchers from **Bologna (Italy)** reported a retrospective case series (Level IV evidence) of a staggering 101 consecutive patients presenting with 114 femoral tumours. All of their patients were treated with the same surgical tactic involving tumour excision and massive allograft reconstruction between 1986 and 2005. A range of 'adjuncts' was used within the series including intramedullary nails, vascularised fibular grafts and, where necessary, post-operative chemotherapy. The authors followed their patients up for an equally impressive median period of nine years. At final follow-up, of the initial 114 allograft reconstructions, 36 (31.5%) had failed, of which 27 (24%) were because of graft failure. Mechanisms of failure included delayed union, fracture and loss of fixation. The poorest prognostic factor was the use of intramedullary nails. Other factors predictive of a poor result were post-operative chemotherapy, massive resection (> 17 cm) and increased age in patients. The investigators found fewer complications in patients in whom vascularised fibular grafts and stainless steel plates were used.[3] Here at *360* we were interested to read this large series of patients having a complex procedure. A reported success rate of 68.5% at over nine years is impressive for this type of surgery, and one wonders how many more successes could have been achieved with the avoidance of intramedullary nails and titanium implants in conjunction with vascularised fibular graft. This paper may have reopened the graft *versus* prosthesis argument again, even for patients with difficult-to-reconstruct femoral defects.

A new look at old risks

Rarely in orthopaedics do we re-examine previous data, and perhaps we should do more often. Researchers in **Toronto (Canada)** felt that the predictors of recurrence in soft-tissue sarcoma should be revisited in light of newer treatments and more sophisticated treatment techniques. We have to say that in view of their results, we at *360* would tend to agree with them. The research team aimed to establish the contribution of known risk factors for recurrence of soft-tissue sarcomas taking into account the interaction of each, and the likelihood of death with different presentation patterns. The researchers used a cumulative probability model, treating death as a competing event, in 1668 patients with soft-tissue sarcomas. This may on the surface seem an odd thing to do as you cannot have a tumour recurrence if you are dead! The researchers identified the hazard ratios (HR) for all previously identified risk factors for recurrence. They found that tumour size (HR 3.3), depth (HR 3.2), and histological grade (HR 4.5) were most predictive of metastasis and consequently most likely to induce competition. The variables most likely to cause local recurrence were margins (HR 3.3), grade (HR 2.1), presentation status (HR 2.4), and depth (HR 1.5). When looking at the results as a whole, the investigators found that presentation status and surgical margins were the variables most likely to be predictive of recurrence. However, because of the higher incidence of death (competing effect), the other factors were not significantly associated with recurrence, tumour depth (12% *versus* 11.4%), size (10.6% *versus* 13.3%), or histological grade (12.6%, 10.7%, and 11.1%).[4] While we agree with the authors that these findings are of interest and shed new light on the likely predictors of recurrence, at *360* we might not just yet be discharging all our patients with clear margins. Metastasis is also something we want to pick up in the clinic, preferably before death.

Reconstruction with excised irradiated bone

Reconstruction of large bone defects following excision of large, less malignant lesions can be difficult, but with less malignant lesions a third way exists. The technique of tumour excision, irradiation and then bulk grafting with the excised bone is a suitable technique for tumours that are highly radiosensitive as, obviously, recurrence in the graft would be unfortunate. We were interested at *360* to see this report of a relatively large number of patients using this technique. Surgeons in **Mumbai (India)** used an *en bloc* resection technique with preservation of adjacent joints as reconstruction with the sterilised tumour bone after exposure to 50 Gy of extracorporeal irradiation. Over a four-year period between 2005 and 2009, the group performed 32 similar operations and entered their patients into a prospective cohort series (Level III evidence). The researchers report the available results for 32 patients at a mean follow-up of 34 months. Their series was evenly split between 16 Ewing's and 16 osteogenic sarcomas. The majority of patients were children (mean age 15 years) and although the majority of lesions were femoral (17/32), the series also included tibial (11/32), humeral (3/32) and a single ulnar tumour. The *en bloc* resection left a mean 19-cm bone defect. The researchers lost a single patient to follow-up and followed all patients to union of their osteotomy site (mean 7.3 months). They noted, as would be expected, that metaphyseal osteotomies united quicker than diaphyseal osteotomies. Sadly the authors report three (9.7%) tumour recurrences at 34 months' follow-up, although they note that all were soft-tissue recurrences.[5] The researchers feel that their technique of extracorporeal irradiation offers a cheap and safe method for treating sarcomas. While we raised an eyebrow here at *360* with a recurrence rate of nearly 10% at less than three years, the researchers are reporting a similar level of recurrence to that in the literature, albeit at shorter follow-up.



Predicting chemosensitivity in osteosarcoma

Some interesting work has appeared from **Shanghai (China)** into the prediction of chemosensitivity in osteosarcoma before any chemotherapy is offered. As the authors state, osteosarcoma has one of the worst prognoses in adolescents; only 20% to 60% of patients have high rates of histological necrosis with intensive neoadjuvant chemotherapy. They thus investigated the prognostic values of hypoxia-inducible factor 1α (HIF-1α), apurinic endonuclease 1 (APE1), vascular endothelial growth factor (VEGF) and cycloogenase-2 (COX-2) protein expression and their predictive value of tumour necrosis rate and prognosis, as well as their interrelationships. Formalin-fixed paraffin-embedded tissue samples were obtained from 49 patients with osteosarcoma. Immunohistochemistry assays were performed in pre-chemotherapy samples to determine HIF-1α, VEGF, APE1 and COX-2 protein expression levels and haematoxylin and eosin staining was performed in post-operative samples to determine the tumour necrosis rate. HIF-1α correlated significantly with every protein the researchers tested: VEGF, APE1 and COX-2. HIF-1α protein expression had a significant impact on disease-free survival. Expression of HIF-1α had a sensitivity of 64.7% and a specificity of 71.9% for a poor pathological response (< 90% tumour necrosis) *versus* a good pathological response (≥ 90% tumour necrosis).[6] At *360* we thought this was an interesting study, as it appears that expression of HIF-1α is a predictor of tumour response to neoadjuvant chemotherapy and outcome in osteosarcoma, and correlates with VEGF, APE1 and COX-2. It is good to know these things before you start.

Chemotherapy, osteoporosis and the risk of fracture

With all treatments, irrespective of circumstance, management is a matter of balancing benefits *versus* risks. Consequently a paper from **Graz (Austria)** into osteoporosis after chemotherapy for bone sarcoma gave *360* some interesting reading. The authors remind us that premature bone loss after childhood chemotherapy may be underestimated in patients with bone sarcoma. Methotrexate, a standard agent in osteosarcoma protocols, reportedly reduces bone mineral density (BMD). The literature, however, has reported cases of BMD reduction in patients with Ewing's sarcoma treated without methotrexate. Thus, it is unclear whether osteoporosis after chemotherapy relates to methotrexate or to other factors. The authors asked themselves three questions: whether 1) young patients with a bone sarcoma had BMD reduction, 2) patients treated with methotrexate had lower BMD, and 3) other factors (e.g., lactose intolerance or vitamin D deficiency) posed additional risks for low BMD. To answer these queries they retrospectively reviewed 43 patients with malignancies who had dual-energy x-ray absorptiometry (DEXA) (lumbar, femoral); 18 with Ewing's

sarcoma (mean age 26 years), and 25 with an osteosarcoma (mean age 27 years). The mean time since diagnosis was 8 years in the group with Ewing's sarcoma and 7 years in the group with osteosarcoma. At last follow-up the authors determined BMD (computing z-scores), fracture rate, and lifestyle, and performed serum analysis. From these measurements they established that BMD reduction was present in 58% of patients in at least one measured site. Seven of the 43 patients (16%) had non-trauma or tumour-associated fractures after chemotherapy. Findings were similar in the Ewing's and osteosarcoma subgroups. The team also found vitamin D deficiency in 38 patients (88%) and borderline elevated bone metabolism; lactose intolerance was present in 16 patients (37%).[7] The authors' message rings loud and clear to *360*. That is, doctors should be aware of the possibility of major bone loss after chemotherapy leading to a risk of pathological fracture. Vitamin D deficiency, calcium malnutrition, and lactose intolerance may potentiate the negative effects of chemotherapy, and should be considered in long-term patient management.

REFERENCES

1. **McNally RJ, Blakey K, Parslow RC, et al.** Small-area analyses of bone cancer diagnosed in Great Britain provide clues to aetiology. *BMC Cancer* 2012;12:270-270.
2. **Bernthal NM, Federman N, Eilber FR, et al.** Long-term results (>25 years) of a randomized, prospective clinical trial evaluating chemotherapy in patients with high-grade, operable osteosarcoma. *Cancer* 2012;(Epub ahead of print) PMID: 22648705.
3. **Frisoni T, Cevolani L, Giorgini A, Dozza B, Donati DM.** Factors affecting outcome of massive intercalary bone allografts in the treatment of tumours of the femur. *J Bone Joint Surg [Br]* 2012;94-B:836-841.
4. **Biau DJ, Ferguson PC, Chung P, et al.** Local recurrence of localized soft tissue sarcoma: a new look at old predictors. *Cancer* 2012;(Epub ahead of print) PMID: 22648518.
5. **Puri A, Gulia A, Jambhekar N, Laskar S.** The outcome of the treatment of diaphyseal primary bone sarcoma by resection, irradiation and re-implantation of the host bone: extracorporeal irradiation as an option for reconstruction in diaphyseal bone sarcomas. *J Bone Joint Surg [Br]* 2012;94-B:982-988.
6. **Chen Y, Yang Y, Yuan Z, Wang C, Shi Y.** Predicting chemosensitivity in osteosarcoma prior to chemotherapy: An investigational study of biomarkers with immunohistochemistry. *Oncol Lett* 2012;3:1011-1016.
7. **Pirker-Frühauf UM, Friesenbichler J, Urban EC, Obermayer-Pietsch B, Leithner A.** Osteoporosis in children and young adults: a late effect after chemotherapy for bone sarcoma. *Clin Orthop Relat Res* 2012;470:2874-2885.