ROUNDUP360

Oncology

More is not always better, especially when its chemotherapy

The biggest revolution in the past 20 years for patients with bone tumours of any type is the development of effective adjuvant and neo-adjuvant chemo and radiotherapy, with improved survival and lower recurrence rates. We were delighted here at *360* to read the report from one of the Italian sarcoma group's trials. Researchers in **Bologna (Italy)** have designed a trial comparing two different chemotherapy regimes. In one arm patients had a standard methotrexate, cisplatin and doxyrubicin combination and in the other arm the addition of routine ifosfamide in patients with non-metastatic extremity primary osteosarcoma. The researchers designed a randomised controlled trial (Level 1 evidence) with patients randomised to the two treatment regimens. In both arms patients received the same cumulative dose of agents (ADM 420 mg/m^2, MTX 120 g/m^2, CDP 600 mg/m^2). In one arm patients received the ifosfamide only if they had a poor response post-surgery whilst patients in the other arm received the ifosfamide primarily. The study team enrolled a hugely impressive 246 patients between 2001 and 2006 and were able to achieve limb salvage in nearly 95% of patients. There were no differences in salvage rates or chemotherapy induced necrosis rates of about 45%. However there were significantly higher rates of toxicity in those receiving ifosfamide (including 3 deaths). The most important finding was similar overall five year survival rates (74% vs 73%) and event free survival rates (64% vs 55%). Although not significant event free survival was better in patients without primary ifosfamide use.[1] We were delighted to see a well conducted study evaluating some of the newer chemotherapy regimes. It is encouraging to see such impressive results of 74% survivorship at 5 years. The researchers conclusively demonstrated no better survivorship with the addition of the 4th agent. In light of these findings their report of higher toxicity without improved survival it seems likely to us at *360* chemotherapy regimes are starting to reach the ceiling of the toxicity/efficacy curve, and perhaps future research should be aimed at reducing the cytotoxic effects of chemotherapy regimens.

New hope for skeletal metastasis

Skeletal metastases present a complex and increasingly common problem with patients surviving almost universally longer with nearly every primary cancer diagnosis. Aside from the disease burden of pathological fractures the systematic biochemical complications are difficult to manage and medical management with zoledronic acid may be suboptimal. Researchers in **Houston (Texas, USA)** have investigated the potential benefits of denosumab, a RANK-L antagonist. They aimed to establish the relative efficacies of zoledronic acid and denosumab with both fractures and pain. The authors report a phase 3 drug trail to establish the efficacy of denosumab in treating both of these end points. Patients included in the study all had solid tumours or multiple myeloma. Patients were randomly allocated to treatment with either therapy or placebo. Denosumab significantly reduced the risk of the patient requiring palliative radiotherapy (a reduction of nearly 22%) and prevented worsening of pain and stronger analgesia requirements when compared to zoledronic acid and placebo. This improvement in pain however was not matched with similar improvements in health related quality of life scores. The results of this study suggest that in terms of reducing skeletal related events (SRE) 3 patient years of therapy (*versus* placebo) and 10 patient years of therapy (*versus* zoledronic acid) will treat a single SRE.[2] It is rare for orthopaedic surgeons to be particularly interested in the development of new drugs, however we at *360* feel this is a very significant study which could have implications not only in cancer related treatments. Denosumab has clearly been shown to be an effective therapy for treating the sequelae of solid tumour metastasis and myeloma. Not only is this key in reducing the need for orthopaedic interventions in palliative care patients but also may have implications in a range of other orthopaedic pathologies. Denosumab is a RANK ligand antagonist which has been implicated in the macrophage mediated osteolysis cascade. Could this trial herald the beginnings of medical therapy to prevent loosening of arthroplasties? We don't expect this to be a rapid development, but this is a very tempting prospect.

To excise or not to excise? Biopsy tracts under the spotlight

Orthopaedic oncology, like all other subspecialities, has a number of 'golden rules'. In many centres throughout the world the careful positioning of the biopsy tract and subsequent excision with definitive surgery has been a central principle to reduce local recurrence rates. Our interest was piqued at *360* by an interesting study setting out to challenge that age old wisdom. Researchers in **Tampa (USA)** examined the rates of recurrence following core needle biopsy for extremity sarcoma. The group designed a retrospective case series (Level IV evidence) to examine the rates of recurrence in stage III extremity sarcomas following biopsy and definitive surgery without excision of the biopsy tract. They included patients treated in a single unit over a 10 year period. All patients had a diagnosis of extremity sarcoma, which were at least 5 cm in size, high grade and stage III tumours. All patients received similar treatment of core biopsy, excision with wide local margins and adjuvant chemo or radiotherapy. However the biopsy tract was not excised during definitive surgery. They report the results of 59 patients, 57 (97%) patients underwent adjuvant or neo-adjuvant radiotherapy and 49 (83%) received additional chemotherapy. Patients were followed up to a minimum of 12 months and a median of 24 months. The investigators

report a low local recurrence rate of 9% with 15 patients (25%) developing metastasis after diagnosis.[3] The results presented represent very similar rates of recurrence and metastasis for this highly malignant diagnosis to others in the literature. The authors therefore conclude that excision of the biopsy tract is not required. Whilst this paper does cause pause for thought, and re-examination of accepted wisdom is always something we like to see at *360* we would offer a note of caution. This study has no comparator arm, and recommends a change in accepted practice without any real foundation. Perhaps the surgery or oncology input here was of particularly high standard offsetting any potential disadvantage of leaving the biopsy site. Most importantly as excision of a carefully placed biopsy site carries no additional morbidity even in light of this study this remains the standard of care.

Intra-operative Imaging of sarcomas

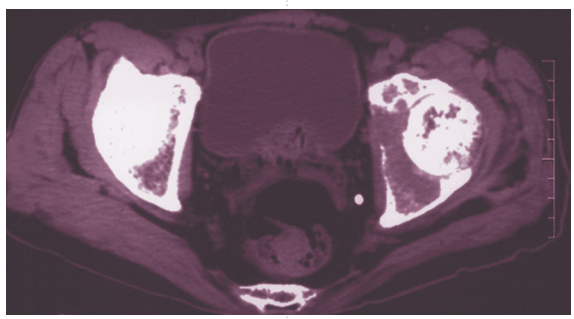
■ Complete excision of the tumour bed has been shown over and over again to be the most important factor in determining outcome. To ensure clear margins and appropriate excision general surgical oncologists have employed methods such as in theatre mammography and PTH biochemistry in parathyroid surgery. No such advantage has been afforded the orthopaedic surgical oncologist to date. An innovative technology reported by researchers in **Durham (USA)** describes the use of an on-table technique to image the tumour bed with the aim of ensuring clear resection margins. The technique involves use of a cathepsin activated probe and then use of intraoperative fluorescence to ensure complete excision. The investigators describe the use of the device in dogs with naturally occurring sarcomas. Nine animals undergoing surgical excision of 10 mast cell tumours were administered a cathepsin fluorescent probe prior to wide local excision under general anaesthesia. After excision the tumour bed was scanned for residual fluorescence and further surgery undertaken if required. The animals were followed up to minimum of 9 (mean 12) months. In 9 cases the intra-operative fluoroscopic imaging reflected the eventual histology with clear resection margins. There were no noted recurrences at final follow up.[4] Here at *360* we were excited by this study, although some way from clinical application in humans this technology offers the tantalising promise of on-table assessment of resection margins. Using this technique the authors achieved 90% clear margins, some way below the current accepted standards. However, we look forwards to reading safety reports for the contrast and first in man studies of this exciting new technology.

Curettage with adjuvant therapy enough for fractured giant cell tumours?

■ One of the most tricky clinical decisions in treating giant cell tumours is what to do with those patients presenting with fractured tumours. As approximately 20% of patents presenting with giant cell tumours do so with a fracture it is all the more surprising that there remains inconsistency in the orthopaedic literature as how best to treat these patients. Is curettage enough, or is en-bloc resection required? A research team in **Leiden (The Netherlands)** aimed to shed some light on this age old dilemma by sharing the results of their own retrospective series (Level IV evidence) of 48 patents treated over an 18 year period, followed up to a minimum of 2 years (mean 8.5 years). They aimed to report the success (recurrence rates), surgical complications, fracture healing and function with both treatment modalities. The initial treatment was curettage in 25 patients and en-bloc resection in 23. The method of treatment did not appear to affect the likelihood of fracture union with healing occurring in all bar one patient. However the results differed substantially with regards to every other aspect of treatment. The patient group undergoing curettage suffered a 30% recurrence rate (with no recurrences in the en-bloc group) but higher functional scores (Musculoskeletal tumour society score 25 *vs* 28) and complications (5% vs 16%). The recurrences occurred almost exclusively in patients with soft tissue extension.[5] The authors make the sensible conclusion that curettage and adjuncts are suitable for patients without soft tissue extension to maximise functional score and reduce complications.

Amputation may be a step too far for distal tibial osteosarcoma

■ The established and accepted treatment for distal tibial osteosarcoma is amputation due to the combination of difficult reconstruction and high rates of recurrence. With advances in surgical technique it has become possible to reconstruct patients with these difficult to treat tumours. However with a lack of evidence it has remained somewhat opaque to us here at *360* as to which is the better option. A research team in **Bologna (Italy)** has attempted to shed some light on the topic by reporting their experience of limb salvage and amputation in a retrospective comparative case series (Level III evidence). The research team reported the results of 42 patients presenting with distal tibial osteosarcoma over a 15 year period, and sought to determine outcomes in terms of survival, local recurrence, function and complications. Of the initial 42 patients 19 underwent primary amputation and 23 had limb salvage and reconstruction using allograft. Patients were followed up to a median of 60 months (minimum 8) and tumours were graded with Broders classification and staged using the Musculoskeletal Tumour Society and American Joint Committee on cancer systems. As would be expected in a series of this nature patients undergoing amputation had higher grade tumours. The major finding of this study was a similar survivorship of patients (84% limb salvage *versus* 74% amputation). Those patients having reconstruction had higher MSTS functional scores (76% *versus* 71%) and a similar incidence of complications. There were 3 local recurrences in the reconstruction group and a similar incidence of complications.[6] Although far from conclusive this study does raise interesting questions about that accepted standard treatment of amputation for distal tibial osteosarcoma. Here at *360* it seems to us that this study suggests limb salvage may well be justified and lead to better functional outcomes without jeopardising survival. Perhaps as more of these procedures are performed it will become clearer which should be the preferred option.



Diaphyseal tibial tumours revisited – what is the value of vascularised fibula graft?

■ In the last edition of *360* we reported on the results of reconstruction of large bone defects with surgeons in **Mumbai (India)** reporting an en-bloc resection technique with preservation of adjacent joints.[7] They reconstructed with the sterilised tumour bone after subjection to 50 Gy of extracorporeal radiation. In their series of 32 prospective patients the authors reported three local (9.7%) tumour recurrences at 34 months follow up. In the scarce few weeks since our last edition a similar case series of patients with similar tumours has been reported by researchers in **Montreal**

(Canada). They report 15 patients treated with excision and reimplantation this time with a vascularised ipsilateral fibula graft as an augment. Patients were followed up to a mean of 5 years, and although 7 required reoperation the authors reported no recurrences. The functional results were surprisingly similar in both studies (musculoskeletal tumour society scores of 26 and 27).It is striking to see two papers using a similar technique of irradiation and reimplantation of diaphyseal bone with similar functional results in the short term. It would be difficult based on this data to decide if the increased morbidity associated with vascularised fibular graft is justified in this diagnosis. Perhaps the authors should both update their reports at ten years of follow up. This may then reveal the answer.[8]

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