ROUNDUP360

Oncology

Anaesthesic modality does not affect outcomes in tumour surgery

There is plenty of preclinical and basic science evidence to suggest that tumour growth increases at times of surgical stress. The combination of relative immunosuppression, use of volatile anaesthetics, opioid analgesics, and blood transfusions (which in themselves have a profound immunomodulatory effect) have all been shown to have a potential permissive effect on tumour growth. Basic science evidence would suggest that the overall effect of the peri-operative period on cancer biology is tumorigenic and immunosuppressive. Different anaesthesia strategies can ameliorate the surgical stress response, and, theoretically at least, may result in a narrower window for cancer cells to seed, invade, and proliferate. Researchers in **Houston (USA)** undertook a systematic review based on this theory to establish if there was any evidence that anaesthesia and peri-operative care might affect tumour outcomes in the longer term.[1] Due to the limited reports of orthopaedic tumour survival, the investigators included studies with data on breast, gastrointestinal and genitourological tumours. They undertook a thorough literature review using a range of search terms to identify a total of 836 studies, of which 693 did not yield useful information and were therefore rejected. Surprisingly, of the remaining 143 studies, the authors were only able to include data from 13 articles and there was so much heterogeneity in the study design that meta-analysis would be inappropriate. There were no eligible studies that directly addressed the question of whether regional anaesthesia and analgesia conveyed a potential survival benefit after musculoskeletal cancer surgery. There were some studies (one breast cancer survival and some preliminary studies in gastrointestinal and genitourinary surgery) which suggested a potential benefit of regional anaesthesia on tumour-free survival after oncological surgery in those patient populations. The authors conclude that there is currently little clinical evidence to support the hypothesis, although given the strong pre-clinical data and suggestive clinical data and despite no studies specifically examining this potential method for improving survival, we do wonder if a properly designed study is warranted.

Infection predictors in orthopaedic oncology

Despite the relatively high rates of infection in orthopaedic oncology surgery, the predictors of infection are poorly studied other than in reconstructive arthroplasty. The nature of the surgery with large incisions, long and complex operations on locally and often systemically immunocompromised patients predisposes to this high rate of infection. Researchers in **Kagoshima (Japan)** set out to establish the rates of infection in a relatively large cohort of 457 cases.[2] Of these consecutive patients, the majority were benign (n = 310) with 147 malignant cases. This detailed retrospective cohort study included analysis of pre- and post-operative haematological and biochemical results, and patient, surgical and tumour risk factors for infection. The researchers identified a rate of infection of just 0.32% in benign tumours, but 12.2% in malignant cases. They identified surgical time, chemotherapy, implants and blood loss as potential risk factors for post-operative infection and propose the musculoskeletal oncological surgery invasiveness (MOSI) index. Their score is calculated using four risk factors: blood loss, operation duration, pre-operative chemotherapy, and the use of artificial implants. One of the most interesting findings of this study is the threshold values used, with duration of surgery at 355 min (far longer than the average four-hour duration) and blood loss of just 190 ml. The authors conclude that the MOSI is a helpful score with infection rates of over 35% in patients with higher MOSI scores (3 or 4 points). While a very interesting paper, here at *360* we have some concerns about scores produced in this manner. The nature of any form of predictive score with a heterogeneous population is that it is likely that covariate factors will interact. Although these are interesting observations of longer surgery, blood loss, chemotherapy and implant reconstruction, this could also be explained by the confounder of lesion type. Benign lesions usually require shorter surgery, lose less blood, and do not require prosthetic reconstruction or chemotherapy (and in this series have infection rates of < 1%). We wonder here at *360* if this may be a topic that requires revisiting.

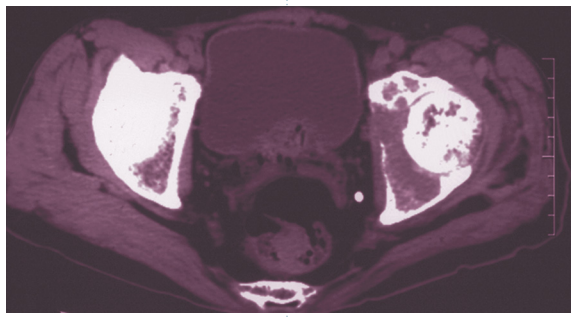
Sarcoma depth unimportant in survival

Accumulated wisdom is important in surgical practice. A combination of research, experience and teaching guides most of our clinical practice. One of the tenets of soft-tissue sarcoma decision making (central dogma if you will) is that the depth of the lesion has a profound effect on prognosis. Researchers at the **Aarhus Sarcoma Centre (Denmark)** are, like many of our Scandinavian colleagues, in the enviable position of having access to almost complete population healthcare records for a very stable national population.[3] These authors set out to re-examine some of the central orthopaedic oncology dogma and designed a study with the aim of establishing prognostic factors for survival following diagnosis of soft-tissue sarcoma in a validated, population-based 30-year study. Their study population consisted of 922 adult patients from western Denmark, all with non-metastatic soft-tissue sarcoma (STS) in the extremity or trunk. The authors used a proportional hazards model with complex statistics to adjust for confounders and produce a competing risks model. Their data set included a range of patient, tumour and demographic information. They

paid specific attention to the tumour factors including size, grade, surgical excision margin and radiotherapy administration, and found that all of these factors were predictive of both disease-specific mortality and local recurrence rates. The anatomical location was prognostic for disease-specific mortality, but not local recurrence rates. Their population-based study suggested an overall five-year local recurrence rate of 16% and a five-year specific mortality of 24%. However, the depth of the tumour itself was not a prognostic factor for local recurrence or indeed disease-specific survival.

Photon/proton radiotherapy surprisingly effective in chondrosarcoma control x-ref

The ongoing evolution of adjuvant and neo-adjuvant treatments has continued to improve outcomes in all varieties of tumour surgery. This is particularly important in certain varieties of musculoskeletal tumour surgery where 'clear margins' are sometimes impossible to obtain. Many types of spinal malignancy (and in particular sarcomas) cannot be treated with clear margins due to invasion of or proximity to the spinal cord. Researchers in **Boston (USA)** have investigated the optimal treatment in the particularly difficult area of spinal sarcomas where adjuvant radiotherapy (RT) is often recommended but total tumour radiotherapy dose may be constrained by tissue tolerance of the spinal cord, nerve, and viscera.[4] These researchers designed a prospective phase II clinical trial incorporating high dose RT. The inclusion criteria included patients with primary or local recurrence of chordomas or sarcomas. Patients were treated with pre- and/or post-operative photon/proton RT with or without radical resection. The investigators were able to report the results of 50 patients, of whom half underwent total resection and the remainder either subtotal (n = 12) or biopsy (n = 3). The patient cohort included a variety of tumours (29 chordoma, 14 chondrosarcoma, 7 other), and radiotherapy regimes were either lower dose (< 72 Gy) or higher dose (76.6 to 77.4 Gy). Outcomes were assessed using actuarial local control rates at over seven-year median follow-up. Local control rates were high, reaching 94% at five, and 85% at eight years of follow-up for primary tumours (81% and 74%, respectively, for the whole cohort). The risk of significant late morbidity was just 13% and there were no cases of myelopathy, although three cases of neurological toxicity were seen in the higher radiotherapy dose group. This interesting paper supports the use of high dose photon/proton radiotherapy in the management of otherwise difficult to treat spinal chordomas and chondosarcomas. The local control rate is impressive with an acceptable later morbidity.



Total humerus replacement a success!

Reconstruction of advanced humeral disease is a challenging and difficult procedure. One possible approach is the 'total humerus replacement' and although this is a widely recognised technique, there is very little published in the academic literature surrounding outcomes and techniques for endoprosthetic replacement. Surgeons in **Birmingham (UK)** have what must be one of the largest series of such patients having undertaken 34 total humerus endoprosthetic replacements.[5] They have published their experience with this challenging and poorly reported technique to assess longevity, complications and clinical outcomes (musculoskeletal tumour society score (MSTSS)). This retrospective series includes 34 patients (10 male, 24 female) with a mean age of 26 years (7 to 86) and, as would be expected, a variety of diagnoses (including Ewing's, metastatic carcinoma and chondrosarcoma). In the vast majority of cases primary reconstruction was undertaken with endoprosthesis, but in five cases this was used as a salvage option after other reconstruction options had failed. The authors report a follow-up to a mean of 8.2 years, by which point there were 16 patients available for follow-up with no evidence of disease. Cumulative ten-year survival was 90% according to Kaplan–Meier analysis. Complications included infection in four patients, radial nerve palsy in a single case and proximal prosthetic migration in three. Although one might expect such major surgery to have very poor long-term outcomes, the functional outcomes assessed by the MSTSS were a mean of 83% (60% to 93%). Although the authors comment that "from this small, preliminary report, we suggest that total humeral endoprosthetic replacement may be a reasonable option of reconstruction", we would be more enthusiastic here at 360. Reports of significant advanced upper limb tumours requiring this form of reconstruction are few and far between and this represents some of the best evidence base with acceptable long-term survivals and excellent functional outcomes.

LDH simple predictor of survival in sarcoma x-ref

Prediction of survival in all forms of cancer is important, not just for patient peace of mind, but also for decision making in terms of reconstructive options. While a large number of individual studies have highlighted the potential importance of lactate dehydrogenase (LDH) in osteosarcoma patients, there are a range of inconsistent and potentially inconclusive clinical results. A review team from **Shanghai (China)** have set out to establish the value of LDH as a biomarker for prognosis in all types of osteosarcoma.[6] The review team undertook a comprehensive analysis of medical indices (including PubMed, Embase and Web of Science). The study team used contemporary methodology to establish a pooled hazards ratio for overall survival and hence the prognostic role of LDH. The study team were able to include reports of 943 osteosarcoma patients published over ten studies over a six-week period. The authors undertook pooled data analysis and calculated a combined hazard ratio of survival with high LDH level as 1.92 (95% CI 1.53 to 2.40). While the authors concluded that high serum LDH is associated with lower overall survival, they did comment that further analysis of the data does suggest that there is a risk of publication bias in the published studies so these results should be interpreted with a note of caution.

Denosumab again!

Excitement continues to run at fever pitch surrounding the use of the 'magic bullet' for giant cell tumours, denosumab. Giant cell tumour of bone (GCT) is an osteolytic tumour which has been shown in recent studies to be extremely sensitive to denosumab (monoclonal antibody to receptor activator of nuclear factor κB ligand (RANKL)). Researchers in **Mallorca (Spain)** have performed further analysis of data from an ongoing, open-label study.[7] The focus of their study was on the efficacy of denosumab in terms of pain and analgesic use in patients with GCT. The study included patients with unresectable GCT (n = 170) and a further group of those with resectable disease where planned surgery would

be associated with severe morbidity. In all cases patients underwent denosumab therapy and reported their outcomes with the Brief Pain Inventory-Short Form (BPI-SF). Around a third of all patients reported a clinically relevant improvement in their pain scores with commencement of denosumab, although the unresectable patients did slightly worse than the morbidity with resection group (29% vs 35%). The results, however, continued to improve and over 50% of patients in each cohort had improvement at each subsequent clinic visit. The median time to improvement was between 15 and 30 days and results were similar for those with moderate and severe pain at baseline, with very few patients requiring 'top-up analgesia'. These results strongly support the use of denosumab to achieve experienced clinically relevant improvement in pain from GCTs within two months.

Oops procedures in triplicate

Although commonly acknowledged to occur, there is surprisingly little known about prognosis following inappropriate surgical procedures (either incomplete resection, erroneous surgical procedures or, at the other end of the spectrum, misdiagnosis). Three articles have caught the eye of the *360* editorial board this month looking at this precise theme. Firstly, researchers in **Seoul (South Korea)** have investigated the impact of erroneous surgical procedures in high grade osteosarcoma.[8] A review of 240 serial admissions revealed that around 10% (n = 26/240) had undergone an erroneous procedure due to misdiagnosis. The investigators case-matched 38 patients to as many variables as possible in an attempt to establish a comparative case cohort, with 19 patients in each group. Erroneous procedures were generally performed in older patients with smaller non-osteoblastic lesions in an unusual location. Surprisingly, the investigators found that after adjustment for confounding variables by propensity score matching, there were no differences in either event-free or overall survivals. In a similar, but much larger study of 95 patients, researchers in **Birmingham (UK)** set out to examine those who underwent a surgical procedure where sarcomas were found unexpectedly.[9] In this rather large series of patients, local recurrence arose in 40% who underwent limb salvage surgery *versus* 12% who had an amputation. Although amputation was able to achieve local control, the overall survival was worse for patients treated with amputation (54% vs 75% five-year survival). The authors conclude that limb salvage in this group of patients is associated with a higher rate of inadequate marginal surgery and, consequently, higher local recurrence rates than amputation, but should still be attempted whenever possible as local control is not the primary determinant of survival when an 'oops manoeuvre' has already been performed. In a third take on this highly controversial topic, researchers in **Nagoya (Japan)** have aimed to establish if outcomes of 'unplanned' excision can be improved with 're-excision' in a tumour unit.[10] They evaluated the outcomes of 113 patients with soft-tissue sarcoma who had undergone unplanned excision over a 14-year period. The overall long-term survivals were excellent although those patients with residual tumour were found to have a poorer long-term survival after re-excision. These three papers add considerably to the volume of knowledge of patients who have had an inappropriate initial operative intervention. Patients certainly do not do as poorly as would initially be expected, although further surgery (either with re-excision or amputation) seems to be appropriate in nearly all of these cases.

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