ROUNDUP360

Oncology

Margin for error?

The most devastating consultation for a cancer patient is the one where they have to be told, 'we didn't get clear margins'. Surgeons and patients both regard this as a likely surgical failure; and one with little room for manoeuvre. We were intrigued, therefore, to encounter a novel approach to improving surgical outcomes. A research team in **Paris (France)** used continuous monitoring, combined with the use of the cumulative sum test (CUSUM), which is a statistical process control method. They set a target performance of 5% of cases with positive margins or tumour contamination. They prospectively evaluated patients undergoing primary excision of sarcomas and evaluated the macroscopic and microscopic appearance of the surgical excision margins. This was undertaken at regular consultations to establish the reason(s) for failure. The study included 146 patients undergoing sarcoma excision; 106 soft-tissue and 40 bone resections. There were six cases (4%) where the surgical result was considered inadequate. Two of these patients had inadequate margins and only one had tumour contamination. The surgical team, not unreasonably, considered their performance to be adequate on all counts.[1] We were really interested to read this report of using a novel statistical technique to approach a common and difficult-to-solve problem: how do we assess performance? With the ongoing push towards evidence-based health care and performance metrics it is refreshing to see a simple and easy approach to quality assurance. Perhaps we should all be 'CUSUM'ing, and not just in tumour practice.

New money for old risk factors?

Some things are sacrosanct and become enshrined in orthopaedic doctrine. The worst offenders for lack of contemporary scrutiny are the lists learned avidly for the boards or fellowship exams. Known risk factors for recurrence, failure of fixation, poor prognosis, etc, are rarely revisited after the initial (often slightly dated) papers that propelled their particular soundbite of information into the collective orthopaedic consciousness. With this in mind, a research team from **Toronto (Canada)** set out to re-examine a number of previously accepted risk factors for predictors of local recurrence for soft-tissue sarcomas. The researchers used up-to-date research methodology to allow adjustment for confounding interactions using a competing risks model. Their study included 1668 patients with a localised soft-tissue sarcoma of the extremity or trunk, all of whom were evaluated for all of the known risk factors. The outcome of interest was the cumulative probability of local recurrence per category of relevant predictors, with death as a competing event. The researchers established those factors with the most significant impact on tumour recurrence. The most strongly predictive risk factors were tumour size (hazard ratio (HR) 3.3), depth (HR 3.2) and grade (HR 4.5). These were most likely to introduce competition to the model, indicative of these variables having an effect on metastasis. Local recurrence was predicted by a slightly different group of variables. As one would expect, the adequacy of excision (margins HR 3.3) and presentation of tumour (grade HR 2.1, presentation status HR 2.4, depth HR 1.5) were strong determinants of the likelihood of local recurrence. The research team identified a statistically significant different probability of local recurrence at ten years with both presentation status and surgical margins. However, due to the competing effect of death, other factors did not affect local recurrence rates at ten years (tumour depth, size and grade).[2] The authors of this interesting study conclude that due to the competing effect of death, local recurrence management should be based on presentation status and surgical margins rather than other previously implicated factors. We read this with interest at *360*. Not only does this study have implications for planning the management of patients at risk of local recurrence, but with the ever more complex biostatistical models we are able to apply to clinical problems it has become increasingly easy to attribute the effects of covariates on different outcomes. Both the positive and negative findings of this study are interesting. Perhaps in addition to the authors' conclusions, the ability to distinguish between risk factors likely to result in death could be used to tailor more aggressive surgical and chemotherapy treatments to improve outcomes in those with the poorest prognosis.

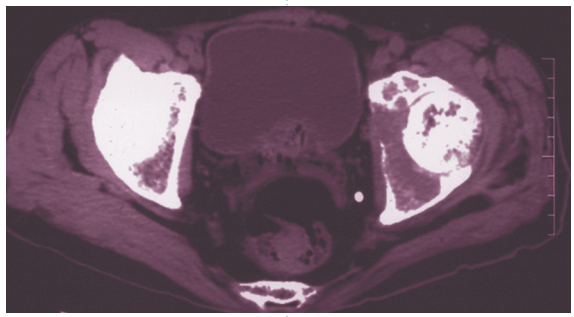
Hindquarter amputation: sometimes necessary

In the past 20 years, much of the focus in orthopaedic oncology has been on the use of limb-sparing surgery in combination with adjuvant and neo-adjuvant chemo- and radio-therapies to reduce the morbidity associated with bone and soft-tissue tumour surgery. With this in mind we read this article from **Birmingham (UK)** with much interest. The authors reviewed 157 hindquarter amputations, perhaps the most debilitating orthopaedic procedure, performed in their institution over a 30-year period, to attempt to establish the indications and outcomes of this procedure. This was the primary treatment modality in just 17% of pelvic sarcomas. They aimed to achieve remission in 140 patients, and palliation in 17. In this series, hindquarter amputation was used as a primary treatment modality in almost 60% of cases and for salvage of a previous procedure in 40% of cases. The authors performed primary amputation for large tumours where limb salvage was not feasible, and this group of patients suffered a 1.3% mortality rate and 71 patients had major complications (41% of which were related to wound healing or infection). The overall five- and ten-year survivals were 45% and 38%, respectively, and local

recurrence was seen in 23 patients (15%) during the study. However, although survival rates were high, the researchers did find phantom limb pain to be a significant problem with only 20% of patients using their prosthesis regularly, achieving a functional score of 57%.[3] To cut to the chase we are slightly surprised, here at *360*, to see the fantastic survivorship results this surgical group were able to obtain. It certainly seems that in some circumstances radical amputation including hindquarter are not only justified but can lead to long-term remission, but based on this study careful patient selection and counselling is required given the relatively poor functional results.

Custom tumour jigs?

We are having an industrial revolution in orthopaedics. Gone is the simple carpenter armed with a few jigs, saw, rasps and a limited inventory. Most definitely in fashion are computers, robots, computer-guidance and customised implants, all of which are struggling to find their place in an increasingly competitive market. Each of these technologies offers a slightly different potential advantage but at the cost of greater expense and additional complexity. In a marketplace with multiple new technologies looking to gain traction, a particularly novel use for custom jigs caught our eye, here at *360*. In the setting of tumour excision and prosthetic replacement, failure to adequately localise the tumour can lead to excessive undiseased tissue loss or compromised margins or poor prosthesis function. A surgical team in **Stonybrook (USA)** report on a (to our knowledge) unique approach to this problem. They devised a system using pre-operative CT images to manufacture custom CAD-CAM jigs. The jigs were designed to fit precisely onto the morphology of the bone at the desired resection level and thus guide the cutting location. They report a cadaveric case series using six matched pairs of femurs. Following a CT scan and pre-operative planning exercise custom jigs were manufactured to conform to a specific location on the femurs. A joint-sparing hemimetaphyseal resection was performed on the test femur with the jig and on the matched control femur, a traditional manual technique was used. The authors then used pre- and post-operative images superimposed to assess the accuracy of the resection. They established that across all six patients the mean deviation from pre-operative plan was by 9 mm in the manual group compared with 2 mm in the jigged group. Similarly, the maximal deviations were much smaller in the jigged *versus* the manual groups (3 mm deviation, 100% *versus* 5.6% and 4 mm deviation, 72% *versus* 0%).[4] The study team have laid an excellent foundation for the use of this technique in the clinical setting. We congratulate them on their fantastic innovation and look forward to the first clinical reports of the use of this technique.



Preserving the tibial epiphysis

Resection of the proximal tibial epiphysis is considered necessary in some limb-preserving tumour resections, but can result in significant morbidity and necessitates the use of a 'growing' prosthesis or contralateral epiphydesis, particularly in younger children. Researchers from **Budapest (Hungary)** have been developing a technique to preserve the proximal tibial epiphysis. They hope that by doing so they will allow for better knee function. This certainly seems an attractive option. The authors report a prospective case series (Level IV evidence) of five patients, three with Ewing's sarcoma and two with osteosarcoma with an average follow-up of around five years (3.5 to eight), all of whom underwent epiphysis-sparing surgery. Their technique involved resection at, or just below, the line of the growth plate with a distal diaphyseal resection and subsequent interposition grafting of both contralateral and ipsilateral fibular grafting, with fixation maintained using an Ilizarov ring. During the follow-up period there were no episodes of recurrence and there were no cases of failure of the free fibula graft fixation. They report excellent joint-specific outcomes with an average flexion of 122°, and that all patients were able to walk fully weight-bearing (although three require an orthosis). The procedure was, however, not without its complications, and three patients sustained fracture of the free fibula graft and there was one case of osteomyelitis.[5] It is always a balance between function and morbidity in limb-preserving surgery. While the authors have clearly demonstrated that this technique is possible and that a preserved knee joint can provide better long-term function, it is important to remember that this series does present an 80% complication rate. Here at *360* we would withhold our judgement until a larger series of patients are reported, hopefully with a lower complication rate, this series does, after all, represent the beginning of the learning curve. A promising prospect, but more evidence is definitely required to establish if this is a triumph of technique over sense or if there really is the prospect of better function here.

How long is long enough?

It is a central tenet of orthopaedic tumour surgery, and orthopaedic surgery in general, that long bone metastases that are either fractured or in danger of becoming so should be stabilised with a method that protects the whole bone. This practice is so enshrined in orthopaedic dogma that woe betide anyone who does, or suggests doing, anything else at the morning trauma conference. However, here at *360* we are not interested in dogma unless it is based in truth. There are some significant potential disadvantages to the protection of the whole bone: risk of fat emboli, higher rates of intra-operative complications, restricted surgical options and a higher incidence of complications, to name just a few. Researchers in **Chicago (USA)** posed a very rational question, and challenged the accepted status quo: is the rate of subsequent re-metastasis high enough to warrant skeletal stabilisation of the whole bone? They designed a retrospective case series (Level IV evidence) and undertook a thorough chart review of 96 patients who underwent stabilisation of the femora for metastasis or haematopoeitic tumour deposits. They reviewed all notes and investigations subsequent to the surgical intervention to establish the rate of secondary metastasis. Of the 96 patients enrolled in the study, an 80% mortality rate was seen at 11 months, and 12% (11/96) experienced local recurrence or invasion following presentation. Of these, eight were local progression at the original site, two were progression of other pre-existing secondary lesions and only one developed a new lesion. The researchers noted that six patients underwent intervention for symptomatic failure, while 12 (12.5%) experienced embolic events from long bone nailing.[6] Although the authors did not perform limited fixation they do make the bold statement

that they believe it may be indicated. Based on the evidence they present here, we are inclined to agree with them. After all, only one patient developed a new lesion that was not visible on the initial radiographs and over 12.5% suffered embolic complications. Although there is no discrete evidence presented here that it would be safe to perform limited fixation, perhaps a carefully constructed RCT with limited fixation *versus* bone stabilisation is indicated.

Genomics and radiation-induced bone tumours

■ Bone tumours secondary to therapeutic radiotherapy are extremely difficult to treat and are often resistant to the majority of conventional therapies. The natural history of radiotherapy-induced bone sarcomas is that of a more aggressive local behaviour and higher resistance to conventional therapies. It is not entirely clear why this should be, and researchers in **Munich (Germany)** conducted an investigation to establish if this behaviour is related to the genomics of the tumour, or the condition of the host. The research team compared the genome mutations in secondary irradiation-induced bone sarcomas with those of the earlier primary sarcomas to give an indication of where the source of this aggressive behaviour lies. The team identified seven patients with radiation-induced sarcomas who had the preceding primary available for investigation. They used a genome-wide loss-of-heterozygosity analysis, using a single nucleotide polymorphism (SNP) approach. A more thorough analysis of copy changes at two specific distinct loci was also undertaken.[7] The authors identified a high level of genomic instability in the secondary osteosarcoma similar to that seen in primary tumour with a poor prognosis. They hypothesise that part of the reason for poor prognosis of these secondary sarcomas is due to the high rates of genetic instability and this certainly seems a rational explanation.

And finally India ink

■ It is widely accepted that following biopsy the entire biopsy tract needs to be excised to reduce the local recurrence rates. Not as simple as one might think. Surgeons from **Stanmore (UK)** reported a very simple method for identifying the biopsy tract at the time of definitive surgery. They reported that only 49% of patients (n = 22 of 45) had easy to identify biopsy tracts at definitive surgery in a short prospective study. Following the introduction of India ink marking, the repeat study of 55 patients yielded a 100% identification rate and the authors conclude, not unreasonably, that this would be a simple and valuable addition to many tumour surgeons.[8]

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