ROUNDUP360

Oncology

Peri-articular resection fraught with complications

Use of endoprosthetic replacement in tumour surgery has grown in popularity over the last few decades. One of the most challenging areas is in the use of prosthesis for peri-articular resection and reconstruction. Little is known about the overall complication rates and long-term results. Researchers in **Muenster (Germany)** set out to establish the exact survival and complication rates associated with this procedure, which is becoming increasingly common. They designed a study focusing on patients who had undergone extra-articular resection of the distal femur or proximal tibia followed by reconstruction with a tumour endoprosthesis. The study team were able to report the results of 59 patients aged a mean of 33 years (11 to 74). Patients had all presented with an initial diagnosis of malignant bone or soft-tissue tumours. Overall survival was estimated (Kaplan–Meier method) at 76% at just over four and a half years of follow-up. Infection was the most common post-operative problem with eight patients (14%) undergoing secondary amputation due to untreatable deep infection, and 37% (n = 22) of patients having established deep infection requiring revision during the observation period of the study. Implant survival was much worse than patient survival, with a survivorship of 48% (95% CI 34.8 to 62.0) at two years and 25% (95% CI 11.1 to 39.9) by five years post-operatively. Other causes of failure included a not insignificant incidence of aseptic loosening (17%) and peri-prosthetic fracture in six patients (10%). Surgery to change bearings was necessary in 12 patients (20%) and classed as minor revision by the study authors (but revision none the less). The patients achieved a mean Musculoskeletal Tumor Society score of 23 (10 to 29) and ten patients (17%) were found to have an extensor lag exceeding 10°.[1] Patients undergoing surgery for these kinds of tumours are known to have relatively high complications rates, and this paper would suggest higher than those with intra-articular resections. The rates of subsequent complication and amputation published here are not insignificant, with survival of the prosthesis at around one in four by five years. Despite this, patients are reporting functional limbs, just not long lasting ones.

Navigated margins

Surgical excision margins are one of the keys to success in complex tumour surgery. Patients with narrow margins or incomplete excision are known in virtually all types of tumour to have much poorer prognoses than those who have adequate resection margins. Researchers in **Birmingham (UK)** have experimented with the use of computer navigation in order to assist with achieving the gold standard 'complete excision'. The research team selected sacral and pelvic tumours as their clinical model, reasoning that the complex anatomy is associated with difficult intra-operative decision making. The study reports the use of navigation in 31 patients aged a mean of 53 years. All patients underwent primary resection of malignant pelvic or sacral tumours with the use of computer navigation-assisted surgery. The study group consisted of 23 primary bone lesions, four metastatic lesions and four locally advanced rectal tumours. The computer navigation system was able to register to within 1 mm in each case, and there were no complications recorded which were directly related to the navigation. Use of the navigation system allowed for preservation of sacral nerve roots (n = 13), resection of otherwise inoperable disease (n = 4) and avoidance of hindquarter amputation (n = 3). Clear bone resection margins were achieved in all cases and there was an 8.7% intra-lesional resection rate. The study was reported up to a little over a year, and by that stage three patients (13%) had developed local recurrence. The mean survival time from diagnosis was 17 months (4 to 48). The authors concluded that computer navigation-assisted surgery was safe and reduced their historic intra-lesional resection rate for primary tumours of the pelvis and sacrum.[2] Certainly there is food for thought here. It seems that application of this technique has allowed the Birmingham group to achieve nerve root sparing surgery and to undertake operations they would otherwise not have been able to do. Time will tell what effect, if any, the improved resection accuracy has on survival.

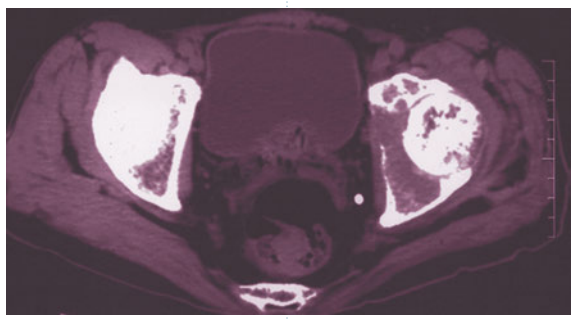
Still lagging behind primary arthroplasty

The tumour team in **Bologna (Italy)** have looked back at nearly 300 recent patients who have undergone tumour reconstructions with current-generation prostheses, in this case the Global Modular Replacement System (GMRS). This is a modular tumour endoprosthesis for application to the lower limb and may be used for primary bone tumour excision and secondary revision procedures. Given the huge leap forward in fixation methods and the convenience associated with modularity, it seems a good time for a retrospective performance review. The study team were able to assemble 295 prostheses that had been implanted over a four-year period. Primary bone tumour excision accounted for the majority of surgeries (n = 197), with the remainder (n = 98) being revision of previously failed prostheses. The revision procedures were mostly performed for failed tumour reconstructions (n = 84) although there were 14 cases of failure for other reasons. The reported series includes a complete range of anatomical sites (199 distal femur; 60 proximal tibia; 32 proximal femur; four total femur). Follow-up was to a mean of 4.2 years (2 to 8), and by that stage there was a failure rate pushing 30%, occurring at a median of 1.7 years. From an oncological standpoint the surgeries were a resounding success (195 disease-free, 43 disease-free after treatment of relapse, ten alive with

disease and 33 dead with disease). There were significant differences in implant failure and survival between primary and revision implants. There were no instances of prosthetic fracture during the study period and patients were able to achieve a mean functional score of 81.6%.[3] While the disease-free status for these patients is remarkably good, they are still understandably lagging behind patients undergoing surgery for primary osteoarthritis in terms of survival and functional scores.

Skeletal tumours and thromboembolism

■ Thromboembolic disease is a current high priority in many western healthcare systems, with the 'disease' of thromboembolism creating clinical and medical legal ripples across the globe. All patients who are high risk now routinely receive prophylaxis, but with improving surgical rehabilitation and a relatively low event rate in many branches of orthopaedic surgery, the risk of thromboembolic disease (and specifically pulmonary embolism (PE)) is surprisingly unknown. Orthopaedic oncology is an area possessing little data. With the twin risk factors of orthopaedic surgery and a tumour diagnosis, one would expect high rates of potentially fatal PEs. A research team in **Tokyo (Japan)** set out to establish if there was indeed a high risk of thromboembolic disease in orthopaedic oncology patients using a Japan-wide database (Japan Diagnostic Procedure Combination). The database included data on 3750 patients (1981 males, 1769 females) who underwent oncological surgery over a three-year period. Potential risk factors including gender, age, primary diagnosis, surgical and anaesthetic details and finally comorbidities were all collected. The analytical team undertook straight forward logistic regression analyses to establish any causal link between risk factors and PE development. Just ten patients (0.2%) were known to have developed a PE. With an event rate this low it is extremely difficult to come to any meaningful conclusions. However, the study team persevered and identified that potentially primary malignant bone tumours were associated with higher risk than soft-tissue sarcomas (OR 5.58). Bone tumour resection (OR 7.94) and prosthetic reconstruction (OR 9.15) were associated with a significantly higher risk of PE than soft-tissue tumour resection.[4] This study raises more questions than it answers as the authors (and indeed the readership) are likely to be flabbergasted by the low incidence of PE in this group. It does beg the question: what is special about this group of patients that they have such a low thromboembolic rate?



To our minds, it is meaningless to perform statistical analysis with such low event rates. A larger study is definitely required.

Conditional survival in Ewing's sarcoma

■ While benchmarks of treatment are measured as survival from diagnosis or initiation of treatment, patients, their carers, and doctors are often far more interested in the 'conditional survival'. Surgeons in **Iowa City (USA)** set out to establish what the conditional survival is for both osteosarcoma and Ewing's sarcoma. Conditional survival estimates the probability of ongoing survival given a known disease-free survival period, and answers the question: given that I've made x years without cancer, what are my chances of another y years? The research team used data collected as part of the Surveillance, Epidemiology, and End Results (SEER) programme which has been running since 1973 and included data from all patients under the age of 40 with a diagnosis of Ewing's sarcoma or osteosarcoma. The researchers used an actuarial life table method to determine cause-specific five-year survival estimates conditional on already achieving one to five years of survival after diagnosis. A similar analysis was also possible for 20-year survival given the large dataset and long-term follow-up associated with the SEER programme. Unsurprisingly, the research team established that the five-year survival improved for each year of survival following diagnosis. In patients with a local or regional osteosarcoma this estimated five-year survival improved from 74.8% at diagnosis to 91.4% when five years had already been survived. There was a similar picture with the Ewing's sarcoma patients improving from 72.9% at baseline to 92.5% at five years. As would be expected, the contrast was greater in patients with metastatic diseases (osteosarcoma 35.5% to 85.4% at five years; Ewing's 31.7% at baseline to 83.6% at five years). Patients who had survived ten years had an almost 90% cancer-related chance of surviving another ten years. While this is surprisingly high, it does emphasise the high rate of complications in patients who have been disease free for a decade, and in whom cancer-related complications can occur after presumed eradication.[5] This study presents extremely valuable data to guide patients and doctors surrounding the likelihood of conditional survival. It also underlines for us the importance of lifelong follow-up in patients with sarcomas who have an appreciable recurrence rate, even when free from disease for over a decade.

Reverse shoulders and tumour

■ It seems when reading the pages of the various academic journals concerning all things related to shoulder surgery, that there are few conditions that don't do better with a 'reverse' polarity shoulder replacement these days. From cuff replacement to fracture and neurological compromise, there are accumulating data that reversing the bearing may very much be the way to go. Surgeons in **Aarhus (Denmark)** have set out to establish what role (if any) there is for reverse shoulder replacement in proximal humeral tumours. The research team included 16 patients who underwent reverse arthroplasty following *en-bloc* excision of a proximal humeral tumour. There were ten patients available for final follow-up at just under four years of follow-up. Patients achieved nearly 80° of abduction and around 100° of forward flexion. Outcomes were generally excellent with a mean Musculoskeletal Tumor Society Score of 77% (60% to 90%). There was a single serious complication (deep infection requiring revision surgery) and two patients developed radiographic signs of loosening.[6] The additional flexibility for muscle resection provided by the reverse prosthesis offers significant advantages in cases of arthroplasty for tumour. We would not be at all surprised if use of the reverse prosthesis continues to grow in popularity for these kinds of cases.

For how long should we follow up sarcoma patients?

■ This is the second article aiming to shed light on the follow-up protocols for sarcomas without resulting in excess healthcare costs or putting patients at risk of undetected recurrence. Current guidance suggests that patients should be followed up for low-grade soft-tissue sarcomas every three to six months for two to

three years, and annually thereafter. For high-grade sarcomas the current guidelines suggest every three to six months for two to five years, then six-monthly for two years, and annually thereafter. The authors note (similarly to the authors of the previous Roundup) that there is little evidence to support this course of action. The research team in **Tokyo (Japan)** used a very similar methodology to their colleagues in Iowa and used a cancer registry stretching back to 1978. They aimed to evaluate timings of diagnosis, local recurrence, diagnosis of distant metastases and differences in those parameters based on tumour size and grade. The study team included all patients who were diagnosed with soft-tissue tumours and underwent surgical excision over a 30-year period (1978 to 2008). The research team were able to collate data pertaining to age, histologic diagnosis, grade of Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC), tumour location, and size. Follow-up was to a mean of six years (one to 30). Patients were all followed up according to the national Japanese guidelines (as outlined above). The study authors were able to report the results of 867 patients with a median age at diagnosis of 52 years. The authors used a different methodology to establish recurrence rates and used a rolling two-year time frame to calculate their recurrence rates per 1000 person-years. In their series, 11% (n = 98) of patients suffered recurrence at a median time of 19 months; 90% of patients who suffered recurrence did so within seven years and 95% within 8.6 years. Distant metastasis was suffered by nearly one in four patients and occurred sooner, at a median of 12 months; 90% of metastases had taken place by 4.2 years and 95% by 7.3 years. The authors conclude that "follow-up beyond 10 years does not yield a sufficient number of local recurrences or metastases to warrant further monitoring." Thus, we have two papers with large numbers, both coming to different conclusions about the follow-up of sarcoma patients. The Japanese tell us not to follow up our patients beyond ten years, while the Americans say we should.[7] It seems to us that this is all about how you spin the numbers; with such a large number of followed-up patients developing recurrence, < 5% of the original study population is the same as 10% of the surviving population. It seems sensible to use the denominator of currently surviving patients, meaning 10% will develop subsequent disease and therefore should be followed up.

Already metastasised?

The management of osteosarcoma is vastly different in patients presenting with solitary primary tumours and those presenting with metastatic disease. It can sometimes be difficult to identify patients who have metastatic disease at presentation, and the ability to identify patients who are most likely at risk of metastasis would aid decision making at diagnosis. The same team from **Iowa City (USA)** who set out to use the Surveillance, Epidemiology, and End Results (SEER) programme database, on this occasion use this data source to identify patients diagnosed with osteosarcoma between 2000 and 2008. Each patient was then sub-classified as having metastatic or localised disease at diagnosis. The authors collated a comprehensive range of patient, tumour and socioeconomic characteristics to determine which factors were most predictive of an increased rate of metastatic disease at presentation. There were 2017 cases of high-grade osteosarcoma, of whom nearly one in four presented with metastatic disease (n = 464). Using a logistic regression analysis, the authors identified a number of factors at presentation that were associated with a higher chance of metastasis; namely, age > 60 (OR 2.22), axial skeleton location (OR 2.47) and low socioeconomic status (OR 1.59). When combined in a multivariate model, all three factors remained significant. Not all patients had tumour size details recorded (n = 1398), but for those that did the odds of metastasis at presentation increased by 10% with each additional centimetre of tumour size.[8] This paper allows prediction of patients most likely to have metastatic disease at presentation. While it doesn't contain any radically surprising information in patients with large tumours at presentation, the clinicians should be vigilant for undiagnosed metastasis.

REFERENCES

1. **Hardes J, Henrichs MP, Gosheger G, et al.** Endoprosthetic replacement after extra-articular resection of bone and soft-tissue tumours around the knee. *Bone Joint J* 2013;95-B:1425-31.
2. **Jeys L, Matharu GS, Nandra RS, Grimer RJ.** Can computer navigation-assisted surgery reduce the risk of an intralesional margin and reduce the rate of local recurrence in patients with a tumour of the pelvis or sacrum? *Bone Joint J* 2013;95-B:1417-24.
3. **Pala E, Henderson ER, Calabrò T, et al.** Survival of current production tumor endoprostheses: Complications, functional results, and a comparative statistical analysis. *J Surg Oncol* 2013;108:403-8.
4. **Ogura K, Yasunaga H, Horiguchi H, Ohe K, Kawano H.** Incidence and risk factors for pulmonary embolism after primary musculoskeletal tumor surgery. *Clin Orthop Relat Res* 2013;471:3310-6.
5. **Miller BJ, Lynch CF, Buckwalter JA.** Conditional survival is greater than overall survival at diagnosis in patients with osteosarcoma and Ewing's sarcoma. *Clin Orthop Relat Res* 2013;471:3398-404.
6. **Kaa AK, Jørgensen PH, Søjbjerg JO, Johannsen HV.** Reverse shoulder replacement after resection of the proximal humerus for bone tumours. *Bone Joint J* 2013;95-B:1551-5.
7. **Sawamura C, Matsumoto S, Shimoji T, Okawa A, Ae K.** How long should we follow patients with soft tissue sarcomas? *Clin Orthop Relat Res* 2013;(Epub ahead of print) PMID: 23716116.
8. **Miller BJ, Cram P, Lynch CF, Buckwalter JA.** Risk factors for metastatic disease at presentation with osteosarcoma: an analysis of the SEER database. *J Bone Joint Surg [Am]* 2013;95-A:89.