

Seminal papers in orthopaedic oncology

D J McCormack

R C Pollock

R U Ashford

Abstract

The management of a patient with a tumour of the musculoskeletal system has progressed over recent decades. The development of evidence based medicine is a key factor in driving such change. Although now predominantly treated within specialist centres, all orthopaedic surgeons require an understanding of such malignancies and the management options available to the patients affected. We review the literature in three main areas; soft-tissue sarcoma (STS), primary malignant bone tumours and skeletal metastases. We take a critical look at the papers which have helped shape modern practice, and offer discussion into their relevance. We have given a historical perspective to demonstrate key themes in tumour surgery, and given examples of on-going research to provide an understanding of current developments.

Keywords Bone tumour; sarcoma; seminal; skeletal metastases

Introduction

The management of patients with musculoskeletal malignancy has evolved over the years. Sarcoma patients in the United Kingdom are now treated in designated sarcoma centres. We review papers from both the orthopaedic and oncological literature that have made significant advances to the care of patients with musculoskeletal cancers, where orthopaedic care is a fundamental part of their management.

Evidence based practice is becoming the norm in orthopaedic and trauma surgery. Level 1 evidence is extremely unusual in bone and STS research, due to the small numbers of patients and the rarity of the diseases. Nonetheless, there are important lessons that can be learned from these papers. We look at the key results from the papers below, and comment on their methodology. We also note their level of evidence, as defined by the Oxford Centre for Evidence Based Medicine (OCEBM) Workforce Group.¹

The management of tumours of the musculoskeletal system requires a multi-disciplinary approach. Although the role of the orthopaedic surgeon is of importance in resecting the tumour, this accounts for only part of a patients' treatment; with chemotherapy and radiotherapy regularly being utilized.

From a surgical perspective, the level of the surgical resection is also of key importance. In tumour surgery, studies often look

at event-free survival as an outcome measure. Orthopaedics, as a speciality, tends to equate positive functional outcome measures with success and, interestingly, a trade-off between the two can form a dilemma in orthopaedic tumour surgery; where limb salvage surgery may be sought to maintain limb function, without sacrificing an adequate resection margin.

We look at some of the key papers in the field, using established critiquing techniques.² We demonstrate the studies which have helped develop orthopaedic oncology, presenting a historical perspective, key developments of themes within the field and also an indication of where these developments continue.

Summary of papers reviewed.

Author	Journal	Year	Pathology	Level of evidence
O'Sullivan	The Lancet	2002	Soft Tissue Sarcoma	1
Cantin	Annals of Surgery	1968	Soft Tissue Sarcoma	3
Pisters	Journal of Clinical Oncology	1996	Soft Tissue Sarcoma	3
Davis	Quality of Life Research	1996	Bone and Soft Tissue Sarcoma	4 and 5
Eiber	Annals of Surgery	1980	Bone and Soft Tissue Sarcoma	3
Enneking	Clinical Orthopaedics and Related Research	1980	Bone Sarcoma	5
Krieg	The Journal of Bone and Joint Surgery: British Volume	2008	Ewings' Sarcoma of the Pelvis	4
Whelan	Annals of Oncology	2015	Osteosarcoma	1 (When complete)
Le Deley	Journal of Clinical Oncology	2014	Ewing Sarcoma	1
Rougraff	The Journal of Bone and Joint Surgery: American Volume	1993	Skeletal Metastasis	4
Wong	Clinical Orthopaedic Related Research	2013	Computer Assisted Surgery	4

Paper 1 – Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomized trial³

O'Sullivan, Brian, Aileen M. Davis, Robert Turcotte, Robert Bell, Charles Catton, Pierre Chabot, Jay Wunder et al. *The Lancet* 359.9325 (2002): 2235–2241.

Level of evidence: I (prospective randomized clinical trial).

Aim – To determine whether preoperative or postoperative radiotherapy has lower rates of wound complications in patients with Soft Tissue Sarcoma (STS) of a limb.

Daniel J McCormack *MRCs Specialty Registrar in Trauma & Orthopaedics, Leicester Orthopaedics, UK.*

Rob C Pollock *BSc (Hons) FRCS (Tr & Orth) Consultant Orthopaedic Surgeon, Royal National Orthopaedic Hospital, Stanmore, UK.*

Robert U Ashford *MD FRCS(Tr & Orth) Consultant Orthopaedic Surgeon, Leicester Orthopaedics & East Midlands Sarcoma Service, UK.*

Methods – An international prospective multi-centre randomized controlled trial. Patients who matched a set of specified inclusion criteria were allocated either preoperative or postoperative radiotherapy. Both treatment regimens were clearly defined. Pre-operative radiotherapy involved a course of a lower dose of radiation (50 Gy in 25 fractions), followed by a postoperative boost of radiation at a higher dosage only if tumour cells were found within resection margins following surgery. The postoperative regimen involved a course of higher dose radiation only (66 Gy in 33 fractions). The primary end-point was the presence or absence of a wound complication within 120 days after surgery. A clear definition of a wound complication was detailed, including a second operation for wound closure, a wound management procedure, including invasive wound procedure, readmission for antibiotics or readmission for wound care. Secondary end-points included local control, metastatic failure, progression free survival and overall survival.

Results – Wound complications occurred in 35% (31 of 88) of the preoperative group and in 17% (16 of 94) of the postoperative group. The study was stopped prematurely after a pre-planned early results analysis showed a statistically significant difference in this primary end-point. This 18% difference has a 95% confidence interval of 5–30, ($p = 0.01$). Tumour size ≥ 10 cm was linked with increased risk of wound complication compared with smaller tumours (odds ratio (1.42, 1.16–1.73)). Anatomical site was also shown to have a statistically significant bearing on wound infection, with infection being more prevalent in the lower limb, especially the thigh region. Only one patient in the study had a wound complication following upper limb surgery (in the preoperative group). No statistically significant benefit was found in either group looking at local recurrence, regional or distant metastases, or disease free survival. There was a slight increase in overall survival in the pre-operative group ($p = 0.0481$).

Discussion – The above study achieves its objective in demonstrating a difference in wound complication rates between the two treatment regimens. Interpretation of the results points towards postoperative radiotherapy being the chosen regimen in terms of favourable wound healing. This is especially the case for large tumours (>10 cm) and those arising in the lower limb. The fact that very few upper limb tumours had wound healing complications may suggest that this may not imply which regimen to use in these cases.

Critique – This randomized controlled trial has a clearly defined goal and uses a well-structured methodology. Although randomization occurred externally, the researchers were not blinded to the patients' radiotherapy regimen. Losses to follow-up were clearly explained, including patients in the preoperative group who did not undergo surgery. The authors attempted to reduce subjectivity in defining wound complications to objective parameters (e.g. requiring a procedure or requiring antibiotics), however it seems likely some subjectivity will remain in deciding whether such interventions are necessary. It is also recognized that the long-term manifestations of the larger field, higher dose approaches in the postoperative group are unknown.

Key points – Postoperative radiotherapy has lower rates of wound infection than preoperative radiotherapy. The tumour size and anatomical site should also be kept in mind when determining which regimen to use.

Relevance to clinical practice – The above study highlights the importance of radiotherapy regimen in wound healing complication rates. Wound complications are known to have a negative impact on quality of life following surgery for STS.⁴ It must be noted that the post-operative regimen involves higher doses of radiation (normally 66 Gy rather than 50 Gy). This has the adverse outcome of damaging collateral tissue and despite this study, there has been a recent trend towards preoperative radiotherapy.

Paper 2 – The problem of local recurrence after treatment of soft tissue sarcoma⁵

Cantin, J., McNeer, G. P., Chu, F. C., & Booher, R. J. Annals of Surgery 168, no. 1 (1968): 47.

Level of evidence: III (retrospective cohort study).

Aim – To evaluate the rates of local recurrence following resection of STS. This study also aimed to quantify how recurrence rates varied depending on the method of excision.

Methods – A retrospective study assessing all STS cases seen at the Memorial Hospital for Cancer and Allied diseases, New York, between 1935 and 1959. All patients were followed up for five years, and data were gained from review of case notes. 'Local Recurrence' was defined as 'recurrence within the confines of the previous surgical dissection, or tissue immediately adjacent to it'. It should be noted that histological confirmation was not confirmed in some instances, where it was inferred from the clinical context. Information gained included the Histological Subtype of the initial sarcoma, the level of surgical dissection, sarcoma site, timing of recurrence and death.

Results – A total of 784 patients were seen with STS. 59% of patients had local recurrence ($n = 465$). Sarcoma of unknown histogenesis (163), liposarcoma (116) and rhabdomyosarcoma (109) were the most common histological types.

Of the 653 patients who underwent primary treatment (excision) at the cancer unit itself, 187 patients later had local recurrence (29%). This suggests outcomes were improved when surgery was performed in a specialist cancer centre. Recurrence rate varied little across all histological subtypes in this group of patients (26%–36%).

Distant metastases were present in 11% of patients on initial diagnosis, and 22% following recurrence. 61% of patients with local recurrence died of sarcoma related illness, compared to 30% without recurrence. 65% of the patients who died of sarcoma did so after one or more local recurrence.

The study characterized three forms of operation for sarcoma. 1) Amputation 2) Wide excision 3) Excision without a clear margin. It is not clear how many patients were treated with each method. Following amputation, recurrence rates were 18%, 30% following wide excision and 42% following excision alone.

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