

**IMPROVING OUTCOMES FOR PATIENTS WITH MUSCULOSKELETAL  
TUMOURS**

by

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**Abstract:**

This thesis summarises the author's lifelong work to improve outcomes for patients with musculoskeletal tumours. It starts with analysing diagnostic features and steps that could be taken to improve the time to diagnosis of these rare tumours. It continues with a number of basic science projects which the author has either carried out or collaborated with. Benign bone tumours are common in children and are discussed. The author has probably one of the largest personal experiences of treating primary malignant bone and soft tissue tumours and this is evidenced by the papers on osteosarcoma, chondrosarcoma, Ewing's sarcoma and soft tissue sarcoma. The indications for and outcomes of major ablative amputations are outlined followed by an extensive review of the outcomes of limb salvage surgery with endoprotheses and other techniques. The role of this type of surgery in metastatic disease is put in context. Finally the importance of follow up and guidelines is considered. The thesis represents an analysis of the huge improvements that have taken place in the past 25 years in musculoskeletal oncology but also reveals the many still unanswered questions in this evolving field.

## **Dedications**

This work is dedicated to the memory of Rodney Sneath and John Scales – two giants who pioneered the art of limb salvage for bone tumours and whose infectious enthusiasm caught me under its spell.

None of this work would have been possible without the help and support of numerous doctors, nurses, secretaries and data managers who have worked in the unit over the years. My thanks go to my professional colleagues Simon Carter, Roger Tillman, Seggy Abudu and Lee Jeys who make the Royal Orthopaedic Hospital Oncology Service such a centre of international excellence.

Special thanks also to my wife, Lesley Ann, who has offered unstinting support and encouragement throughout my career.

## Acknowledgments:

The following have collaborated in the publications listed here. For many of the junior staff and medical students this was their first publication and I hope that the support and training this offered them will have led to an enthusiasm for continued academic work.

They are entered as the status they were at the time of their first publication:

<b>Medical Students</b> Aneel Bhangu Sam Ford David Hartwright Charles Johnson Graham Johnson Anup Pradhan Adnan Saithna Gemma Smith Will Taylor	<b>Junior Doctors (SHO)</b> Seggy Abudu E Aldylami S Bhagia M Chowdhry Paul Cool Richard Dias Ben George James Gray Lee Jeys Ashwin Kulkarni V Neelapala Emma Shears K Srikanth Dan Strong Raj Suneja Raj Thangaraj	<b>Trainees</b> Rafiq Abed Khaled Ayoub Khaled Baloch Mohan Belthur Jos Bramer (Holland) Daniel Chan Coonor Chandrasekar Frank Chotel (France) Asterios Dramis (Greece) Emil Elek (Hungary) Peter Ferguson (Canada) Fabrice Fiorenza (France) Dan Ford Asteriois Foukas (Greece) Masa Hatori (Japan) Marrti Hirn (Finland) Allan Inglis (USA) Rahul Jain Paresh Jaiswal Y Kabukcuoglu (Turkey) Suckman Kalra Mark Karpinski D Kumar James Metcalfe James Mitchell Graham Myers Emilios Pakos (Greece) James Phillips Gareth Prosser Sam Patton Mat Revell Paul Roberts Oscar Schindler Phil Shaylor Scott Somerville (Australia) Maria van Kampen Hazem Wafa (Egypt)
<b>Consultant colleagues</b> Viv Bramwell Simon Carter Alan Craft Mark Davies Hans Gelderblom Craig Gerrand Esther Hauben Ian Lewis Chas Mangham Michael Paulussen Roger Tillman	<b>Scientists</b> Colin Cooper Christine Eiser Jay Meswania Helen Patterson Paul Pynsent Paul Unwin Simon Weeden Sue Wilson Jay Wunder	

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## **Background**

In 1976 I qualified as a doctor and had the privilege of working as House Surgeon at the Middlesex Hospital in London to Rodney Sweetnam (later Sir Rodney, PRCS). At the time he was the secretary of the MRC Bone Tumour working party and was recognised as one of the country's leading surgeons dealing with bone tumours. As a result of this I saw a lot of patients with bone tumours, almost all of whom were treated by amputation, despite which, most succumbed rapidly to metastatic disease. In 1980, with a FRCS qualification, I was appointed as a Registrar to the Royal Orthopaedic Hospital in Birmingham, where I was sent to work with Rodney Sneath who 'did' the bone tumours.

In four short years the management of bone sarcomas had changed dramatically from amputation and almost certain death to the use of chemotherapy, limb salvage and a chance of cure. The limb salvage operations were made possible because of Rodney Sneath's strong links with Prof John Scales of the Institute of Bioengineering who manufactured custom made prostheses for these patients. 'Prof' would deliver them himself to the hospital and would regularly attend clinics and operating lists to evaluate the success of the implants. He was an inspirational character and realising my enthusiasm for the subject he suggested that I might like to 'record some of the outcomes for posterity'.

In 1986 I took a year out of the training program to establish a database to record patient, tumour, treatment and outcome data for patients referred to the Unit. This database was originally written in Informix but was later rewritten in SQL. This proved too cumbersome and for many years Filemaker Pro was used as the basis for the database. In 2005 this was replaced with a new SQL version.

This database has proved to be a goldmine of information and has in large part been responsible for the plethora of publications which constitute this thesis. The vast majority of the statistical analysis for these papers has been done by myself. This was based on attending a number of statistical training courses over the years and becoming familiar with Statview – a user friendly statistics package

The chapters of this thesis reflect the differing emphasis of the publications over the past 25 years, all of which have been designed with one aim: ***to improve outcomes for patients with musculoskeletal tumours.***

## **Towards earlier diagnosis**

Sarcomas are rare, representing just 1% of all malignancy. The clinical features of both bone and soft tissue sarcomas are subtle and delays in diagnosis are common. In my first few years in oncology it soon became apparent that there was a very low level of recognition of these tumours and analysis of all new patients referred over one year confirmed this. The average time to diagnosis of patients with osteosarcoma was 13 weeks but for Ewing's sarcoma was 47 weeks. Whilst one third of this was due to patient delay before they had seen a doctor, approximately 2/3 was after they had consulted a doctor. Our article highlighting this was rejected as it was felt 'to show doctors in too poor a light', but we were instead invited to write an editorial on the subject.(1)

Subsequent reviews of delays in diagnosis showed little change. This became a national issue in 1999 and I was invited to lead a group defining the diagnostic criteria for patients with possible bone and soft tissue sarcomas. This was very apposite as Charles Johnson (a medical student) and I had just completed an analysis of what were the worrying symptoms for patients with soft tissue sarcomas (STS).(2) We used the sum weights of evidence method to demonstrate how the presence of four features led to an increasing likelihood of malignancy. The findings of this study were subsequently directly adopted in both the 2000 Publication and the subsequent Guidance issued by NICE in 2005.(NICE Guidance. *Referral Guidelines for Suspected Cancer*. Available from:

[http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/@dh/@en/documents/digitalasset/dh\\_4014421.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4014421.pdf) [Accessed 14<sup>th</sup> November 2010] and NICE Guidance.

*Referral Guidelines for Suspected Cancer 2005*. Available from:

<http://www.nice.org.uk/nicemedia/live/10968/29816/29816.pdf> [Accessed 14<sup>th</sup> November 2010].

Despite this there has been very little change in the time to diagnosis and this has led to a further editorial in 2010.(3) Specific features that lead to delay have been highlighted for both sacral chordomas,(4) and synovial sarcoma in children.(5) Research by Smith and Johnson (medical students at the time) confirmed the long delays in patients with STS(6) showing that it was mostly doctor delay rather than patient delay, with referrals often being sent to the wrong place. Subsequent initiatives such as the 'two week wait' were

anticipated to speed up the referral process but Taylor (again a medical student) found this was not the case.(7) Over the years many patients have been referred to us with lumps 'the size of grapefruits or plums, or oranges ...' We did a light hearted look at this in 2003, demonstrating that orthopaedic surgeons have no idea how big fruit really is and we found that they had a much better idea about how big inanimate objects were – with the best concordance being with the size of a golf ball! (8) This size however (42mm) fits very neatly with the recommended size for early referral. A further plea for earlier diagnosis was made in my Hunterian lecture "Improving outcomes for patients with sarcomas".(9) This suggested that a golf ball should be used as an ideal size to detect possible soft tissue sarcomas.

The significance of delays in diagnosis was investigated for soft tissue sarcomas by Saithna, demonstrating that long duration of symptoms was correlated with lower grade, slower growing tumours – and thus with better prognosis.(10)

In 1993 we became aware of problems with the histopathological reporting of cases in our unit. An independent enquiry identified that there had been 87 errors in reporting of 1996 cases (4.4%). Some cases had been over-reported and some under-reported. Some patients had therefore had excessive treatment. The error rate was considered unacceptable even though the error rate was lower than any previously reported for bone and soft tissue pathology.(11) Partly as a response to this, quality assurance was introduced and the mandate for double reporting of all malignancies.

Staging of patients is important to assess the extent of their disease and Christie-Large showed the whilst CT will pick up most metastases it was only needed for large, deep high grade STS if the CXR was normal.(12) The radiology of important differential diagnoses of bone tumours such as stress fractures has been clarified in several publications. (13-16) Patton showed that primary bone sarcomas can arise in patients with previous other malignancy either because of association with that malignancy, treatment of it or independently.(17)

## Basic Science

Collaboration is essential for fruitful scientific work and for a very clinically based orthopaedic surgeon (RJG) this is essential for any productive work in this area. The two units with whom we have had the greatest collaboration are the Royal Marsden Hospital in London and Mount Sinai Hospital in Toronto. These collaborations have resulted in a number of highly respected publications. The one with the highest citation index (275 citations) was one identifying the responsible gene for synovial sarcoma in 2002.(18) Further work on synovial sarcoma and other soft tissue sarcomas was also produced.(19-23) The work with the team in Toronto was restricted by the terms of the Human Tissue Act which prevented further exchange of tissues for analysis but by then two useful studies had shown the lack of value of both the TP53 mutation and the MDR1 gene in predicting outcome for osteosarcoma. (24, 25)

We have been able to carry out a number of limited studies in Birmingham. Foukas showed that MMP-9 levels may be a prognostic indicator for osteosarcoma, Mangham showed that RT-PCR could be applied to both decalcified and non-decalcified paraffin sections to detect translocations diagnostic of Ewing's sarcoma whilst Abudu showed that overexpression of p53 in Ewing's sarcoma was an independent poor prognostic factor. (26-28). Dalal showed that VEGF may be the single most important regulator of angiogenesis in Ewing's sarcoma and could be a target for future therapeutic interventions.(29)

Karpinski and I investigated the bone and serum levels of a (then) new antibiotic-Augmentin. We showed that there was differential absorption of the two components (clavulanic acid and ampicillin) into bone and thus recommended that it should not be used for prophylaxis in bone operations.(30)

## **Benign tumours**

Benign tumours considerably outnumber malignant ones but sometimes they present equally challenging management problems, particularly if they arise in children where the effects of a progressive lesion can lead to lifelong disability.

Over the past 25 years our unit has continued a policy of largely conservative management of benign tumours, using detailed curettage for those requiring it. Chondroblastomas are nowadays treated by radiofrequency ablation but any results from that would need to be compared with the gold standard of detailed curettage as shown by our paper of 2005 detailing a 13% risk of local recurrence, all of which arose within 18 months.(31) Not all chondroblastomas are that easy to treat and we described in more detail how to access chondroblastomas of the femoral epiphysis (32) and the very unusual circumstance of an apparently benign chondroblastoma which recurred aggressively and metastasised.(33)

Giant cell tumours are one of the more aggressive 'benign' tumours with a high risk of local recurrence and occasional metastasis. Our unit policy of detailed curettage without adjuvant resulted in a 19% risk of local recurrence.(34) In the sacrum however treatment is far more difficult and a suggested algorithm has been produced based on our units experience.(35) The distal radius is another site where treatment is difficult as is shown by Khan's paper.(36)

Curetting out a benign bone tumour leaves a defect in bone. Many people fill this with a variety of bone grafts or bone substitutes, most of which are expensive and which have never been shown to be effective, let alone cost effective. We analysed the size of defects left after curettage and identified 60ml as being the critical volume where filling the defect was required to avoid the risk of bone collapse.(37, 38) In the proximal femur however structural support is often needed and a fibula strut graft is cheap and effective.(39) Jeys showed that if more than 54% of the bone is destroyed then the risk of fracture increased in the distal femur.(40)

Benign soft tissue tumours excite less interest but can still present challenges in diagnosis as in the case of one leiomyoma around the elbow. (41)

## **Primary Malignant Bone Tumours**

There are three main primary bone tumours with an annual incidence in the UK of about 9/million population. Since the database was established we have treated over 3327 of these patients, with an experience of 1527 osteosarcomas, 861 chondrosarcomas and 682 Ewing's patients. Several overviews of treatment for these have been published in prestigious journals.(42, 43)

**Osteosarcoma** is the most common primary bone tumour. Low grade varieties such as parosteal osteosarcoma do not require chemotherapy but there remains uncertainty as to whether periosteal osteosarcoma requires this. Neither our own study nor a collaborative study with the members of the European Musculo-Skeletal Oncology Society (EMSOS) was able to answer this.(44, 45) In high grade osteosarcoma there have been sequential chemotherapy trials in the UK over the past 30 years during which time there has been a disappointingly small change in overall survival (stuck at 53% at 5 yrs for the past 20 years or so). (46, 47) Partly as a result of these disappointing outcomes I arranged for two medical students (Ford and Saithna) to visit the Rizzoli Institute in Bologna to do a matched comparison of outcomes. Their results showed a significantly worse outcome in UK patients and presented a furore when presented at an International meeting, but this was in part responsible for a change in chemotherapy in the UK to a multiagent regime which appears to be improving outcomes.(48) Bramer showed that change in alkaline phosphatase levels may allow risk stratification for osteosarcoma.(49) Bramer and Pakos in separate studies have confirmed a wide range of prognostic indicators for osteosarcoma.(50, 51) Jeys showed that one of the most unexpected of these was the observation that patients with infected prostheses used for limb salvage had an increased survival,(52) an observation that fits with current osteosarcoma trials of immune modulators and with observations dating back to Coley's toxins in the 1890s.

One of the more difficult challenges clinicians face in managing osteosarcoma is what should be done with a patient with a pathological fracture. This question was originally addressed by Abudu in 1996 and later by Bramer (53, 54) both of whom showed that

fractures did not affect outcome per se but although there was a higher rate of amputation, limb salvage was safe if clear margins could be achieved. Local recurrence in osteosarcoma is a feared outcome but is usually an indicator of aggressive and non responsive disease.(55)(56) Outcomes following recurrence have also more recently been reviewed by Gelderblom combining data from three large osteosarcoma studies which our patients participated in, showing that outcome following local recurrence alone is not as bad as it is for metastases.(57)

16% of osteosarcomas arise over the age of 40 and until a few years ago these patients were excluded from chemotherapy trials. Another combined paper from EMSOS showed that they did only marginally worse than younger patients when treated in a like manner.(58) We have shown that outcomes for patients with pelvic osteosarcomas (59) and Paget's osteosarcoma, (60) are worse, although fortunately Paget's osteosarcoma appears to be becoming rarer.(61) Kalra found that patients with radiation induced sarcomas also tended to do worse largely because of the awkward sites these tumours arose.(62) A most unusual case where tumour appears to have migrated to a site of increased vascularity following resection of an osteosarcoma was reported by Dias.(63)

**Chondrosarcomas** may arise de novo or arise in patients with solitary or multiple osteochondromas. They tend to be slow growing and frequently arise in the pelvis. They do not respond to chemotherapy or radiotherapy and surgical excision with clear margins gives the best prospect of cure. Our experience of treating chondrosarcoma is one of the largest in the world and confirms the effect of grade on survival and margins on local recurrence.(64) A less aggressive tumour is clear cell chondrosarcoma but this also requires recognition and treatment with wide excision.(65) A most unusual case where the tumour was possibly 'reactivated' after 21 years by revision hip surgery indicated the possible role of growth factors in facilitating tumour growth.(66) Of all the types of chondrosarcoma, the dedifferentiated type carries the worst prognosis and this was confirmed not only by our own experience but by the pooled results of a large consortium, the members of EMSOS. (67, 68) Srikanth described the case of clear cell chondrosarcoma arising in association with Niemann-Pick disease.(69)

**Ewing's** sarcoma on the other hand responds well to both chemotherapy and radiotherapy but there is increasing evidence that surgery is essential to optimise local control. (70) Our unit has been involved in sequential trials of chemotherapy for this disease and RJG has been the surgical co-ordinator for these trials since 1990.(71, 72) Ewing's sarcoma can present in unusual ways (73) and a high level of awareness is needed to consider it as a possible diagnosis. As long ago as 1999 Abudu showed a clear correlation between change in tumour size and histological response to chemotherapy, which helps allow planning of operative intervention.(74)

**Spindle cell sarcomas** of bone comprise a rare group of bone tumours which are treated much like osteosarcoma with similar outcomes.(75) We identified a previously unreported association of Neurofibromatosis Type 1 with an increased risk of bone tumours.(76)

Although not a primary bone tumour, **lymphomas** of bone frequently present in a similar manner and have a better prognosis than bone sarcomas.(77)

## Soft Tissue Sarcomas

Soft tissue sarcomas (STS) are far more common than bone tumours. When I qualified they were very poorly recognised, were often diagnosed late and were usually treated with amputation. Improvements in staging, surgery and adjuvant treatment have improved outcomes but up until the last 10 years most STS were still treated outside a specialist centre with worse outcomes.(78) STS can present in varied ways (79, 80) but most are large by the time of presentation. Concern over our high rate of complications with adductor compartment STS led me to arrange for two students (Pradhan and Cheung) to visit two North American centres to do a comparison study of outcomes. Survival at all three centres was similar but aggressive local therapy improved local control significantly.(81) This was not so apparent when a comparison was done of STS in the hand. (82) Aldlyami showed that Triton tumours are rare but behave aggressively (83) whilst Sommerville confirmed the satisfactory outcomes for low grade liposarcomas (aka atypical lipomas) treated by marginal excision alone.(84)

Inadvertent excision of a lump which turns out to be a sarcoma (the “whoops” procedure) is still unfortunately not uncommon and Chandrasekar’s paper showed that following re-excision residual tumour was found in 66% of cases and that local recurrence was related to grade of the tumour and margins of re-excision.(85) Ferguson showed that local recurrence was of a higher grade in 20% of cases but this not predict a worse outcome.(86) Technical tips on resecting various soft tissue tumours have included how to resect a dumb bell tumour of the pelvis,(87) an intravascular leiomyoma (88) and a chest wall sarcoma in a patient with aortic stenosis.(89)

## **Amputations.**

Approximately 15% of patients with bone or soft tissue sarcomas will need an amputation at some stage. The majority will have a primary amputation as a result of the extent of their tumour but some will need it following a complication of the original treatment such as a local recurrence or an infection. The higher in the limb the more devastating the amputation will be and also the likelihood that the reason the amputation was required was because the tumour was that much larger. Arguably the most mutilating of all amputations is the hindquarter amputation, where not only the leg but also part of the pelvis is removed. We reviewed our experience of 34 of these amputations in 1996, finding that when the amputation was done with curative intent there was a 85% survival at five years.(90) Disarticulation of the hip stays outside the pelvic cavity but functionally is almost as debilitating as hindquarter amputation. It is mainly needed for large primary or recurrent tumours of the thigh.(91) Outcomes are worse than those of hindquarter (only 32% survival at 5 yrs even for those done with curative intent) and this is probably a reflection of the fact that more hindquarter amputations are done for low grade chondrosarcomas. (10% of those having disarticulation compared with 32% for hindquarter). Following high amputation extra strain is placed on the contralateral limb and one of our surviving patients developed severe osteoarthritis of the remaining hip requiring a challenging hip replacement.(92)

In the upper limb forequarter amputation has the same fearful reputation, only being required for massive inoperable tumours of the shoulder girdle. We found a 30.2% survival at five years for those done with curative intent.(93)

## **Endoprosthetic Replacement**

Joint replacements have been used since 1940 for arthritis and it was a logical step to use them for tumours. As the technology of joint replacement became more sophisticated so did the ambition of orthopaedic oncology surgeons to replace even larger parts of bones affected by tumours. In Birmingham this work was pioneered by Rodney Sneath who had learnt of the possibilities for endoprostheses to replace large segments of bone while working at Stanmore.

On my arrival at the Royal Orthopaedic Hospital I was amazed to find that most surgeons were still doing knee replacements with an old fashioned hinged knee, the Stanmore knee. It soon became apparent that the results, even in the medium term were very poor. Karpinski and I obtained permission from the Consultant body to review outcomes and we reported on this in 1984.(94) This paper was a landmark paper for two reasons. Firstly, it used the recently described actuarial survival to estimate failure rates (all the calculations were done using a calculator and the graphs were then drawn by hand) and secondly because it was the first paper to define three different endpoints for failure of an arthroplasty – removal of the prosthesis, the onset of pain or finally the onset of some other complication which detracted from the expected function. The failure rates using these three different criteria were 15%, 23% and 30% respectively at 5 years. As a direct result of this paper the hospital changed to using more sophisticated knee replacements. A follow on paper also showed that using this knee for revisions resulted in only a 23% success rate.(95)

This work however acted as a catalyst for subsequent reviews of the whole spectrum of endoprosthetic replacements which were by now increasingly being used in limb salvage surgery for bone tumours. Interestingly the most common implant – to replace the distal femur, was initially based on the very same Stanmore knee replacement which had such a high failure rate when used for arthritis. The paper by Roberts in 1991 showed a 28% failure rate at 5 years(96) whilst using the same prosthesis for proximal tibial replacements showed a 40% failure rate at 5 years.(97) This paper however also showed early improved results with the use of a rotating hinge type of implant and this has been confirmed by subsequent analysis. It also showed the value of the gastrocnemius muscle

flap in reducing infection rates. The main cause of failure of the early implants was aseptic loosening and Unwin demonstrated this in his paper of 1996.(98) Myers showed that the change of implant to a rotating hinge and the use of hydroxyapatite collars at the bone/prosthesis interface has been responsible for a dramatic improvement from a 35% rate of aseptic loosening to 0% at ten years in the distal femur and similar in the proximal tibia.(99, 100)

Although prostheses are expensive and do fail, they are still very cost effective compared to the costs of an amputation with the need for lifelong provision of artificial limbs, an important point to consider for health care economists.(101)

Apart from the knee, other sites where tumours commonly arise include the hip, pelvis and humerus and papers have reviewed our experience at all these sites. The proximal femur replacements do little worse than hip replacements in patients of the same age (102) and are especially useful for metastatic disease where a modular system is now available.(103) Proximal humeral replacements have the lowest complication rate of all the implants used although they allow only limited function at the shoulder and are realistically only spacers.(104) The first patient to ever have a tumour prosthesis in Birmingham, in 1970, is now 91 years old and had her distal humerus prosthesis revised for loosening after 31 years. Endoprostheses of the distal humerus do surprisingly well considering the forces put upon the joint,(105) but in the distal tibia Abudu showed that the failure rate is very high and better function is usually achieved with a below knee amputation.(106)

One of the main advantages of a diaphyseal prosthesis is that it allows immediate weight bearing but may fail in the longer term.(107, 108) Replacing the entire bone is more challenging but may be needed for extensive tumours or revision procedures.(109, 110) Pelvic replacements are technically some of the most challenging surgical reconstructions and have a high complication rate which does not seem to have improved much with time.(111, 112)

Unfortunately, inserting these large prostheses does not come without complications. The main continuing risk has been infection and the incidence of this is significantly higher

than in patients with conventional joint replacements. Abudu showed that if a superficial infection persists for more than 6 weeks it will almost certainly lead to a deep infection.(113) Philips reviewed all deep infections in 10,735 primary arthroplasties carried out at our hospital over a 18 year period and found a deep infection rate of 0.57% for hip and 0.86% for knee replacements. (114) Jeys found an 11% infection rate for patients with endoprostheses over the same time period, also showing that pelvic, tibial and extendable prostheses were at greatest risk as were patient who had radiotherapy.(115) Dramis concluded that culture of Propionibacterium remained of uncertain significance. (116) Jeys showed that infection and local recurrence were the main reasons a secondary amputation was required after endoprosthetic replacement. (117, 118) Management of infection has not changed much over the past 20 years with two stage revision remaining the best way of resolving the problem.(119) Although radiotherapy may prevent tumour recurrence it dramatically increases the risks of failure around a prosthesis.(120)

In children, our unit pioneered the use of extendible replacements, with the first one being done in 1982 in a patient who remains alive and well 29 years later. Early work concentrated on the concept of inserting an uncemented prosthesis across the growth plate opposed to the resected tumour (121) and subsequent review of this by Cool confirmed that growth continued despite the damage done to the growth plate.(122, 123) Early lengthenings were done 'open' with a distraction device and we measured the forces required to lengthen the soft tissues around the prostheses.(124) These results helped plan future lengthening devices and in particular the non invasive lengthening device where the lengthening is done using a motor. Results of extendible replacements have been reported for the distal femur(125), proximal femur (126), total femur (127), proximal tibia (128)and humerus.(129) van Kampen showed that carrying out a hip replacement for tumour in an immature child is fraught with problems, especially subluxation, which have yet to be fully resolved.(130)

## **Other Surgery**

Other options for surgical reconstruction including biological solutions or rotationplasty should not be forgotten.(42, 43, 131) Although fibula grafts in isolation are useful they are slow to heal and consolidate.(132) In 1995 I began to use the technique of extracorporeal irradiation and reimplantation of bone tumours for selected cases. This is really most useful for unusual sites where there is no other good reconstruction available such as the pelvis (P1,2 resections), scapula, (133) mid tibia and in one case a metacarpal in a concert pianist!(134)

Other inventive techniques have been developed in our unit to solve particular problems: the use of a prosthesis cemented over an existing one following a periprosthetic fracture being one neat solution described by Tillman.(135) The use of an 'ice cream cone' prosthesis to reconstruct the pelvis also helps resolve the problem of the 'missing hip joint'.(136) Prostheses have also been used to resect bones affected by hydatid disease. (137)

## **Metastases**

Metastatic disease is usually incurable but effective palliation may often involve surgery. Chan and Baloch showed that resecting solitary metastases for renal cell carcinoma can provide prolonged palliation and occasionally cure.(138, 139) The most common site for osseous metastases is in the proximal femur and the advantages of a modular system to allow early surgery and mobilisation for these patients has been demonstrated by Chandrasekar.(140) Reconstructing pelvic defects using a modified Harrington technique has also met with considerable success in our hands as described by Tillman.(141) Abed showed that soft tissue lumps which turn out to be metastases are uncommon but present in a near identical way to soft tissue sarcomas – except that they are usually painful.(142)

## **Follow Up**

The aim of follow up is to reassure patients and detect problems at a stage when (in theory) they can be dealt with more easily. There is remarkably little evidence about the value of this for sarcomas. Cool showed that most local recurrences are detected by the patient themselves(143) and Gerrand showed the wide variation in follow up regimes used around the country.(144) This topic is currently being investigated in collaboration with the University of Birmingham through a large grant from RFPB for the SOFI study. (Sarcoma Optimum Follow up Investigation). Hauben showed that late relapse in osteosarcoma was not related to any clear histological factor.(145)

## **Guidelines**

Guidelines on management are best achieved on a background of evidence supported by consensus. The British Sarcoma Group (of which RJG is the founder and secretary) has produced these for both bone and soft tissue sarcomas.(146, 147)

## **Quality of life (QoL)**

A fruitful association with Eiser produced a number of papers showing how difficult it is to measure QoL in children with bone tumours and how it is often the child's 'coping ability' that best determines their perceived QoL.(148-153) It also showed that children have better function following limb salvage but those who undergo secondary amputation following failed limb salvage adapt well to this.(154)

## **Conclusion**

Musculoskeletal oncology has emerged as a specialty in its own right since the 1980s. This is thanks to huge advances in imaging, surgical technique, chemotherapy and methods of limb reconstruction. It has been a privilege to be a part of this 'revolution'. It has resulted in improved outcomes for patients both in terms of diagnosis, survival, limb salvage and quality of life. The papers quoted in this thesis have highlighted many of the factors which have led to these improvements and demonstrated the author's contributions to this subject over the past 30 years. The problems identified by this review will point the direction for the next generation of researchers. Already a list of 80 potential avenues for further investigation has been produced by the author.

4925words

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The author has a total of 234 references quoted on Pubmed. He is first author of 36 of these.

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