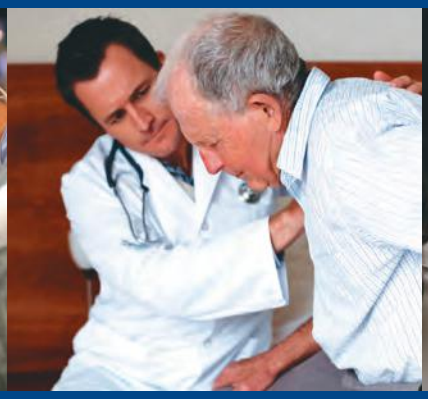
CANCER FORUM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Australian behavioural research in cancer

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Cancer Forum
GPO Box 4708
Sydney NSW 2001

Telephone: 02 8063 4100
Facsimile: 02 8063 4101
Email: info@cancerforum.org.au
Website: www.cancerforum.org.au

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Contents

Bone and soft tissue sarcoma

BONE AND SOFT TISSUE SARCOMA – DIAGNOSIS, CURRENT MANAGEMENT AND THE FUTURE

Paul D Stalley[1] and Martin HN Tattersall[2]
1. Bone and Soft Tissue Sarcoma Unit, Royal Prince Alfred Hospital, New South Wales.
2. University of Sydney and Sydney Cancer Centre, Royal Prince Alfred Hospital, New South Wales.
Email: pdstalley@optusnet.com.au

In introducing a forum on bone and soft tissue sarcoma, there are difficulties in view of the wide range of tumours involved and their relative rarity. In New South Wales, soft tissue sarcomas account for 0.5% of new cancer notifications per year, and bone sarcomas for 0.2%. There are over 70 sub-types of sarcoma, all with different behaviour, incidence, and age incidence. Although sarcoma is rare in adulthood, it forms one of the large peaks of malignant disease in children. It is, however, an area where there has been tremendous improvement in outcomes over the last 30 years. We are on the threshold of a molecular biological revolution which is likely to change the diagnosis and management of sarcoma profoundly.

Diagnosis

Many sarcomas, unfortunately, present late and in some cases up to 15% of cases will have metastatic disease at the time of presentation. Most present with either a mass or pain or both and radiological assessment is the most common initial investigation. In their article Soper, Brown and Schatz demonstrate a change towards specific imaging, with an emphasis on MRI, CT and PET scans, and where available, these three modalities produce the best information to guide biopsy and establish the extent of disease.[1]

In sarcoma, biopsy has proven to be a crucial stage due to the risk of error, as demonstrated by the results of an audit done by Stalley.[2] Histology for sarcoma relies extensively on the histological structure, meaning that on many occasions fine needle aspiration and cytology are inadequate or provide misleading information for diagnosis. Adequate tissue specimens are mandatory, particularly in view of the wide use of immunoperoxidase stains and cytogenetics for diagnosis.

With sarcomas so frequently affecting the limbs, it is important that biopsy procedures not compromise subsequent limb salvage opportunities. For this reason, it is recommended that, where possible, biopsy should be undertaken in the unit that is likely to be doing the limb salvage surgery.

Current therapeutic options

The mainstay for the management of sarcoma in 2010 remains the trilogy of surgery, chemotherapy and radiotherapy. Not all sarcomas lend themselves to all three modalities. For example, chondrosarcoma is predominantly a surgical disease.

Paediatric sarcomas, such as rhabdomyosarcoma and Ewing sarcoma, are responsive primarily to chemotherapy regimes, therefore surgery and radiotherapy must be regarded as adjuvant treatment modalities. The survivorship of children with Ewing sarcoma in the last 30 years has changed from 15% to 70%, mainly due to the advent of new and better chemotherapy regimes, and a more profound understanding of how to apply those regimes. The articles on Ewing sarcoma by Padhye and McCowage,[3] and Rhabdomyosarcoma by HarilalChawla, Atern, Karpelowsky and McCowage,[4] illustrate the significant change that has occurred in recent times in the management of both of these tumours.

The role for chemotherapy in all sarcomas remains hotly debated. While we have some evidence of improvement in outcomes for tumours such as synovial sarcoma, for many soft tissue sarcomas there is little evidence of overall increased survival.

Radiation therapy clearly has a major role to play in both primary care and palliative management of sarcoma. As outlined in the article by Hong,[5] there are multiple modes of radiotherapy delivery available and the sequencing of that delivery is highly critical.

Limb sparing surgery in sarcoma is often the patient's major episode of treatment and comprises a wide range of surgical options. The tumour surgeon must tailor the chosen procedure carefully as many of these patients, if the disease is cured, will have decades of life remaining. Limb salvage procedures must, therefore, be able to stand the test of time to avoid multiple repeat surgeries.

As outlined by Steadman,[6] functional outcomes of amputation versus limb salvage demonstrate significant patient preference for limb salvage, where possible,

and biological reconstruction appears to have greater longevity without reoperation.

The single most important principle in limb salvage surgery however, remains the clearance of disease with adequate margins. In his article, Choong demonstrates the established fact that despite the cost of many prostheses, limb salvage surgery, with time, is a less significant cost impost on the community than is amputation.[7]

As many patients present or develop pulmonary metastases in this area, the somewhat controversial role of pulmonary metastatectomy is discussed by Dear and Tattersall,[8] and the indications for this treatment which, although may have very low cure rates, appears to have significant and appropriate indications.

The future

The two papers on the importance of molecular biology and new drug management in sarcoma by Thomas,[9] and Moore and Desai,[10] clearly demonstrate the exciting future for progress in sarcoma management. Molecular biology is demonstrating not only a more accurate method of categorising these difficult tumours, but is also demonstrating pathways for new therapeutic interventions.

Our understanding of this disease must be at a molecular level for progress to occur, and the complex understanding of the modes of action of targeting agents available to us will be a future management focus for these conditions.

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RADIOLOGY OF BONE AND SOFT TISSUE SARCOMAS

Judy R Soper, Wendy E Brown and Julie A Schatz
Department of Radiology, Royal Prince Alfred Hospital, New South Wales.
Email: jrsoper@gmail.com

Abstract

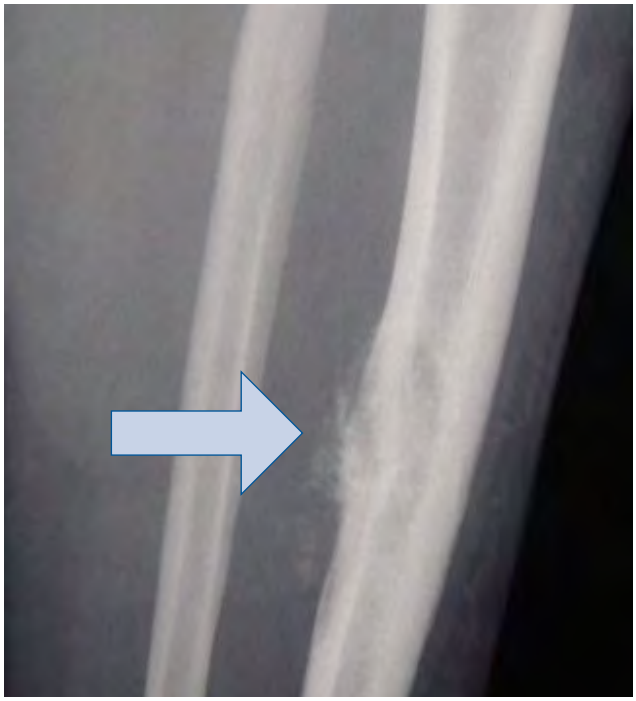
The role of radiology in assessing bone and soft tissue sarcomas encompasses the initial detection and diagnosis of the lesion, staging the lesion both locally and systemically, guiding biopsy of the lesion and monitoring the lesion, both the response to treatment initially and over a longer period, excluding recurrence. The imaging modalities used for these purposes have changed over the past two decades. While plain x-rays remain the most important technique in both detection and diagnosis, computerised tomography scanning and Technetium99m bone scanning have been increasingly replaced by magnetic resonance imaging scans, and more recently positron emission tomography and positron emission tomography computerised tomography scans, for the staging and monitoring of these tumours.

The evaluation of bone and soft tissue sarcomas involves initial detection of a clinically suspected mass, diagnosis of the mass, staging of a suspected or known malignant neoplasm prior to treatment and monitoring treatment response. Prior to the advent of magnetic resonance imaging (MRI) and more recently positron emission tomography (PET) scanning, plain films, nuclear scintigraphy (Technetium99m bone scans) and computerised tomography (CT) scans were the major means by which bone and soft tissue lesions were evaluated. Out unit sees approximately 100 new bone and soft tissue sarcomas each year. Plain radiographs and MRI scans are the mainstay of diagnosis, while MRI and PET CT scans are performed for staging and restaging following treatment. Other modalities such as CT, bone scans and less commonly ultrasound and angiography are used only in specific cases.

Plain x-rays

Both bone and soft tissue sarcomas can present as a palpable mass, although bone tumours frequently present with pain and change in function.[1] The most useful initial radiological investigation is plain radiography and this should be performed first. Information that can be gleaned from the plain film includes the site of the lesion, whether it arises from bone or soft tissue or involves both, some indication of size of the lesion, presence of bony destruction or periosteal reaction which gives some information regarding rapidity of growth, and characteristics such as calcification or ossification (figure 1). Plain radiography is more useful than MRI for characterising the aggressiveness of most bone lesions.[2]

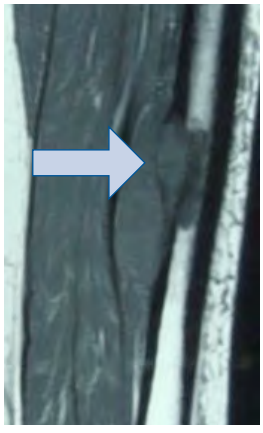
Figure 1a: *Plain radiograph of the tibia in this 26 year-old female shows a calcified lesion involving soft tissue and tibia. The pattern of calcification suggests a cartilaginous lesion. Involvement of the tibial cortex by this mesenchymal chondrosarcoma is evident.*



By identifying the bone involved, the site of the lesion in the bone and the age of the patient, the potential diagnoses can be narrowed. The diagnosis of some malignant lesions may be evident on the x-ray, for example some osteosarcomas and Ewing sarcomas have a typical appearance which is diagnostic, however further imaging is always required for staging.

Although plain x-rays are less useful in the assessment of soft tissue sarcomas, they should be performed as part of the work up of all soft tissue masses. Calcification on an x-ray associated with a soft tissue mass is always worrying. Only myositis ossificans and haemangiomas with phleboliths are common benign lesions that calcify. More often it is an indication of malignancy.[1]

Figure 1b: *Coronal T1 MRI demonstrates the soft tissue mass with extension into the tibia.*



MRI - Detection and diagnosis

MRI is the most useful investigation following plain x-rays in the detection and further evaluation of both bone and soft tissue sarcomas. The multiplanar capability, combined with the excellent soft tissue contrast and anatomical detail, mean that even small soft tissue or bony lesions can be detected with accuracy (figure 2).

Figure 2a: *A coronal fast spin echo T2 (FSE T2) scan reveals an elliptical mass in the superficial aspect of the gracilis muscle. The ill-defined slightly lobular T2 hyperintense mass suggests it may be a vascular lesion.*

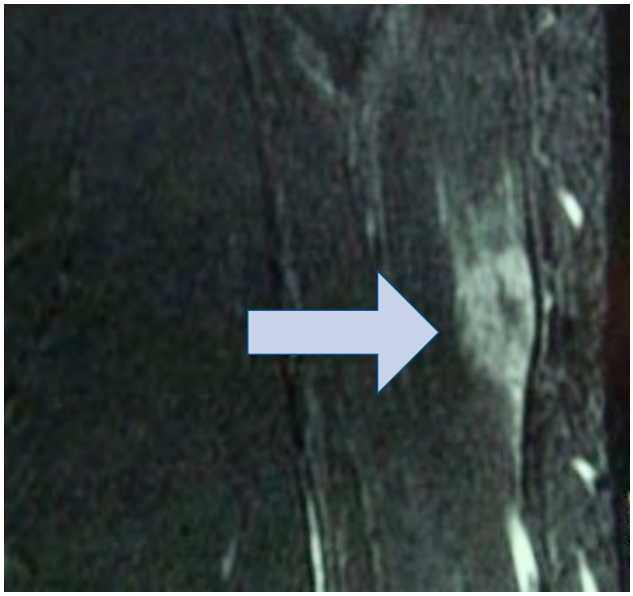
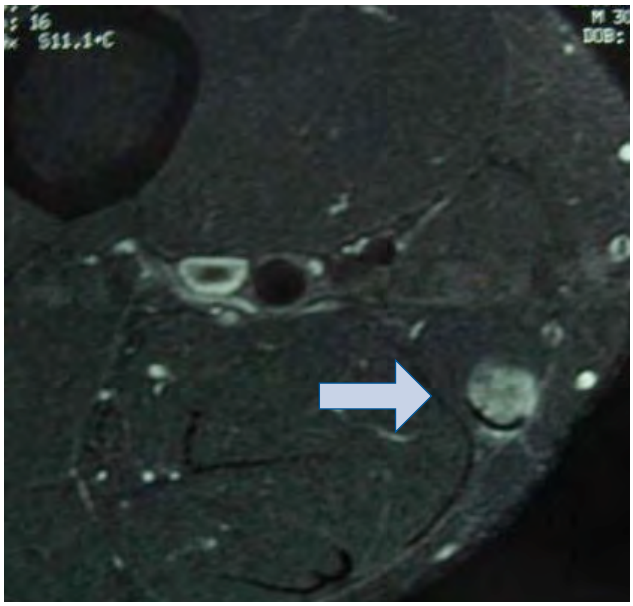


Figure 2b: *The lesion enhances on the axial fat saturated post gadolinium scan. It proved to be a haemangioendothleioma on histology.*



The MRI appearance of some tissues is characteristic, so that the diagnosis may be apparent or the differential diagnoses narrowed following the MRI scan. Tissues that have a characteristic appearance on MRI include fat and hyaline cartilage. Some vascular lesions are also typical, such as arteriovenous malformations that exhibit flow voids due to rapid blood flow and venous malformations with bright slow flowing or stagnant blood. Other tissues may have an appearance that, while not diagnostic, may be suggestive of a few tissue types, for example fibrous tissue, haemorrhagic tissue or calcification.

Although initially there was debate in the literature regarding the value of MRI in assessing cortical involvement in

comparison with CT, other studies have shown MRI to be comparable to CT in assessment of cortical involvement. [3, 4, 5]

Staging

When either a bone or soft tissue lesion is suspected of being malignant, staging is necessary. Cross sectional imaging for local staging should be performed prior to biopsy, as it can assist in planning the biopsy to ensure that other compartments are not contaminated and image interpretation is not compromised by post-biopsy oedema or haemorrhage. As the biopsy track should be excised with the tumour, there should be consultation with the surgeon prior to biopsy. The biopsy must not contaminate other compartments, neurovascular structures or areas that might be used for reconstruction.[2] Biopsies that are poorly planned or executed can influence the subsequent treatment options available to the patient.

MRI is the examination of choice for local staging of both bone and soft tissue tumours.[2,6,7] As McDonald states, an MRI of the entire bone gives the most accurate representation of intra and extraosseous extent of lesion.[8]

Various scanning protocols for performing MRI for staging purposes have been proposed. These involve a combination of T1, T2, fat suppressed T2 or short tau inversion recovery STIR and post-gadolinium sequences performed in multiple planes. The particular sequences employed are largely influenced by machine capability radiologist and referring clinician preference. While not commonly used in the published literature for tumour imaging, we have found the same fast spin echo proton density (FSEPD) sequences that are used in other musculoskeletal imaging to be useful as part of the MR protocol for local staging. These sequences permit high resolution imaging without a long acquisition time. The tissue contrast achieved allows identification of the neurovascular bundle, fascial planes and the tumour mass. While the TNM system for staging bone tumours reflects the size and grade of the tumour, the Enneking system reflects whether a tumour is intra or extra-compartmental.[9,10] This is important for surgery. Owing to the clear delineation of adjacent anatomic structures, the radiologists and referring orthopaedic oncologists at our centre favour this FSEPD sequence over T1, T2 or post-gadolinium T1 scans in determining anatomical relationships and for operative planning (figure 3).

Figure 3a: *Axial T1 scans show an aggressive intramedullary lesion with soft tissue extension.*

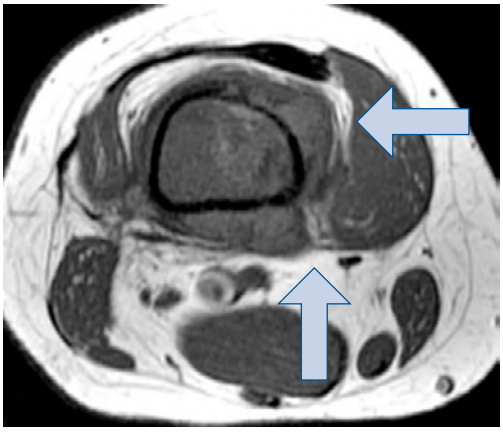


Figure 3b: *Axial FSEPD scan shows greater contrast details. The cortex is better defined and areas of cortical destruction are more clearly seen than on the T1 image. Tissue contrast is greater on this sequence, so a focus of hypointensity that represents tumour ossification, allowing prediction of the pathology, becomes apparent. The margins of the soft tissue mass are clearly seen. Biopsy revealed an osteoblastic osteosarcoma.*

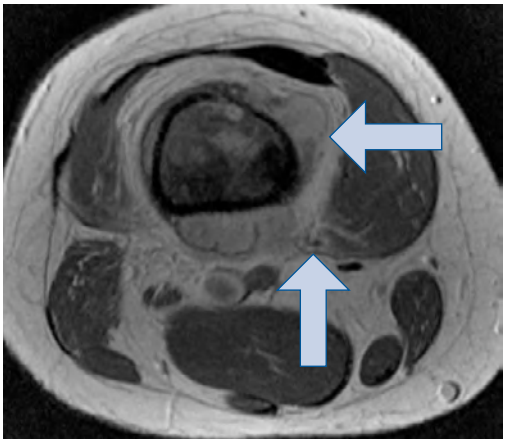


Figure 3c: *Axial fat saturated T2 scan highlights the mass and the peritumoural oedema, but the sciatic nerve is no longer as conspicuous with fat suppression.*

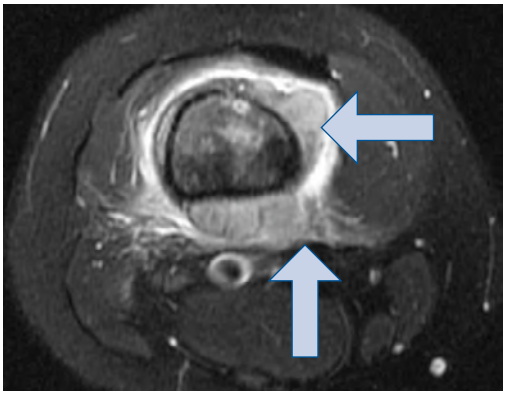
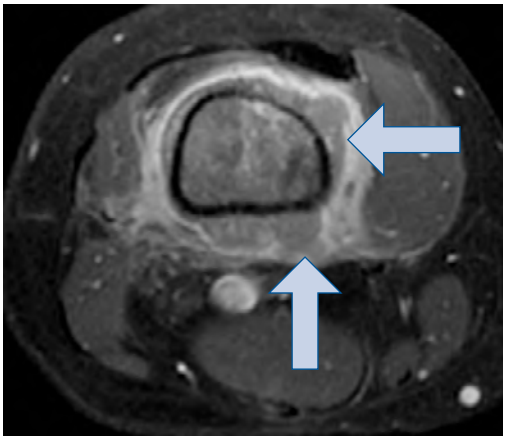


Figure 3d: *Axial post gadolinium T1 fat suppressed scan shows that the tumour enhances less than the surrounding reactive zone. The neurovascular structures critical for surgical planning are less clearly delineated due to the fat suppression technique reducing tissue contrast.*



Although gadolinium is now generally used in the evaluation of soft tissue masses, its use remains controversial. Contrast frequently increases signal intensity of tumours on T1 images and may enhance demarcation between tumour and surrounding soft tissue, however the distinction between tumour and adjacent muscle is usually well demarcated on non-contrast scans.[6] Not only does the administration of contrast increase the time and cost of the examination, significant but rare adverse reactions can occur including bronchospasm, anaphylaxis and death.[11,12,13] More recently the development of nephrogenic systemic fibrosis has been reported in patients with renal impairment following gadolinium administration.[14,15,16]

As a result of these reports the renal function in patients with, or considered at risk of, renal impairment must be assessed prior to administration. The advantage of gadolinium is that tumours become more conspicuous on T1 imaging and tumour margins are more distinct. It is generally considered of little value in the assessment of primary bone tumours because of sufficient contrast between the tumour and normal marrow.[2] Although it can assist in distinguishing tumour margins from reactive oedema, this is of little value for the zone of oedema is resected en bloc with the tumour in a limb salvage procedure.[8]

Dynamic gadolinium enhanced MRI refers to the process by which MR images are obtained at time intervals during and immediately following injection of gadolinium, as opposed to conventional or static gadolinium scans where scanning is performed after injection. Graphs charting rates of tissue enhancement (concentration) versus time can be generated. This technique has been widely studied as a means of identifying benign from malignant masses. In general, malignant lesions show more marked enhancement and a greater rate of enhancement than benign lesions, but there is such a broad overlap that the distinction has not been found to be of practical value.[17]

While we perform gadolinium enhanced fat suppressed sequences on all patients with a soft tissue mass or bone lesion with a soft tissue component, we do not use dynamic sequences.

Similar limitations with this method have been found in assessing treatment response with dynamic enhanced images. Overlap complicates the distinction between responders and non-responders. However, Dyke et al suggest that there may be a role for dynamic contrast enhanced gadolinium imaging in patients with osteogenic or Ewing sarcomas who are undergoing chemotherapy prior to surgery.[18]

The administration of gadolinium with static MRI has been found to be particularly useful in the assessment of tumour recurrence. In the post treatment monitoring of patients with both bone and soft tissue sarcomas, like others we have found the scans with gadolinium and fat suppression to be of the greatest value in the detection of recurrent tumour.[7]

PET CT

Identifying systemic disease in initial staging of sarcomas has previously been done by chest radiographs and/or chest CT scans and bone scintigraphy.[8,19] Subsequently, Positron emission tomography added to conventional imaging was shown to improve pre-operative staging.[20] More recently PET CT scans have been demonstrated as having higher sensitivity, specificity and accuracy than PET or CT alone.[21]

Follow-up imaging to detect recurrent tumour for three to five years after treatment had until recently been assessed by MRI of the primary site, with 99mTC MDP bone scanning and chest CT for systemic disease. However PET, and more recently PET CT have been found to be useful in both initial staging and detecting recurrence in the evaluation of sarcomas and are being increasingly used (figure 4).[22] There are exceptions where PET may be less useful in detecting recurrence, particularly with less metabolically active tumours where sensitivity is reduced, such as low grade liposarcomas.

Figure 4a: *Sagittal T1 scan through the forefoot in this 27 year-old man demonstrates a rhabdomyosarcoma arising from the plantar soft tissues.*

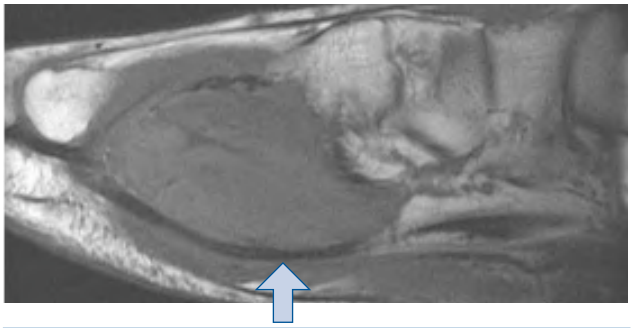


Figure 4b: *After treatment a pelvic recurrence is detected by a follow-up PET scan.*

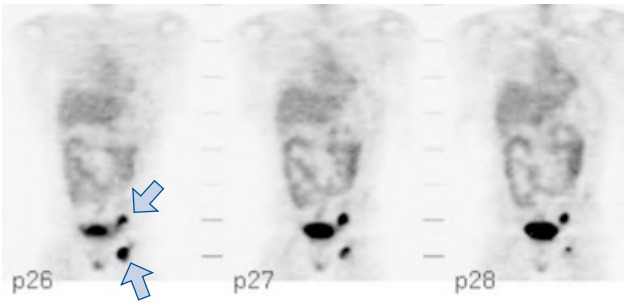
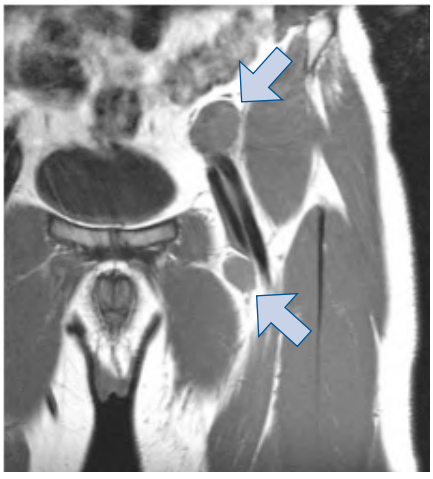


Figure 4c: *A T1 coronal MRI scan shows this recurrence to be two lymph node metastases along the external iliac and common femoral vessels.*



Bone scintigraphy

According to the American College of Radiology Appropriateness Criteria for Bone Tumours, nuclear medicine bone scanning is a good option if there are persistent symptoms and a bone lesion is suspected, but the patient cannot have an MRI.[23] It is deemed slightly more appropriate than CT in this circumstance.

CT

Where MRI is unavailable, CT can be useful to detect and diagnose a lesion not evident on plain x-rays, although as mentioned above it is rated as slightly less useful in the detection of a suspected lesion, with a negative radiograph by the American College of Radiology Appropriateness criteria.

CT is of use in assessing cortical breakthrough and pathological fracture. A lesion arising in or from a bone may be identified. Some soft tissue lesions can be diagnosed, as some tissue types such as fat, are characteristic.

CT is more sensitive to calcification than MRI, so small foci of calcification can be detected that would not be seen on MRI. If calcification is faintly evident on the initial plain film, CT may be more useful than MR as characterisation of calcification is possible. For example, punctate dystrophic calcification seen in some synovial sarcomas can be distinguished from ossification seen in myositis ossificans, or chondroid calcification that occurs in cartilage forming lesions.

Although CT scanning is not generally used in local staging, Panicek et al found that it was comparable to MRI.[24] While it may be used for local staging in circumstances where the patient is unable to have an MRI, its current use in staging is confined to chest CT scanning to exclude pulmonary metastatic disease.

Ultrasound

Ultrasound is readily accessible and frequently performed to evaluate a palpable soft tissue mass. It is useful to confirm presence of a mass and assess size and depth. Ultrasound can be particularly useful if the mass is cystic and close to a joint. It has no role in assessment of bone sarcomas.[1]

Ultrasound is also widely used in image guidance for biopsy, particularly for superficial masses. However, if a malignancy is suspected cross-sectional imaging by MRI, or CT if MRI is unavailable, should be performed prior to biopsy so local assessment and staging can be performed using images not already altered by intervention. Soft tissue compartments are more readily assessed on cross-sectional imaging, permitting biopsy planning so other compartments are not unintentionally breached.

Although suspicion of a sarcoma is raised if a lesion is large and deep, numerous sarcomas are small and superficial in location.

Angiography

Angiography is now generally reserved for those bone and soft tissue lesions that appear to be vascular on MRI or CT scan. Pre-operative angiography and possibly embolisation is performed for clarification and potential control of feeding vessels.

Conclusion

Soft tissue sarcomas are two to three times more common than malignant bone tumours.[6] Imaging plays a role in the assessment of bone and soft tissue sarcomas in the initial detection and diagnosis, staging of both local and systemic disease, monitoring response to treatment and detection of recurrence. The most important modalities currently are plain radiographs, MRI and PET/CT. Nuclear medicine (Te 99m), bone scanning and CT scanning are generally reserved for situations where MRI is unavailable or contraindicated, or where specific further information is sought.

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CHEMOTHERAPY REGIMENS IN NEWLY DIAGNOSED AND RECURRENT EWING SARCOMA IN CHILDREN AND YOUNG ADULTS

Bhavna Padhye and Geoffrey McCowage
Department of Oncology, The Children's Hospital at Westmead, New South Wales.
Email: geoffm@chw.edu.au

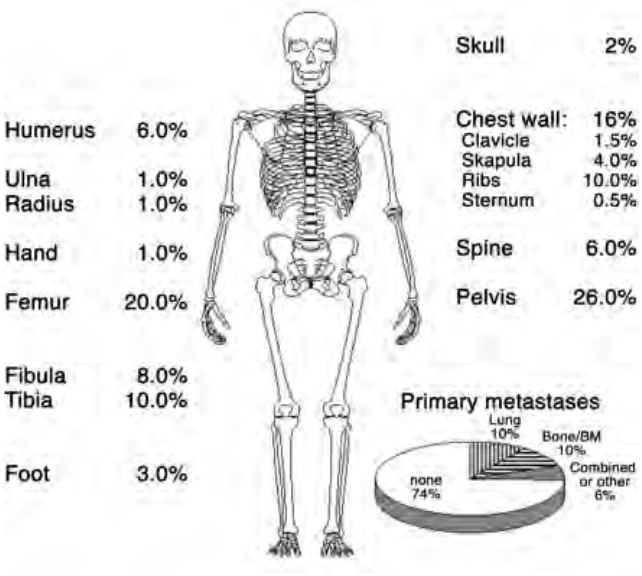
Abstract

As the second most common bone malignancy in children and young adults, Ewing sarcoma represents almost 3% of paediatic cancers. Multi-disciplinary care incorporating advances in diagnosis, surgery, chemotherapy, supportive care and radiation has substantially improved the survival rate of patients with localised Ewing sarcoma from 10%, four decades ago, to more than 70% in recent times. Unfortunately, these advances have not significantly changed the long-term outcome for patients with metastatic or recurrent disease; five-year survival for this group remains less than 25%. Over the last four decades the chemotherapy for Ewing sarcoma has advanced from use of single agents to multiagent chemotherapy including vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide, more recently in dose intense fashion with cytokine support. Multi-institutional co-operative group trials across North America and Europe have been invaluable in this effort. New agents like topotecan, irinotecan, temozolomide, gemcitabine and docetaxel, have been evaluated in phase I and II trials for recurrent disease. The role of high dose chemotherapy and autologous stem cell rescue for metastatic and recurrent tumours remains inconclusive. Enhanced understanding of the biology of Ewing sarcoma has identified new targets like IGF-1R and mTOR amenable to biological therapy. Future clinical trials will focus on how and when to integrate such therapies into clinical practice.

Ewing sarcoma (ES) is the second most common primary bone tumour in children and young adults. Included among the paediatric "small round blue cell tumours", classical ES of bone, extra-skeletal ES, Askin tumour of the thoracic wall and peripheral primitive neuroectodermal tumour are highly aggressive, poorly differentiated neoplasms with unknown histiogenesis. For this group the unifying terms EFT (Ewing sarcoma family of tumours)/Ewing tumour has been coined after molecular evidence was obtained for shared immunologic (expression of CD99) and genetic traits. Most consistently a reciprocal chromosomal translocation t (11; 22) (q24; q12) is present in about 85% of these tumours, and is considered pathognomonic for the disease. The frequency of ES in the population younger than 20 years is approximately 2.9 per million. It is much more common in white populations, and has a slight male predominance (55% males: 45% females). About a quarter of ES arise in soft tissues rather than bone and about a quarter of patients have detectable metastases at diagnosis. The lungs are the most common site for metastases, followed by bone and bone marrow.[1]

Large tumour volume, axial/pelvic location, poor response to neoadjuvant chemotherapy, metastatic disease (extra pulmonary metastasis worse than pulmonary metastasis), and older age at diagnosis adversely affect survival in patients with ES. In contrast to retrospective studies, a prospective evaluation did not confirm a prognostic benefit for type 1 EWS-FLI1 fusions.[36]

Figure 1: *Primary tumour sites and metastasis in ES (Data based on 1426 patients from the European Intergroup Cooperative Ewing Sarcoma Studies trials).*



Chemotherapy for newly diagnosed Ewing sarcoma

Before the era of chemotherapy, fewer than 10% of patients with ES survived, despite the well known radio sensitivity of this tumour. Patients commonly died of metastases within two years, indicating the need for systemic treatment. With use of modern multimodal therapeutic regimens, including combination chemotherapy, surgery and radiotherapy, cure

rates up to 75% and more can be achieved in localised tumors.[35]

Conceptually, treatment for those with localised disease includes three distinct phases: cytoreduction (to eradicate micrometastatic disease and facilitate effective local control measures); definitive local control to eradicate all known disease (surgery or radiotherapy or both); and adjuvant chemotherapy to minimise tumour recurrence.

The first reports of drug treatment of ES stem from the 1960s. In 1962, Sutow and Sullivan and Pinkel independently published reports on the use of cyclophosphamide for ES.[2,3] With Hustu et al's publication on the combination of cyclophosphamide, vincristine and radiotherapy that resulted in sustained responses in five patients, the era of modern multimodality treatment of ES began.[4] In 1974, Rosen et al, from the Memorial Sloan-Kettering Cancer Center, published the first results of a trial of radiotherapy given with a four-drug regimen consisting of vincristine, actinomycin D, cyclophosphamide and doxorubicin used in combination rather than sequentially (the VACD scheme), leading to long-term survival in 12 patients with ES.[5] The VACD scheme then became a standard therapy in numerous clinical trials.

The first North American randomised study, Intergroup Ewing Sarcoma Study, IESS-I 1973-1978, showed the superiority of the VACD four-drug regimen over a three-drug VAC regimen (without doxorubicin), in terms of effectiveness of local control (96% v 86%) and event-free survival (EFS) (60% v 24%).[6]

In IESS-II 1978-1982, two schedules of the four-drug combination VACD were compared.[7] The authors of the original report claim a "high-dose intermittent" regimen with three-weekly, higher doses of cyclophosphamide was superior to a "low-dose continuous" schedule, in which lower doses were administered weekly, but with identical cumulative drug doses in both arms.

The importance of doxorubicin, and especially of a high initial treatment intensity, was subsequently highlighted by a systematic meta-analysis of clinical trials in ES by Smith et al, concluding that of all drugs administered in ES, doxorubicin was probably the most active, followed by alkylating agents.[8] In view of these findings, results of the IESS-II study may have to be reconsidered. There was another significant difference between the two IESS-II treatment schedules, with patients randomised to the high-dose intermittent regimen receiving higher initial doxorubicin dose intensity, than those on the low-dose continuous schedule. Smith et al speculated that at least part of the superior outcome of patients on the high-dose intermittent schedule may have been due to the higher initial doxorubicin dose intensity. Total drug doses of every drug for the whole regimen were comparable between regimens, however those in the high-dose intermittent arm had received all 450 mg per m2 of doxorubicin by week 36, whereas those on the low-dose continuous schedule had received only 180 mg per m2 of doxorubicin by the same time point.

Because the total dose of doxorubicin is restricted owing to the risk of cardiomyopathy, cumulative dose intensification of alkylating agents was studied, both using cyclophosphamide as the main alkylator and using ifosfamide as an alternative alkylating agent, replacing or supplementing cyclophosphamide. In the early 1980s, treatment with ifosfamide, with or without etoposide, produced remarkable responses in patients who had had a relapse after standard therapies for ES. [13-17] Of 72 patients treated with ifosfamide plus etoposide, 30 had complete or partial responses (combined data from two separate trials).[16,17] Ifosfamide and etoposide was also introduced into several studies for newly diagnosed patients (EW 92, St.Jude, UKCCSG ET2, CESS 86, INT 0091).[9,10,11,12]

The promising results of ifosfamide and etoposide in relapsed patients led the Children's Cancer Group and the Pediatric Oncology Group to initiate a randomised control trial, INT 0091, in which they investigated whether the combination of ifosfamide and etoposide, when alternated with standard drugs, would improve the outcome in ES.[12] The patients were assigned randomly at study entry to receive standard chemotherapy (arm A) with doxorubicin, vincristine, cyclophosphamide and actinomycin, or experimental therapy (arm B) consisting of these four drugs alternated with courses of ifosfamide and etoposide. The patients were stratified into groups according to the presence or absence of metastases. A total of 518 patients met the eligibility requirements. Of 120 patients with metastatic disease, 62 were randomly assigned to the standard therapy group and 58 to the experimental therapy group. There was no significant difference in five year EFS (22%) between the treatment groups (P=0.81). Among the 398 patients with non-metastatic disease, the mean (± SE) five year EFS among the 198 patients in the experimental therapy group was 69 ± three per cent, as compared with 54 ± four per cent among the 200 patients in the standard therapy group (P=0.005). Overall survival was also significantly better among patients in the experimental therapy group (72 ± 3.4 per cent v 61 ± 3.6 per cent in the standard-therapy group, P=0.01). The study concluded that the addition of ifosfamide and etoposide to a standard regimen did not affect the outcome for patients with metastatic disease, but it significantly improved the outcome for patients with non-metastatic ES.

After accrual of non-metastatic patients was completed according to protocol design, the study was amended to enrol only patients with detectable metastases at diagnosis to a single arm trial, arm C 1992-1994, with higher doses of chemotherapy.[18]

Table 1: *Chemotherapy regimen with cumulative dose (mg/m2) for each agent by regimen INT 0091.*

Agent	Regimen A	Regimen B	Regimen C
Vincristine	40	16	48
Doxorubicin	375	375	450
Cyclophosphamide	21600	9600	17600
Ifosfamide	0	90000	140000
Etoposide	0	5000	5000

Of the 60 patients with metastatic ES of bone enrolled on to this single arm trial, there were three toxic deaths. Six patients (six-year cumulative incidence: 9%) developed second malignant neoplasms and died. The six year EFS

was 28% and overall survival was 29%. The study concluded that an intensified treatment regimen using higher doses of cyclophosphamide, ifosfamide and doxorubicin increased toxicity and risk of second malignancy without improving EFS and overall survival.

In the absence of new active agents, a strategy to improve outlook was to increase dose intensity. Dose intensity is defined as the amount of drug delivered over unit time. Therapy can be dose intensified either by keeping the interval stable while escalating the dose(s) of the chemotherapeutic agents, or by shortening the interval between cycles.

Since the dose limiting toxicity of the alkylating agents is myelosuppression, they are ideal agents for dose escalation with cytokine support. The dose limiting toxicities of doxorubicin include myelosuppression and mucositis, which are ameliorated by cytokine support, and cumulative cardiac toxicity which may be decreased when doxorubicin is delivered by continuous infusion, rather than bolus administration.

Dose intensification was evaluated within two US paediatric co-operative trials.

INT 0154 (dose escalation) and AEWS 0031 (interval compression) both accrued patients with localised disease. In INT 0154 (1995-98) the investigational regimen used dose-intensified alkylating agents, yet kept the cumulative doses of the drugs similar between the two arms.[19] Patients were randomly assigned to standard or intensified therapy as shown in figure 2. Granulocyte colony stimulating factor support for both regimens was used.

The total doses of all agents were similar. The intent was to deliver similar cumulative doses of the agents to determine the effect of early dose intensification without a change in total chemotherapeutic drug exposure.

Figure 2: *Chemotherapy regimen INT 0154.*

Standard

Week																	
0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
V	I	V	I	V	I	I	V	I	V	I	V	I	V	I	V	V
D	E	D	E	D	E	E	D	E	D	E	D	E		E		
C		C		C			C		C		C		C		C	C
Local control																

Intensified

Week											
0	3	6	9	12	15	18	21	24	27	30	
VVV	I*	VVV	I*	V	I*	I*	V	I*	V	I*	
D	E	D	E	D	E	E	D	E	D	E	
C*		C*		C			C		C		
Local control											

Total Chemotherapy Doses

Agent	Amount per dose		Total planned dose	
	Standard	Intensified	Standard	Intensified
V = Vincristine	1.5 mg/m²	1.5 mg/m²	13.5 mg/m²	13.5 mg/m²
D = Doxorubicin	75 mg/m²	75 mg/m²	375 mg/m²	375 mg/m²
C = Cyclophosphamide	1,200 mg/m²	2,100 mg/m² x 2*	10.8 g/m²	12 g/m²
I = Ifosfamide	1,800 mg/m² x 5	2,400 mg/m² x 5*	72 g/m²	72 g/m²
E = Etoposide	100 mg/m² x 5	100 mg/m² x 5	4 g/m²	5 g/m²

Local control – surgery or radiotherapy or surgery + radiotherapy for close margins

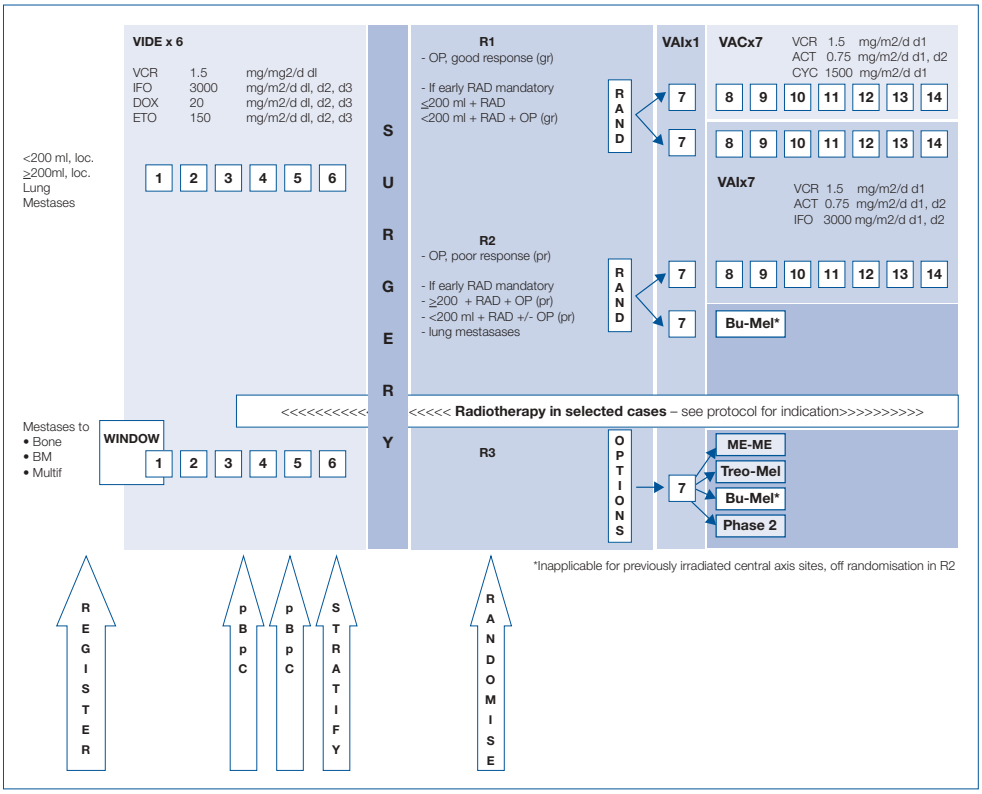
Four hundred and seventy eight patients met eligibility requirements: 231 patients received the standard regimen; 247 patients received the intensified regimen. The five year EFS and overall survival rates for all eligible patients were 71.1% and 78.6% respectively. There was no significant difference (P =0 .57) in EFS between patients treated with the standard (five year EFS, 72.1%) or intensified regimen (five year EFS, 70.1%).The study concluded that dose escalation of alkylating agents as tested in this trial did not improve the outcome for patients with non-metastatic ES of bone or soft tissue.

AEWS0031, 2001-2005, compared VDC–IE treatment every two weeks with VDC–IE treatment every three weeks for patients with localised disease, with 14 cycles and equal cumulative doses in each group.[20] Interval compression provided a 25% increase in dose intensity of all agents without an increase in toxicity. Overall survival and EFS were both improved in the interval-compressed group (EFS 79% v 70% at four years, p=0·023).The regimen of alternating VDC–IE every two weeks has now become standard for North American patients with ES.

A different approach evolved among the European cooperative groups, through independent studies by the UK Children's Cancer Study Group (UKCCSG) and the German–Dutch–Swiss Cooperative Ewing Sarcoma Studies (CESS). The CESS classified patients with localised tumours with radiographically determined volumes of 100 or 200 mL (depending on the study) as standard risk, and those with larger tumours or metastases as high risk. They also identified a poor histological response to initial chemotherapy as a poor prognostic factor.[21] Both the CESS and UKCCSG adopted a chemotherapy design in which four drugs are given at once, and this evolved from VACA (vincristine–doxorubicin–cyclophosphamide–actinomycin), to VAIA (substituting ifosfamide for cyclophosphamide), to EVAIA (adding etoposide), to the current VIDE (omitting actinomycin). The only randomised control trial in this series, EICESS-92, found no difference between VACA and VAIA for standard risk patients with ES, and a slight advantage (although statistically insignificant) for EVAIA over VAIA in patients with high risk localised or metastatic tumours.[22]

The current study Euro-EWING-99 (combined European and American study for localised and metastatic Ewing Sarcoma) uses VIDE (vincristine, ifosfamide, doxorubicin, etoposide) as initial chemotherapy for all patients. In a complex scheme, as shown in figure 3, it compares VAC (vincristine-actinomycin-cyclophosphamide) with VAI (vincristine-actinomycin-ifosfamide) as continuing chemotherapy for patients with good histological responses to VIDE, or small (<200 mL) tumours treated with radiation. For patients with poor histological responses, or large tumours treated with radiation, or lung metastases, it compares VAI and lung radiotherapy with busulfan–melphalan high dose chemotherapy/autologous stem cell rescue (HDCT/ASCR). Patients with extra pulmonary metastasis are non-randomly assigned to HDCT/ASCR arm.[23]

Figure 3: *Chemotherapy regimen EUROEWING 99.*



Treatment approaches for metastatic disease: Role of high dose chemotherapy+/- total body irradiation and autologous stem cell rescue (HDCT+/-TBI /ASCR)

The prognosis for patients with metastatic disease remains poor, with patients having extapulmonary metastasis seldom surviving. Reports on outcomes in patients with metastatic disease are confounded by the varying number of patients included with lung metastases as the sole metastatic site. The addition of ifosfamide–etoposide to vincristine–doxorubicin–cyclophosphamide in the INT-0091 study did not improve the outcome for patients with metastases.[12] Increasing the doses of doxorubicin, cyclophosphamide and ifosfamide by 20%, 83% and 56% respectively, in regimen C of the same protocol, also produced no improvement, and greatly increased acute toxicity and the incidence of secondary leukaemia and myelodysplasia.[18] Patients with metastases outside the lungs at diagnosis seldom survive, and this has led to several studies using HDCT +/-TBI /ASCR. In a prospective Children's Cancer Group study of 36 patients with bone or marrow metastases at diagnosis, high dose melphalan, etoposide and total body irradiation did not improve outcomes over those obtained with conventional chemotherapy.[24] A prospective French study of HDCT/ASCR with busulfan, melphalan,[25] and a European Intergroup Co-operative Ewing sarcoma study which enrolled 17 patients with bone, marrow, or other extra-pulmonary metastases, in a study of HDCT/ASCR26, did not show benefit of this therapy. A subsequent study used two sequential (tandem) transplants with high dose melphalan and etoposide; there were four event-free survivors among 17 patients, which was not a statistically significant improvement.[27]

An analysis of the European Group for Blood and Marrow Transplantation registry data showed a better outcome for patients with ES who received a busulfan containing regimen as compared with other HDT regimens.[48,49,50]

The ongoing EuroEWING-99 trial provides the first randomised evaluation of HDCT/ASCR in patients with ES. Patients with localised tumours and a poor response to initial VIDE chemotherapy, or with lung metastases at diagnosis, are randomly assigned to either further chemotherapy (vincristine, actinomycin and ifosfamide, and whole lung radiotherapy if pulmonary metastases) or busulfan–melphalan with autologous stem cells. EuroEWING 99 recently reported outcome results of 281 patients with extra pulmonary metastases of ES.[46] Following six cycles of VIDE and local treatment, 169/281 patients received HDCT/ASCR, 112 patients did not receive HDCT because of early progression, physician and patient choice, and collection failure in four patients. The three year EFS rate in the 281 patients was 27% and the overall survival rate 34%, with a median follow-up of 3.9 years after diagnosis. Patients who receive Busulfan-melphalan HDCT and local radiotherapy for pelvic tumours are at high risk for gastrointestinal (GI) toxicity, due to irradiation of bowel; three patients in this study died due to GI toxicity. Local radiotherapy is recommended, 8-10 weeks after busulfan based chemotherapy in these patients.

The Children's Oncology Group recently completed a study in patients with metastatic ES, adding metronomic anti-angiogenic therapy with vinblastine and celecoxib to the VDC IE backbone; results are pending.

Chemotherapy for recurrent ES in children and young adults

Thirty to forty per cent of patients with ES experience recurrent disease, despite multimodal therapy, and have a dismal prognosis. Patients with primary metastatic disease have a higher risk for relapse than those with localised disease. Survival after relapse of ES is poor, with only about 10% of patients event free at five years.[28, 29] To evaluate prognostic factors in patients with recurrent disease, the Children's Oncology Group examined data from the phase III, multi-institutional study INT0091, which accrued patients with ES between 1988 and 1994.[12] The most important prognostic factor in this study was time to first recurrence.[37]

There is no established treatment regimen for patients with recurrent disease. Chemotherapy options are limited and

dependent on the patient's prior treatment and possible impaired function of vital organs (eg. heart and kidneys). Agents that are considered for combination therapy are chosen to potentiate each other's activity and circumvent the emergence of drug resistance. These have included combinations of topoisomerase I or topoisomerase II inhibitors with alkylating agents and, in addition, several myeloablative high dose consolidation therapy regimens with and without total body irradiation.

Ifosfamide and etoposide have been shown to be active agents for recurrent ES, but most patients these days receive these in upfront therapy. High dose ifosfamide (15 gm/m2, two courses) has been used with some success in patients with recurrent disease who had received ifosfamide as part of upfront therapy.[41]

The combination of topotecan and cyclophosphamide has proved to be synergistic; with proven efficacy in paediatric solid malignancies.[30] A German group published results of cyclophosphamide and topotecan in 54 patients with relapsed /refractory ES.[31] At median follow up of 23 months, 25.9% patients were in complete/partial remission, with overall survival at one year being 61%. A recent Children's Oncology Group study has established the feasibility of combining bevacizumab, an antiangiogenic agent, with topotecan, cyclophosphamide and vincristine for treatment of recurrent ES.[47]

Wagner et al reported effectiveness of the combination of temozolomide and irinotecan for ES.[38, 39] This regimen can be delivered in the outpatient setting with limited cytopenias.

Investigators from MSKCC published results on 20 patients with recurrent/progressive ES treated with temozolomide and irinotecan. Of 19 evaluable patients, there were five complete and seven partial responses (a 63% overall objective response); median time to progression for the subset of 14 patients with recurrent ES, was 16.2 months. Median time to progression was better for patients who sustained a two year first remission than for those who relapsed <24 months from diagnosis and for patients with primary localised v metastatic disease.[40]

At present, either of these two combinations is considered for use as second-line or salvage therapy for recurrent ES.

Gemcitabine and docetaxel have demonstrated activity in the treatment of soft tissue sarcomas.[32, 42] The Sarcoma Alliance for Research through Collaboration (SARC) is currently accruing paediatric and adult patients for a phase II study of gemcitabine and docetaxel in relapsed ES.

The role of HDCT/ASCR in relapsed ES remains controversial and is even more difficult to evaluate because there are fewer patients available for evaluation in contrast to newly diagnosed patients. The European Bone Marrow Transplant Registry reported similar outcomes for patients with ES receiving HDCT/ASCR in first or subsequent remission, suggesting that HDT might be beneficial for a small number of patients with recurrent EFT.[33] However, because the use of this modality is limited to patients with responsive disease, evaluating its impact on outcome is difficult, and most reported series are biased by including only patients with responsive disease. They reported that response to salvage therapy was the single most important factor correlating with outcome after HDT. Barker et al reported on intensive chemotherapy followed by HDCT/ASCR as consolidation therapy for patients with ES in second remission.[34] They found that patients with a prolonged relapse free interval and responsive disease and those patients receiving HDCT/ASCR have an improved EFS and overall survival.

Biologically based approaches to treatment

Conventional cytotoxic chemotherapy is ineffective in some patients with localised tumours, and the majority of patients with metastases or recurrent ES. The growing understanding of ES biology has identified several therapeutic targets. The unique fusion gene, its transcript and protein product, and the pathways it activates all provide opportunities for therapy. Various targeted approaches have been investigated in pre-clinical and clinical phase I and phase II trials. These include inhibition of fusion product, a small molecule targeting the RHA-binding site on the EWS–FLI1 protein, IGF-1R mAbs (insulin like growth factor I receptor monoclonal antibody), Imatinib (C kit inhibitor), Rapamycin and its analogues, antiangiogenic therapy.

ES is associated with enhanced IGF-1R activity, via an autocrine/ paracrine mechanism, through the inhibitory binding of the EWS/ FLI-1 fusion protein to the IGFBP-3 promoter, consequently reducing IGBP-3 levels and increasing the level of free IGF-1R ligands. The strategies for blocking or disrupting IGF-1R activity in patients include the reduction of ligand levels or bioactivity or the inhibition of the receptor function using receptor-specific antibodies or small-molecule TKIs (tyrosine kinase inhibitors).

Monoclonal antibodies against IGF-1R represent the most evaluated option in sarcoma, with initial promising results in early clinical studies and several ongoing phase II studies. At present, eight different mAbs have been tested in clinical trials - Figitumumab (Pfizer), AMG479 (Amgen), R1507 (Roche), cixutumumab/IMC-A12, (ImClone Systems), SCH-717454 (Schering-Plough), MK0646 (Merck), AVE-1642 (Sanofi-Aventis) and BIIB-022 (Biogen Idec).[51] A phase II SARC study reported a CR/PR rate of 14.4% using R1507 for recurrent/refractory ES.[52] Ongoing studies are evaluating IGF 1R mAbs alone, and in combination with chemotherapy or mTOR inhibitors. Despite robust pre-clinical evidence supporting the role of IGF-1R targeted agents in ES, clinical results show that only a proportion of patients derive significant benefit, with many progressing or developing resistance to IGF-1R mAbs quickly.

Although initial reports suggested an association between the EWS/FLI-1 type 1 translocation and response in ES, the predictive value of translocation type has not been observed consistently. Further evaluation of predictive biomarkers for IGF-1R targeting drugs needs to be pursued. A current challenge in developing new clinical trials for ES is how and when to integrate biological agents with conventional chemotherapy.

Late effects of chemotherapy

In addition to long-term orthopedic outcome which is dependent on location of the primary tumour and local treatment modality used, chemotherapy agents lead to late effects affecting many organ systems, mandating a need for ongoing medical care for years after the primary treatment is completed.

These late effects include therapy related myelodysplasia and acute myeloid leukemia (t-MDS/AML), cardio-toxicity, infertility and renal impairment.

Bhatia et al described the magnitude of risk of t-MDS/AML in

578 individuals with ES enrolled on INT0091. Eleven patients developed t-MDS/AML, resulting in cumulative incidence of 2% at five years. While patients treated on regimens A and B were at low risk (0.4% and 0.9% respectively) patients on regimen C were at 16 fold increased risk of developing t-MDS/AML (cumulative incidence 11% at five years),when compared to regimen A.[43] Increased exposure to cyclophosphamide, ifosfamide and doxorubicin increased the risk of t-MDS/AML in regimen C. Several biological factors have been studied to identify patients who are at increased risk of t-MDS/AML. These include polymorphisms in GSTT1 and GSTM1, CYP1A1, and NAT-2 genes. Development of a "mutator phenotype" as demonstrated by developing microsatellite instability is a possible early marker of individuals likely to progress to t-MDS/AML.

Doxorubicin induces a dose related cardiomyopathy. Protocol doses are therefore usually limited to less than a cumulative total of 450 mg/m2. In addition, administration is often prolonged over a 48 hour period. Thoracic irradiation that includes the heart can augment the cardiotoxicity of anthracyclines. A Children's Oncology Group study examined the role of functional polymorphisms in CBR3 (carbonyl reductase enzyme catalyses reduction of anthracyclines to cardiotoxic alcohol metabolites) and CBR1 on risk of cardiomyopathy.[53] It showed a clear dose response relation between anthracyclines and cardiomyopathy, and selectively greater impact of CBR3 on risk of cardiomyopathy after low dose anthracycline exposure. Patients with CBR3 may benefit from cardio protection, surveillance or pharmacologic interventions.

The alkylating agents cyclophosphamide and ifosfamide are associated with infertility, especially male infertility, so that sperm cryopreservation is offered to post pubertal boys prior to the institution of chemotherapy. Ovarian cryopreservation can be offered to female patients. Ifosfamide can cause a persistent renal tubular electrolyte loss and, less commonly, a decrease in glomerular function, again in a dose-dependent fashion.[44] Despite these concerns, the overall functioning of survivors of ES is reasonably good. Survivors of lower extremity bone tumours had high employment (97%), graduation (high school, 93%; college, 50%) and marriage (67%) rates.[45]

Conclusions

- With modern multimodality treatment survival rates up to 75% are achieved in localised ES, whereas survival in primary metastatic and recurrent tumours remains poor.
- The role of HDCT/ASCR remains inconclusive for patients with high risk and recurrent tumours.
- EuroEWING 99 is the first randomised study to determine the role of HDCT/ASCR in patients with high risk tumours.
- Improved understanding of biology of ES has identified many targets amenable to targeted therapy.
- Current clinical trials aim to incorporate targeted therapeutic agents with conventional chemotherapy.
- Since the number of patients with ES is limited, such integration will require new statistical and study design strategies and further international collaboration.

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RHABDOMYOSARCOMA: CONSIDERATIONS IN ACHIEVING LOCAL CONTROL

Bhavna HarilalChawla,[1] Verity Ahern,[2] Jonathan Karpelowsky[3] and Geoffrey B McCowage[1]
1. Departments of Oncology and Surgery, The Children's Hospital at Westmead, New South Wales.
2. Department of Radiotherapy, Westmead Hospital, New South Wales.
3. Department of Radiation Oncology, Westmead Hospital, New South Wales.
Email: geoffm@chw.edu.au

Abstract

Rhabdomyosarcoma is the most common soft tissue sarcoma in childhood, accounting for approximately 6% of paediatric tumours. These tumours arise in various different locations, at all age groups in childhood and adolescence, and with various different histologic subtypes. As a result, there are a number of important considerations that affect the choice of local control measures. Our aim here is to explore these issues. Local control of rhabdomyosarcoma can rarely be achieved by chemotherapy and so local treatment in the form of surgery and/or radiotherapy is essential in most circumstances. Risk stratification which incorporates clinical group stage, TNM stage, histology and tumour location is an important consideration in determining the modality of local control. Other important considerations include resectability and age of the patient. The timing of local treatment is dependant on the tumour location, feasibility of complete resection without unacceptable loss of function or cosmesis, and the presence of an acute emergency such as spinal cord compression.

Rhabdomyosarcoma is a chemotherapy-responsive tumour, and all patients are treated with chemotherapy because this is a systemic disease.[1] The principle North American chemotherapy regimen is vincristine, actinomycin-D and cyclophosphamide (VAC). In European studies, ifosfamide has been substituted for cyclophosphamide (IVA). The role of anthracycline drugs remains controversial; in randomised studies, the addition of doxorubicin or epirubicin did not lead to improved outcomes. However, these drugs do have activity against rhabdomyosarcoma, and some units routinely incorporate them into treatment protocols. A current European study is re-examining the role of doxorubicin, while a recent rhabdomyosarcoma trial within the Children's Oncology Group for patients with 'high risk disease' incorporated doxorubicin in a

single arm trial. This latter trial also added irinotecan, ifosfamide and etoposide; early outcome data appear promising.[2] Irinotecan had earlier been shown to be active in a phase II trial given with vincristine,[3] and is being studied in randomised fashion within an ongoing Children's Oncology Group trial. Other active agents include carboplatin, topotecan, and melphalan.

The use of irinotecan as a radio-sensitiser to improve local control in patients with intermediate risk disease is being evaluated in the most recent Children's Oncology Group study. Doxorubicin is a potent radiosensitiser, however anthracyclines are usually used only at the beginning of a radiotherapy regimen. The administration of anthracyclines concurrent with radiotherapy, or in the immediate post-radiation period, should be avoided as it often results in unacceptable augmentation of normal tissue radiation toxicity and a radiation recall phenomenon. Other novel radiosensitising agents, including idoxuridine, razoxane and ifosfamide have also been evaluated.[4]

Within North American studies, local therapy, comprising surgery and/or radiation therapy, has been applied systematically.

A different philosophy was adopted in European trials. Because of the long-term morbidities often associated with local therapies, a strategy of evaluating chemotherapy response prior to local therapy was adopted. Those patients, who responded promptly, and completely, did not undergo radiation therapy. The expectation was that there would be patients who had a recurrence, but that a second course of treatment, including a local therapy, might be able to achieve a durable second remission. Indeed, this is what the data showed, and so these European trials have lower event free survival than the North American trials, but equivalent overall survival rates confirmed that certain relapsing patients were indeed salvaged.[5]

It is clear that local treatment is essential for local control at least in certain settings.

Initial surgery and work up

Patients with rhabdomyosarcoma are allocated a pre-treatment clinical stage and a post surgical clinical group, both of which carry prognostic significance.

Staging is a modification of the UICC-TNM staging system and is based on site, size, clinical regional nodal status and distance spread. 'Staging' is clinical and should be performed by the responsible surgeon based on pre-operative imaging and physical findings (table 1). Intraoperative and/or pathologic results do not affect the stage. Site designation alters stage, with certain sites considered favourable and others unfavourable. Careful evaluation of clinical and/or imaging finding should precede multi-disciplinary site assignment.

The surgical-pathologic (clinical) 'group' is based on intraoperative findings and postoperative pathologic status, and includes final pathologic verification of margins, residual tumour, node involvement, and cytological examination of pleural, peritoneal and cerebrospinal fluid when applicable.

Final risk stratification within recent North American studies has combined group and stage with histological sub-type. Low, intermediate and high-risk groups are therefore defined (table 2). Similarly complex stratification takes place within European trials.

Table 1: *The distribution of histological types in 142 patients with musculoskeletal tumours – 2002.*

Group	Definition
I	Localised tumour, completely removed with pathologically clear margins and no regional lymph node involvement.
II	Localised tumour, grossly removed with (a) microscopically involved margins, (b) involved, grossly resected regional lymph nodes, or (c) both
III	Localised tumour, with gross residual disease after grossly incomplete removal, or biopsy only
IV	Distant metastases present at diagnosis

Stage	Sites of primary tumour	Tumour size (cm)	Regional lymph nodes	Distant metastases
1	Orbit, non-PM head/neck; GU non-bladder/prostate; biliary tract	Any size	N0, N1	M0
2	All other sites	< 5	N0	M0
3	All other sites	< 5 > 5	N1 N0 or N1	M0
4	Any site	Any size	N0 or N1	M1

PM, Parameningeal; GU, genito-urinary; N0, regional nodes not clinically involved by tumour; N1, regional nodes clinically involved by tumour; M0, no distant metastases; M1, distant metastases at diagnosis

Table 2: *RMS risk stratification as per recent North American Studies.*

Histology	Clinical Group	Stage	Age	Risk Group
Embryonal, with variants	I, II, III	1	All	Low
Embryonal, with variants	I, II	2, 3	All	Low
Embryonal, with variants	III	2, 3	All	Intermediate
Embryonal, with variants	IV	4	< 10 years	Intermediate (moved to high for ARST0431)
Embryonal, with variants	IV	4	> 10 years	High
Alveolar	I, II, III	1, 2, 3	All	Intermediate
Alveolar	IV	4	All	High

When possible and reasonable, a wide and complete resection of the primary tumour, with a surrounding envelope of normal tissue, should be performed as an initial and/or subsequent operation. This may be possible with extremity or trunk primaries, but is often not possible with head and neck, orbital and some genitourinary sites. Procedures which would lead to an unacceptable loss of function or cosmesis are not recommended.

Approximately half of all patients have unresectable tumours (clinical group 3) at presentation and 15% have metastatic disease (group 4). Microscopically complete (group 1) and incomplete (group 2) resections are achieved at diagnosis in 16% and 20% respectively.

Patients with unresectable tumours undergo biopsy. Adequate tissue needs to be obtained to facilitate immuno-histochemical and molecular studies. Fine needle biopsies are generally inadequate.

Selected sites require further surgical staging. Patients with extremity tumours should have aggressive sampling of relevant lymph nodes. Lymphoscintography may guide this nodal sampling, especially in truncal tumours; radical lymph node dissection is not performed. Patients over the age of 10 years with para-testicular rhabdomyosarcoma routinely undergo selective ipsilateral retroperitoneal lymph node dissection in North American trials.

The remainder of the staging studies include a computerised tomography scan of the chest, bone scan or positron emission tomography scan, bilateral bone marrow trephines and lumbar puncture in patients with para-meningeal tumours.

Sites considered to be parameningeal:

- Middle ear
- Nasal cavity and paranasal sinuses
- Nasopharynx
- Infratemporal fossa/pterygopalatine and parapharyngeal area.

Modalities for local control

Surgery and external beam radiation therapy are the principle modalities. In general, surgery is preferred where wide resection can be obtained without unacceptable loss of function. Radiation therapy is effective for local control, however is generally associated with growth, developmental and cosmetic abnormalities, as well as a small risk of secondary malignant neoplasia, in the order of 2% long term.[6]

As discussed above, an initial wide resection of the primary tumour at diagnosis is optimal. Primary re-excision of a tumour is defined as a second attempt at complete resection before the initiation of any other forms of therapy. This should be encouraged when an initial excision results in positive margins and further resection can be accomplished without significant functional or cosmetic morbidity. This strategy has been shown to improve survival in selected tumours. In patients with microscopic or macroscopic residual disease, North American investigators have systematically applied external beam radiation therapy following a phase of induction chemotherapy.

More recently, the Children's Oncology Group studied the role of a delayed, or "second look" operation to resect residual tumour at selected sites after induction chemotherapy, and before radiation therapy. The goals of second look surgery are to remove residual tumour and to determine pathological response. The rationale was that the tumour may become amenable to resection following chemotherapy, and that the second look procedure would improve local control and/or allow the use of a lower dose of radiation therapy. The radiotherapy dose was adjusted according to the completeness of the delayed resection - patients with gross residual disease received 50.4 Gy, microscopic residual received 41.4 Gy and those with a complete resection received 36 Gy. Seventy three patients with tumours at the selected primary sites (bladder/extremity/trunk) underwent second look surgery and 84% of these achieved removal of all gross disease and were eligible for a reduced dose of radiation therapy. The authors concluded that a second look operation was feasible, and

was able to be performed in approximately half of the patients with tumours at the selected sites. A majority of patients who underwent induction chemotherapy and delayed surgery were then eligible for radiotherapy dose reduction. Long-term follow-up of disease control is awaited.[7]

Radiation treatment, whether definitive or post-operative, may be delivered by external beam or brachytherapy. Brachytherapy involves the insertion of a radioactive source directly into the tumour or tumour bed, concentrating the radiation dose here rather than scattering radiation dose to surrounding structures. This technique is suitable when the area to treat is small and accessible to implantation or is in proximity to a body cavity.

External beam radiation is delivered by a linear accelerator on a daily outpatient basis and may require the use of general anaesthesia to ensure immobilisation of a younger child. Three dimensional conformal radiation and intensity modulated radiation therapy are technologies in current practice designed to conform the radiation treatment to the target volume as concisely as possible.

Tumour location

Rhabdomyosarcomas occur at multiple different locations throughout the body. Typical rhabdomyosarcoma clinical trial protocols give comprehensive recommendations for local control measures at the various sites. Within this review, we will limit discussion to a few general points at key anatomical sites:

- Orbit Surgery - is generally limited to biopsy and treatment is with chemotherapy and radiotherapy.
- Head and neck (non parameningeal) - Wide excision is appropriate when feasible, giving regard to cosmetic and functional outcomes. Otherwise biopsy is followed by chemotherapy, possible second look surgery and radiotherapy.[8]
- Head and neck (parameningeal) - Sites that are considered parameningeal have been listed previously. In addition to tumour location, tumours are considered parameningeal when there is cranial nerve palsy, skull base bone erosion, or intracranial tumour extension.[9] Radical surgery is usually not indicated. Radiotherapy to parameningeal tumours is generally given following a phase of induction chemotherapy. The exception is with those parameningeal tumours where there is intracranial extension demonstrated on magnetic resonance imaging scans. These patients undergo radiotherapy as soon as possible after diagnosis, along with the initiation of chemotherapy.[10]
- Paratesticular - Paratesticular rhabdomyosarcoma should be excised using an inguinal approach. Transcrotal resection will result in contamination of inguinal lymphatics, and North American studies would suggest hemiscrotectomy in these instances. Staging of retroperitoneal nodes in boys over the age of 10 years is discussed above. Radiotherapy to the nodes is not required in group I tumours, but is used in other groups.[11]
- Genitourinary (non bladder-prostate) - Complete gross removal is appropriate if this is possible without a radical procedure. There is no role for initial aggressive resection such as vaginectomy or hysterectomy. The extreme chemosensitivity of the tumours in this location usually precludes the need for radical surgery. For patients with clinical group III tumours of the uterus or cervix that cannot be completely resected, radiation is recommended at week 13; brachytherapy should be considered. However, the European trials SIOP MMT 84 and 89 concluded that local treatment is not necessary in patients who have a complete response to chemotherapy.[12]
- Genitourinary (bladder/prostate) - Salvage of the bladder and urethral function is an important consideration for tumours arising in this site and can be achieved in at least half the patients. The initial surgical procedure is typically a biopsy usually performed cystoscopically. In the unusual situation of a laparotomy, iliac and para-aortic node sampling should be included, as well as biopsy of any other clinically involved nodes. Martelli et al described conservative surgery with brachytherapy treatment for boys with prostate and/or bladder-neck rhabdomyosarcoma as an alternative to external radiotherapy or radical surgery. It allowed normal continence in nearly all of 24 patients.[13] Despite a conservative approach, 30% of patients may still require ablative surgery and those who are able to preserve their bladders may have significant bladder dysfunction. Brachytherapy allows normal growth and function of the unirradiated bladder and bowel as well as normal growth of pelvic bones and the hips.
- Extremity - The extremity is an unfavourable site for rhabdomyosarcoma, explained only partly by the higher frequency of alveolar tumours at this location. Regional node evaluation is discussed above. Extremity tumours are often amenable to wide or radical resection while sparing the involved limb. The role of primary re-excision should be employed where feasible, if clear margins were not attained at the initial surgery, as this has been shown to improve survival in tumours less than five centimetres. Surgical margins of two centimetres may not be feasible in children and there is no clear evidence that larger margins decrease the chance of recurrence. Post-operative radiation is required for close surgical margins and for all patients with alveolar histology. Brachytherapy may be considered in this situation as well.
- Other sites - These include tumours of the chest wall, paraspinal region, abdominal wall, retroperitoneum, pelvis, biliary tract, perineum, perianal and other locations. As a general principle, complete excision should be performed if feasible and with acceptable morbidity. Radiotherapy is employed if wide resection cannot be obtained.

Timing of local therapy

As discussed above, a wide local resection should be performed at initial diagnosis, or as pre-treatment re-excision following an initial biopsy, if possible with

acceptable morbidity. Resection at a second look operation may be performed following induction chemotherapy; post-operative radiotherapy has been employed in this context within American studies.

The timing of radiotherapy varies. It is given at the start of treatment for those patients with parameningeal tumours with intracranial extension, or if there is an acute emergency such as spinal cord compression. Otherwise radiotherapy is generally given following approximately 12 weeks of induction chemotherapy.

A research question within an ongoing trial of the Children's Oncology Group is whether the delivery of radiotherapy earlier in treatment, at week four of chemotherapy, may improve local control.

When radiotherapy is to be applied to metastatic sites, treatment generally follows a longer phase of chemotherapy, for instance being given at week 20.

Miscellaneous criteria

Special considerations are required for the very young patient, particularly those under the age of 24 months. The long-term sequelae of radiation therapy given to such young patients may make that modality of therapy unacceptable. Clinical trial protocols acknowledge this, and often allow for the clinical team to deviate from those local control guidelines employed in older children.

Very young children with parameningeal tumours and intracranial extension should still undergo radiation therapy early in treatment, as cure cannot be achieved without radiotherapy.

The prognostic significance of tumour histology is well known. Patients with group I embryonal tumours do very well with multi-agent chemotherapy alone, hence radiotherapy is not recommended. However, those with group I alveolar or undifferentiated tumours achieve superior outcomes when radiotherapy is administered.[14] Conversely, in group III tumours, histology did not correlate with the risk of relapse.[15]

Depending on the primary tumour location, consequences of local treatment of rhabdomyosarcoma may include growth disturbances, pituitary failure, cataract formation, hearing loss and dentition malformations. Early referral to a paediatric dentist, endocrinologist, facio-maxillary surgeon or orthopaedic surgeon needs to be co-ordinated through a multidisciplinary clinic.

Failure of local control remains the major cause of treatment failure in rhabdomyosarcoma. Data analysed from the Third Intergroup Rhabdomyosarcoma Study for Group III patients showed that the risk of relapse was 33%, and 71% of relapsing patients had local relapse with or without distant relapse.[15] Radiotherapy as a modality for local control was less frequently used in frontline treatment in European trials; in those studies local recurrence accounted for 85% of treatment failures.

Conclusion

Myriad factors impact on decisions regarding local control. These decisions are best made in the context of a multidisciplinary team, incorporating the sarcoma surgeon, radiation oncologist, paediatric oncologist, radiologist and pathologist.

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ROLE OF RADIATION THERAPY IN THE MANAGEMENT OF SOFT TISSUE SARCOMA

Angela Hong
Department of Radiation Oncology, Royal Prince Alfred Hospital and Central Clinical School, University of Sydney, New South Wales.
Email: ahon6809@mail.usyd.edu.au

Abstract

External beam radiation therapy (pre-operative or post-operative) is an essential part of limb conservation in the management of soft tissue sarcoma of the extremity. The addition of radiation therapy improves local control and provides functional limb conservation. Preoperative and postoperative radiation therapies have different toxicity profiles. Advances in radiation therapy delivery using intensity modulated or volumetric modulated arc therapy have allowed better target coverage and sparing of normal tissues.

The primary management of localised soft tissue sarcomas is surgical resection to achieve a negative margin. Historically, local excision of soft tissue sarcoma resulted in local failure of 50-70%. Generally adjuvant radiation therapy is recommended for all intermediate to high grade sarcomas, with the exception of small (<5 cm) superficial tumours which have been widely excised. For low grade sarcomas, adjuvant radiation therapy is not recommended in the setting of a clear margin. In case of close/positive margins, further surgical excision is the preferred option to adjuvant radiation therapy.

A landmark study by Rosenberg et al established the role of limb conservation in extremity soft tissue sarcoma.[1] Forty three patients were randomised to amputation or limb sparing surgery and postoperative radiation therapy. There was no significant difference in local recurrence, disease free survival and overall survival in the two treatment groups.

The role of postoperative radiation therapy after limb sparing surgery is supported by two randomised studies. The National Cancer Institute randomised 91 patients with high grade extremity tumours to limb sparing surgery followed by chemotherapy alone or chemotherapy plus radiation therapy.[2] A second group of 50 patients with low grade tumours was treated with resection alone versus resection with radiation therapy. With a median follow-up of 9.6 years, the 10 year local control rate for all patients with high grade sarcoma treated with radiation therapy was 98%, compared with 70% for those not treated with radiation therapy, but no overall survival benefit was shown. Of 50 patients with low grade lesions, there was also a significantly lower probability of local recurrence in patients receiving XRT, again, without a difference in overall survival.

A second randomised study by the Memorial Sloan Kettering Cancer Center also confirmed the role of post-operative radiation therapy in local control.[3] In this study of 164 patients, patients were randomised to observation or post-operative brachytherapy after limb sparing surgery. For patients with high grade sarcoma, the five year local control rate was significantly better for those who were randomised to post-operative brachytherapy (89%) than those who were observed (66%). There was no difference in the five year disease specific survival in the two groups. For those with low grade sarcoma, there was no significant difference between the two groups of patients. However, these two randomised trials may not have been large enough to detect a small difference in survival, and the issue between local control and overall survival remains controversial.

In the setting of positive resection margins, the risk of local recurrence remains high despite the addition of postoperative radiation therapy.[1,4,5] Further re-excision to achieve a clear margin should be considered. Several studies have shown that local recurrence is significantly associated with reduced survival on multivariate analysis,[6-9] suggesting that wide surgical margins are necessary. However, an analysis by Heslin et al demonstrated a statistically significant association between a positive surgical margin and the development of distant metastases.[10] Therefore, the positive margin was believed to be simply an indicator of a biologically aggressive tumour. This data suggests that patients who require an extensive surgical resection to obtain negative microscopic margins have a poor prognosis, related to the development of distant metastasis, and that further debilitating surgery or amputation to obtain a clear margin may not be appropriate.

Pre-operative v post-operative radiation therapy

The sequencing of surgery and radiation therapy is often determined by institution preference. The advantages of pre-operative radiation therapy include smaller field size and lower radiation dose, facilitating surgical resection by tumour shrinkage and reducing the risk of seeding at the time of surgery. In the post-operative setting, there is no delay in definitive surgery, less wound complication and no interference with pathological analysis of the resection specimen.

There is only one randomised study comparing pre-operative radiation therapy with post-operative radiation therapy in extremity soft tissue sarcoma.[11] This multicentre trial performed by the National Cancer Institute of Canada compared 50 Gy in 25 fractions of pre-operative radiation therapy with 66Gy in 33 fractions of post-operative radiation therapy. The primary end point of this study was the rate of major wound complication. The trial was closed early by the data monitoring committee because of a significant difference in the primary endpoint. The rate of major wound complication within 120 days of surgery was 35% in the pre-operative group and was significantly lower in the post-operative group (17%, p=0.01). There was no difference in local recurrence rate, or regional and distant failure rate. This study also examined the functional outcome and quality of life using three different instruments in the first year after treatment.[12] The timing of radiation therapy had minimal impact, but there was a detrimental effect on the functional outcome in patients with a major wound complication. As expected, with longer follow-up, patients treated with post-operative radiation had more fibrosis because of the higher radiation dose and larger field size used in the post-operative setting.[13] Pre-operative radiation therapy should only be given to tumours suitable for limb conservation. For extensive tumours where limb conservation surgery is not feasible, pre-operative radiation has no role in limb salvage

Advances in external beam radiation therapy

Traditional 3D conformal radiation therapy in extremity soft tissue sarcoma uses parallel-opposed field or 3-field arrangement covering a large volume of the limb. Sparing of normal surrounding tissue is technically difficult. Large areas of irradiated normal soft tissue increase the risk of severe late morbidity such as fibrosis, decreased range of movement, osteonecorsis, nerve injury and oedema.[14, 15]

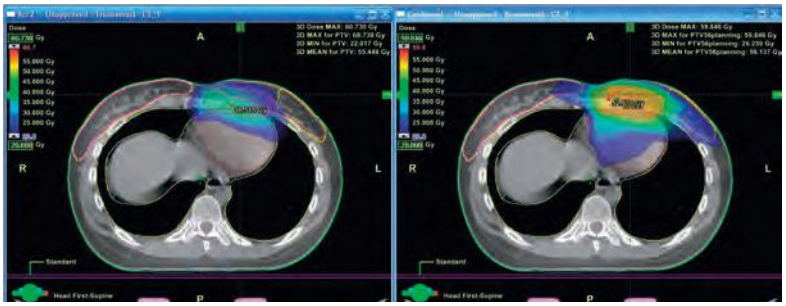
In the last decade, advances in radiation therapy delivery have allowed better sparing of normal tissue outside the treatment target volume. Reduction of the normal tissue exposed to higher doses can be expected to yield significant benefits in terms of decreasing the severity and frequency of radiotherapy related toxicities. Intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) have both been shown to provide better target coverage and tissue sparing than traditional 3-D conformal radiation therapy.[16] Figure 1a shows the dose distribution of a VMAT plan (left panel) and a 3D conformal plan (right panel) for chest wall soft tissue tumour. The VMAT plan has a more homogenous cover and better sparing of the heart, lungs and breasts. Figure 1b shows the better conformality and sparing of the femur and normal structures outside the target volume with VMAT (right panel) than traditional 3D conformal plan (left panel).

In the pre-operative setting, Griffin et al assessed the potential of IMRT to spare future surgical skin flaps in extremity sarcoma IMRT.[17] This was achievable without compromising target coverage and at the same time provided better target volume conformality. The ability of sparing the femur, neurovascular bundle and soft tissue using IMRT in soft tissue sarcoma of the thigh has also been demonstrated.[16, 18]

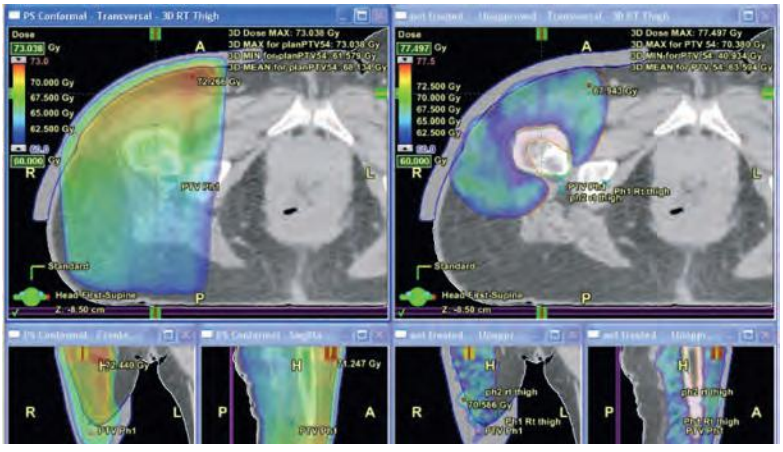
VMAT can sculpt 3D dose distribution with 360 degree rotation of the linear accelerator, while simultaneously varying the rotation speed of the gantry, dose rate and the treatment aperture. It has been shown to be superior to IMRT in terms of target coverage conformality, better sparing of normal structures and significant reduction in treatment time, with the potential of minimising intra-fraction variation for different clinical scenarios.[19, 20] The demonstrated technical superiority of VMAT and IMRT approaches does not automatically imply that this will be associated with a patient derived clinical benefit, however the data presented make this highly suggestive.

Figure 1: *Comparison of VMAT (left panel) and traditional 3D conformal radiation therapy. (a) 33 year-old female with a soft tissue tumour of the chest wall. VMAT provides more homogenous target coverage and better sparing of normal structures (heart, lung and breasts). (b) 57 year-old female undergoing post-operative radiation therapy for a soft tissue sarcoma of the thigh. VMAT (right panel) provides much better sparing of the femur.*

(a)



(b)



Retroperitoneal soft tissue sarcoma

Retroperitoneal soft tissue sarcoma account for about 10% of all soft tissue sarcomas. In most series, complete resection is achieved in less than 70% of cases and local recurrence occurs in more than 50% of patients who have macroscopic complete resection.[21-23] The use of combination surgery with radiation therapy is based on phase III data from soft tissue sarcoma of the extremity. The delivery of adjuvant radiation therapy is complex because of the proximity of radiosensitive normal surrounding structures. Pre-operative radiation therapy is the preferred because of the lower dose required and the displacement of the small bowel away from the radiation field by tumour mass. A prospective study of 72 patients on pre-operative radiation therapy in retroperitoneal soft tissue sarcoma showed 52% local recurrence despite a macroscopic complete resection.[24] The five year local recurrence free survival and overall survival were 60% and 61%.

Conclusion

Radiation therapy has an important role in the management of soft tissue sarcoma. Patients with soft tissue sarcoma should be referred to a multidisciplinary clinic attended by surgeon, radiation oncologist and medical oncologist - where the relative merit of each treatment modality and sequencing of treatment can be discussed. Advances in radiation therapy have the potential of lessening long-term toxicities.

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PRINCIPLES OF LIMB SPARING SURGERY IN BONE AND SOFT TISSUE SARCOMA

Peter FM Choong
Department of Surgery, University of Melbourne, Department of Surgery and Orthopaedics, St. Vincent's Hospital, Melbourne, Bone and Soft Tissue Sarcoma Service, Peter MacCallum Cancer Centre, Victoria.
Email: pchoong@unimelb.edu.au

Abstract

The standard for local control of malignant bone and soft tissue tumours has been amputation. Advances in multimodality treatment have seen a shift towards preservation of the limb. Sophisticated techniques that employ combinations of prosthetic and biologic material now provide a greater opportunity for functional reconstruction of the limb. This review covers the principles of limb sparing surgery and highlights the importance of preoperative staging, adjuvant and neo-adjuvant treatments and surgical margins. Complications are common and should be pre-empted. Limb sparing surgery is a complex procedure that requires expert knowledge of the requirements and criteria for its use. It is an important part of multidisciplinary management of sarcoma and the success of such surgery is maximised when conducted in centres with specific interest and expertise in this field.

Bone and soft tissue sarcomas are rare mesenchymal malignancies that arise in two to four per 100,000 head of population.[1,2] The limbs are the commonest sites for sarcoma, with over 50% of soft tissue and bone sarcomas occurring in the lower limb. The advent of multimodality treatment with advances in chemotherapy, radiotherapy and surgery, all supported by more sophisticated diagnostic and imaging techniques, has led to considerable improvement in long-term survival. Overall survival following treatment of primary sarcoma now approaches 75% at five years, and surgery remains the mainstay of treatment.[1, 2] Surgery to resect the tumour followed by reconstructions to preserve function, mobility and aesthetics (limb sparing surgery) has now replaced amputation as the primary form of surgical intervention.[3-5]

Criteria

Limb sparing surgery may be considered when specific criteria are met, including:

- tumour resection occurs with oncologically sound margins
- reconstruction leads to a functional limb
- all soft tissue defects can be closed primarily or with soft tissue transfers.

Previously a sensate lower limb was thought to be mandatory for limb sparing surgery. Sacrifice of the sciatic nerve traditionally led to lower limb amputation for fear of developing chronic non-healing trophic ulceration of the foot. However, with better awareness of foot hygiene and shoe wear, limb sparing surgery is now practised despite the need to include the sciatic nerve in resections of proximal thigh or pelvic tumours.[6, 7]

Indications

Limb sparing surgery is indicated when:

- tumour is resectable with oncologically sound margins
- survival is long enough to justify complex surgery
- the patient refuses amputation and accepts the risk of local recurrence of disease from inadequate margins
- palliating patients with limb disease that is easily and safely operated on to improve quality of life eg. impending fractures, fungation.

Contraindications

Limb sparing surgery is contraindicated when

- surgical margins are expected to be inadequate for managing the primary tumour
- survival is not expected to exceed three months
- there is gross contamination of the adjacent soft tissue compartments with tumour through poorly performed biopsy, pathologic fracture or inadvertent surgery with positive margins
- local or systemic sepsis is a concurrent problem, or patient co-morbidities do not permit safe anaesthesia or surgery.

Diagnosis and staging

Accurate diagnosis is critical to successful treatment. Appropriate choices of chemotherapy agents or radiotherapy depend on correct identification of the type of sarcoma.[8-13] For example, chemotherapy differs between osteosarcoma, Ewing sarcoma and myxoid liposarcoma. Soft tissue sarcomas comprise a heterogeneous group and consensus on grade, type and subtype of sarcoma can be difficult to achieve.

Biopsy is fundamental to obtaining an accurate histological diagnosis. In principle, the same group that will be undertaking definitive treatment should perform biopsy of primary bone and soft tissue sarcomas. This is because the placement of the biopsy site and the avoidance of post-biopsy complications, such as haematoma or

infection, may influence the potential for undertaking limb sparing surgery. Biopsy, whether open or closed, should always be done in the line of the operative incision to allow inclusion of the biopsy site in the definitive resection. It is our preference to perform CT-guided core needle biopsies.[14]

Local staging of the tumour is important for planning surgery. The tumour size, site, shape, consistency, edge, capsule and adjacent structures are important information for planning the surgical margins and reconstructions after assessing response to neoadjuvant therapies. Imaging of the limb should include plain radiographs, CT, MRI, PET or thallium scans.[15, 16] In addition, CT scans of the chest are mandatory for assessing systemic spread, because pulmonary involvement is the commonest site for first metastases. Evidence of metastasis is likely to affect the nature of care and therefore all efforts to diagnose metastases should be undertaken.

Adjuvant therapy

Pre-operative (neoadjuvant) chemotherapy or radiotherapy is fundamental to managing bone and soft tissue sarcomas, respectively. The benefits of adjuvant therapy include:

- inducing local tumour necrosis
- reducing tumour size
- formation of a peritumoral "rind" of fibrous capsule.

These effects may aid the planning of surgical margins, improve the resectability of tumours and allow greater safety when dissecting close to vital neurovascular structures.

The response to neoadjuvant therapy may be critical for determining if limb sparing surgery or amputation should be performed. For example, there is a correlation between local recurrence and response to chemotherapy in osteosarcoma.[17] Moreover, the risk for local recurrence rises substantially when margins of resection diminish.[17] Therefore, if pre-operative imaging demonstrates that the response to neoadjuvant chemotherapy is poor and if planned surgical margins are expected to be close, then to avoid locally recurrent disease, amputation may be preferable over limb sparing surgery. This information is valuable in the pre-operative counselling of patients and for the obtaining of informed consent for surgery.

Surgical margins

Adequacy of surgical margins correlates directly with the incidence of local recurrence and relates to the quality and quantity of tissue around the tumour that is included in the resected specimen.[18-20] The definition of surgical margins are as follows:

1. Intralesional margins are those where the resection enters the tumour.
2. Marginal margins are those where the surgery passes through the reactive zone of inflammation that surrounds the pseudocapsule of a tumour. "Shelling out" of a tumour is said to be marginal surgery.
3. Wide margins are those where the resected specimen includes at least two centimetres of normal tissue in the longitudinal plane and one named normal anatomic boundary in the radial plane. A named fascia, or muscle layer would represent an anatomic boundary.
4. Radical margins are those where the resected specimen includes the entire tumour bearing compartment. For example, resection of the entire quadriceps musculature from origin to insertion, and from lateral to medial intermuscular septae, may be regarded as a compartectomy because the quadriceps musculature is the sole content of the anterior compartment of the thigh.

The quality of the anatomic boundary is also relevant when determining the adequacy of the margin. The fascia lata is a very tough tissue, although it may be only a few millimetres thick. If the fascia lata is included as an uninvolved boundary, then the resection may be regarded as wide.

Intralesional and marginal margins are regarded as being inadequate surgical margins, while wide and radical margins are regarded as adequate surgical margins in the management of sarcoma. Marginal margins may be equivalent to wide margins alone when combined with radiotherapy or chemotherapy. Marginal margins are usually avoided, however may be important when having to preserve important neurovascular structures.

Reconstructive options

A wide variety of reconstructions are available for limb sparing surgery. These include:

- prosthetic reconstructions
- biologic reconstructions
- combination of biologic and prosthetic reconstructions.

Reconstructions may also be mobile or rigid. These refer to the preservation or fusion of a previously mobile joint at reconstruction.

Tumour prostheses take their origins from the evolution of standard joint prostheses. Advances in metallurgy, tribology and prosthetic fixation have allowed the development of modular implants that can be individualised to each patient, while exhibiting strength and durability.[21-23] Prostheses for the hip and knee were the first to be developed and today, prostheses are also available for the shoulder joint, scapula, elbow, total humerus, ulnar, total femur, pelvis and the ankle.

Improvements in computer aided design of prostheses and manufacturing techniques now allow the custom creation of unique prostheses to accurately match the defect created by tumour resection. Such customised machining of prostheses is matched with computer guided surgery to ensure that the exact resection shape is created during surgery, to allow accurate matching of resection defect with the customised implant. These techniques require rigorous planning and dialogue between manufacturer, surgeon and imaging specialists.

Biologic reconstructions

One of the earliest attempts at limb sparing surgery was the arthrodesis of the knee after resection of tumours of the distal femur. In an attempt to span the gap between femur and tibia created by distal femoral resection, a segment of the ipsilateral tibia would be elevated and used to span the tibio-femoral gap in an arthrodesis procedure. Held by a long arthrodesis nail, the construct would permit full weight bearing after the bone graft united with the remnant femur and tibia.

The popularity of bone banks soon permitted harvest and storage of large structural allografts, which were then employed in place of autograft bone to fill the defect of tumour resection.[24] Allograft bone had a number of advantages including:

- reducing donor site morbidity
- ready availability
- unlimited supply.

The disadvantages of allograft bone included:

- potential for disease transmission
- graft disintegration
- infection
- non-union.

The availability of modern internal fixation devices has helped to support the allograft constructs and long-term results have been acceptable.

The fibula has been a versatile resource for reconstructing defects of up to 22 centimetres. The fibula may be used as a vascularised or non-vascularised graft and has been utilised in a number of innovative ways,[25, 26] including spanning defects, creating articulations, arthrodesis of joints and in combination with allografts.

Other innovative methods of biologic reconstruction include the role of extracorporeal radiotherapy to sterilise the tumour bearing bone immediately after resection, and then to reimplant the resected bone back into the resection site.[27] This technique utilises established radiotherapy techniques to deliver up to 10 times the normal radiotherapy dose to tumour bearing bone in a single fraction. By performing this in an extracorporeal fashion, the anticipated toxicities of such high doses can be avoided. Moreover, the technique has the advantage of reconstructing the defect with a perfectly sized matched construct. To date, reported series have not encountered recurrent tumour following reconstruction using this technique.

Allograft prosthetic composites

Allograft prosthetic composites (APC) capitalise on the advantage of allograft bone to rebuild bone stock to the post-operative defect, while permitting the predictability of prosthetic joint replacement to regain stable joint motion. Large defects created by the resection of a joint and the adjacent diaphysis and metaphysis can be reconstructed by the use of allograft bone that includes a metaphyseo-diaphyseal segment, on to which a standard joint prosthesis may be cemented. The most common sites where APC are used include the hip (proximal femur), knee (distal femur or proximal tibia) and the shoulder (proximal humerus). Residual soft tissue attachments on the allograft allow host to allograft tendon and ligamentous reconstructions, which improve the stability and function of the reconstructed joint.

Complications specific to limb sparing surgery

Complications following limb sparing surgery may be devastating, with the potential for loss of the limb or unplanned cessation of chemotherapy.

1. Limb sparing surgery typically entails prolonged surgical time with exposure of the operative field to the external environment. The risk of infection is directly correlated with the duration of surgery, and the lowered resistance of the patient through chemotherapy and that of the tissue through radiotherapy further compound this. Infection has been reported to be as high as 30% in some series. The addition of prosthetic material also raises the risk of local infection, because foreign bodies can act as nidus for infection. Infection not only can lead to prolonged delays in wound healing, but may also delay the recommencement of chemotherapy. The use of antibiotics during and after surgery, regular irrigation of the operative field with sterile fluid and antiseptic, careful handling of tissue, minimising the creation of dead spaces and observance of sterile technique, lower the risk of infection.
2. Unplanned neurovascular injury usually results from dissection around large tumours or in confined spaces where there is a confluence of vital structures eg. popoliteal fossa. The need to create an oncologic margin may bring the dissection close to nerves and vessels, which lie adjacent to the tumour. Careful dissection and retraction can help to minimise injury. Patients undergoing chemotherapy may be more susceptible to neuropraxia during surgery because of the “priming” of nerves by the toxicity of chemotherapeutic agents. The peroneal nerve is not infrequently a victim of neuropraxia.
3. Devascularisation of soft tissue flaps is a constant threat in large and complex dissections. This may lead to skin necrosis and dehiscence of the wound, which in turn is an important antecedent factor behind infection. Wound healing problems are most common after preoperative radiotherapy, however few require reoperation for resolution. Careful dissection and preservation of muscle vascularity, avoiding narrow soft tissue flaps and skin islands, minimising tension across wounds during closure, judicious use of soft tissue transfers to obliterate dead spaces after surgery and using drains to avoid deep haematomas are ways of protecting soft tissue from necrosis.

4. Dislocations on the hip and shoulder are a risk after limb sparing surgery because of the need to remove important and significant quantities of soft tissue structures that may be critical for maintaining joint stability. For example, resection of the joint capsule and abductors of the hip predispose that joint to dislocation. Excision of the rotator cuff musculature during proximal humeral resection may predispose the humeral prosthetic reconstruction to instability. Careful reconstitution of restraining forces by soft tissue transfers or plication, and addition of pliable synthetic material around joints, may help to reduce the incidence of joint dislocation.

5. Fractures may occur after limb sparing surgery because of the potential to devascularise bone from radiotherapy, extensive ligamentous or muscular detachment or subperiosteal dissections. Almost one fifth of long bones which have undergone circumferential subperiosteal dissection of tumour after radiotherapy fracture, with the majority of these occurring within two years of the index surgery. Prophylactic internal fixations with intramedullary rods are indicated where high risk of fracture may be anticipated.

Salvaging limb sparing surgery after a complication is a complex task, but may be undertaken in certain circumstances. Careful planning and a multidisciplinary approach is required. Innovative techniques are available that may result in a functional limb.[28, 29]

Conclusion

Limb sparing surgery is the technique of choice for surgical management of limb sarcomas. In comparison to amputation, limb sparing surgery:

- has the same overall survival rate
- has higher patient satisfaction
- has a lower energy expenditure for walking
- has a lower cost to the community.

Limb sparing surgery is a complex procedure that requires expert knowledge of the requirements and criteria for its use. It is an important part of multidisciplinary management of sarcoma. The success of such surgery is maximised when conducted in centres with specific interest and expertise in this field.

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ROLE OF PULMONARY METASTASECTOMY IN OSTEOSARCOMA AND SOFT TISSUE SARCOMA

Rachel F Dear[1] and Martin HN Tattersall[2]
1. Sydney Cancer Centre, Royal Prince Alfred Hospital, New South Wales.
2. University of Sydney, New South Wales.
Email: rachel.dear@sydney.edu.au

Abstract

There are no randomised control trials to guide the management of patients with potentially resectable lung metastases from osteosarcoma and soft tissue sarcoma, however evidence from retrospective cohort series supports that all patients should be considered for pulmonary metastasectomy. Pulmonary metastasectomy can improve overall survival and some patients may even be cured. Careful patient selection is important. The most important favourable prognostic factor after pulmonary metastasectomy, in both osteosarcoma and soft tissue sarcoma, is the ability to achieve complete resection of metastatic disease. Incomplete resection carries a shorter survival than complete resection of lung metastases in almost all series. The outcome is poorer if the primary tumour is not controlled or, if there is a local recurrence that is not controllable. Patients with metastatic disease outside the lung are generally excluded from pulmonary metastasectomy. The number of lung metastases is not a contraindication to metastasectomy, nor a poor prognostic factor if it is assessed the metastases can be resected. It is not uncommon to perform sequential metastasectomies for bilateral disease. Even when features associated with a poor prognosis are present (for example high grade tumours), pulmonary metastasectomy may improve the survival of these patients because their survival without it is less than one year. Recurrence of lung metastases after pulmonary metastasectomy should be treated with repeat pulmonary metastasectomy if complete resection can be achieved. The addition of peri-operative chemotherapy is widely used, but its effectiveness remains an area of controversy and is a priority for future research.

Epidemiology

Patients with metastatic sarcoma were rarely considered for pulmonary metastasectomy (PM) prior to the 1970s, were treated palliatively and most died within one year of the development of metastatic disease. Variability in individual survival reflected the different histological types and biological behavior of the histological subtypes of soft tissue sarcoma (STS).

The lungs are the most common site of metastatic disease in sarcoma. Pulmonary metastases develop in 20% to 38% of all STS patients.[1-3] Even today, 30% of patients with osteosarcoma develop disease recurrence even after optimal surgery and chemotherapy, and more than 80% of these relapses are in the lungs.[4, 5] Long-term survival after recurrence is reported to be less than 20 to 30%.[4, 6-9] Most patients who die of metastatic sarcoma will have pulmonary metastases.

Pulmonary metastasectomy

PM is a surgical procedure to resect metastases from the lung. The surgical approach is similar whatever the primary tumour site of origin. Currently, PM may be considered in a number of primary cancers, including colorectal cancer, germ cell tumours, melanoma and renal cell cancer, as well as osteosarcoma and STS.

Surgical exploration of the chest may be performed by thoracotomy or thoracoscopy. The surgical approaches and procedures to resect metastases include segmentectomy, wedge resection, lobectomy and rarely pneumonectomy. Most pulmonary metastases can be removed by wedge resection. Bilateral synchronous metastases are usually treated with staged (sequential) procedures.

Advances in anaesthesia, surgical techniques and peri operative care have resulted in low peri-operative mortality and morbidity. Thoracoscopic resection has reduced peri operative complications and in-hospital stay. Mortality rates in recent series are less than one per cent and operative complications less than 10%. Potential complications include haemorrhage, infection, prolonged thoracostomy tube drainage, chest wall pain and reduced lung function.

Metastases to lung are most commonly blood borne. The growth rate of micrometastases is conventionally thought to be continuous at least until metastases are detected.[10] However, clinical observation is not always consistent with this model and some patients followed closely without recurrence for several years suddenly present with large volume metastatic disease. The continuous growth model does not explain these events.

Alternative models of metastastic growth have been proposed. Demicheli et al propose that micrometastases present in the pre-clinical phase, grow at different rates depending on tumour and/or host factors.[11] Micrometastases can escape dormancy by at least two different mechanisms: a) the loss of an angiogenesis inhibitor; or b) the transformation of a subpopulation of tumour cells to an angiogenic phenotype.

The continuous growth model predicts that metastatic cancer will rarely be curable by surgical removal. Long-term survival after resection of the primary tumour can be explained by the absence of metastases or by the slow growth of microscopic metastases. In contrast, the tumour dormancy model predicts elimination of metastatic disease is possible by a complete response following systemic treatments or removal of tumour cells with an angiogenic phenotype. A complete response is essential for long-term survival and this most commonly may be achieved by metastasectomy in selected cases.

An alternative hypothesis is that adjuvant chemotherapy eliminates rapidly dividing tumour cells in micrometastases, but slow growing or dormant micrometastatic disease can remain. These transiently dormant or slow growing cells are the source of isolated pulmonary or hepatic metastases, which become apparent after completion of adjuvant chemotherapy. Surgical removal can potentially eliminate all disease.

Another rationale for metastasectomy is that untreated metastases may give rise to other metastases - tertiary spread.[12,13] Metastasectomy may prevent further dissemination of disease to other metastatic sites.

Retrospective single institution cohort studies have reported that PM has significantly improved the life expectancy of patients with metastatic osteosarcoma and STS, with five year overall survival rates of 25 to 40%. Some of these patients are 'cured'. In STS, five year overall survival of 18% to 44% is reported after PM.[2, 14-18] The variability in survival is most likely due to patient selection and the different duration of follow-up in reported series.

A number of studies in osteosarcoma have retrospectively analysed outcomes in all patients presenting with disease recurrence, both limited to the lung and outside the lung. Overall survival is improved in those who achieve a complete surgical resection. In almost all patients surgery was for lung metastasectomy rather than resection of other sites of metastatic disease. Five year overall survival reports range from 39% to 50% for those with complete surgical resection compared to 0% who did not have surgery.[19, 20] In the former study, the median survival period for patients achieving a second surgical remission was 2.2 years (range, five days to 18.4 years), compared with 0.6 years for other patients (range, two days to 3.7 years).

There are a number of problems with the existing evidence that supports PM. Retrospective studies are subject to selection bias. In many reports it is unclear if the survival figures relate to overall survival (any death after PM) or crude survival (death related to sarcoma after PM). Disease free survival data are rarely presented. The absence of randomised control trials makes the survival effects of PM difficult to assess.

Prognostic factors for overall survival

The prognostic factors statistically significantly associated with survival vary across the reported series of PM. Below is a summary of the existing evidence about the effect of the most commonly assessed prognostic factors.

Two studies have reported a better outcome for patients younger than 40 years compared to older than 40 years at diagnosis.[16, 21] One study reported females have a better outcome than males, but in the majority of studies where it has been examined there is no significant gender difference.[14, 22-29]

Two studies have found a longer survival for a trunk primary, [22, 23] and one study has found a better prognosis for a limb primary.[21] Primary tumour histological type has been reported to influence survival after PM. Malignant fibrous histiocytoma was reported to have a better outcome than other types.[15] In other studies malignant fibrous histiocytoma has been reported to have a worse outcome.[17,30] Synovial sarcoma has been reported to have a worse outcome.[17,25] High tumour grade is reported to be a poor prognostic feature.[16,25, 26, 31] Others have found no association.[14, 21, 27-29, 32]

Disease free interval (DFI) (time from treatment of primary tumour until evidence of lung metastasis) is considered one of the most important prognostic factors and is thought to be a surrogate marker for disease biology. Although not confirmed in all reports,[15,21,25,26,28,29,33] a longer disease free interval is associated with a long overall survival after PM. Most studies report improved survival for a DFI longer than 12 months.[3,22-24, 27, 34] Others have found a statistically significant advantage for a DFI of more than 18 months,[30] more than 2.5 years,[16] and more than 25 months.[14]

Apart from one report showing a longer survival for unilateral disease,[15] the majority of studies show no difference in survival for unilateral metastases compared to bilateral metastases. Many studies report that the number of metastases, either on pre-operative imaging and/or on surgical pathology, has no bearing on prognosis.[16,21-23,28,29,32,33] In contrast, other studies report a shorter survival after PM for a greater number of metastases. The cut-off varies from two or more,[30] three or more,[35] four or more,[15] or five or more.[24] The maximum diameter of metastases on pre-operative imaging and/or surgical pathology has been examined as a prognostic factor in a limited number of studies.[17, 30] In both cases a diameter greater than two centimetres was found to carry a worse prognosis. Studies report that there is no difference in life expectancy in patients treated by unilateral thoracotomy (or thoracoscopy) and a bilateral (staged) procedure.[2, 16, 25, 26, 29]

Almost all studies report that complete resection of metastatic disease (histologically clear margins) is critical for long-term survival after PM. For example, Billingsley reported that the median survival time among patients with completely resected disease is 20 months, compared with 10 months for patients who have incompletely resected disease.[3] It seems that patients with an incomplete resection have a prognosis similar to patients who do not have a PM. Two small studies did not report a statistically significant effect on survival for complete resection.[21, 25]

In osteosarcoma most studies addressing prognostic factors for survival concentrate on children and adolescents, whereas adult patients constitute only a small proportion.[5] Complete resection of metastatic disease has consistently been shown to be an independent prognostic factor for survival.[20, 36-39] Patients with residual microscopic compromised surgical margins, or measurable disease, are unlikely to be cured. As for STS, a longer DFI is also associated with a longer survival after PM.[36, 40, 41] In most reports a DFI of less than 12 months carries a worse prognosis,[5, 42, 43] but others have found a cut-off of 24 months to be important.[7] In contrast to STS, the number of lung metastases appears to be an important prognostic factor for survival in osteosarcoma. Some reports show solitary lesions have a better prognosis.[19, 20, 42, 44] In other reports less than three to four nodules is favourable compared to more than four.[5, 7, 36] Only a few studies report the number of lung metastases is not a prognostic factor for overall survival.[43, 45]

Age, sex and metastases in one or both lungs have not been shown to be important prognostic factors. In 247 patients with lung metastases (47 of which had a PM) there was no survival difference for patients greater than or equal to 40 years, compared to those less than 40 years.[5] In one report of paediatric patients, males had a better overall survival than females.[8]

Patient selection

All patients with metastatic osteosarcoma and STS should be evaluated for the possibility of PM.[3, 14, 25, 29, 46-49]

Careful patient selection is important. The most important favourable prognostic factor after PM in both osteosarcoma and STS is the ability to achieve complete resection of metastatic disease. Incomplete resection carries a poorer prognosis in almost all series. Patients being considered for PM should have a good performance status and be a medical candidate for anaesthesia and lung resection. The primary tumour site should be controlled or, if there is a local recurrence, it should be controllable. Patients with metastatic disease outside the lung are generally excluded from PM. In general a high number of metastases is not a contraindication if it is felt they can be resected. It is not uncommon to perform sequential metastasectomies for bilateral disease. Even when features associated with a poor prognosis are present (for example high grade tumours) these patients are most likely to live longer with PM because their life expectancy without PM is less than two years.

Data collected by the International Registry of Lung Metastases, established in 1991 to assess the long-term results of PM, highlight important prognostic factors.[50] Of 5206 cases of PM from departments of thoracic surgery in Europe, the United States and Canada, the primary tumour was epithelial in 2260 cases, sarcoma in 2173, germ cell in 363 and melanoma in 328. The actuarial survival after complete resection was 36% at five years (median 35 months) and for incomplete resection was 13% at five years (median 15 months). Among complete resections, the five year survival was 33% for patients with a DFI of less than 12 months and 45% for a DFI of greater than 36 months; 43% for solitary metastases and 27% for four or more metastases. Multivariate analysis demonstrated a better prognosis for patients with germ cell tumors, DFI of greater than 36 months and solitary metastases. These three factors were used to develop a useful prognostic grouping applicable to sarcoma, as well as melanoma, epithelial and germ cell tumours:

- Group I resectable, no risk factors (DFI greater than or equal to 36 months, solitary metastasis), median survival 61 months
- Group II resectable, 1 risk factor (DFI less than 36 months or multiple metastases), median survival 34 months
- Group III resectable 2 risk factors (DFI less than 36 months and multiple metastases, median survival 24 months and
- Group IV unresectable, median survival 14 months.

Peri operative chemotherapy

Peri operative chemotherapy in conjunction with metastasectomy may destroy micrometastatic disease. It may be given pre or post thoracotomy or both. Peri operative chemotherapy (particularly given pre-operatively) may be particularly advantageous for patients with a DFI of less than one year and other unfavourable prognostic factors. If recurrence occurs more than one year after treatment for the primary sarcoma, consideration of PM alone without chemotherapy is reasonable. Alternatively, PM followed by adjuvant chemotherapy may be considered. Peri operative chemotherapy does not lead to increased morbidity or mortality after thoracotomy.[21]

Existing evidence does not support the routine use of peri operative chemotherapy. This might be a problem of selection bias in the retrospective case studies because chemotherapy tends to be used in patients where the relapse pattern suggests aggressive tumour behaviour.

There is conflicting evidence about the benefit of peri operative chemotherapy in STS. Pastorino reported a longer three-year survival (from 27% to 60%) when peri operative chemotherapy was included with surgical treatment of lung metastases.[51] It is possible that this benefit was due to patient selection. On the other hand, Lanza showed no survival benefit for 26 patients who had peri operative chemotherapy followed by PM.[52]

Some studies have shown children have better survival when peri operative chemotherapy is given with PM.[44,53] Kempf-Bielack demonstrated chemotherapy use correlated with a favourable event-free survival compared to those who did not have chemotherapy.[19] However, most studies do not demonstrate a survival benefit with the addition of chemotherapy to PM in osteosarcoma. In 125 patients made surgically disease free by PM, chemotherapy did not increase post-relapse free survival, although there was a suggestion of a positive role in patients with three or more pulmonary nodules.[7] One other study confirms this finding.[4]

Cost effectiveness

Porter compared the cost effectiveness of four treatment strategies for pulmonary metastases in STS: 1) PM; 2) chemotherapy (doxorubicin and ifosfamide); 3) PM and chemotherapy; and 4) no treatment.[48] In 1999, the mean cost of PM was US$20,339 per patient and the mean cost of six cycles of chemotherapy was US$99,033. Compared with no treatment and assuming a 12 month survival advantage with chemotherapy, the incremental cost effectiveness ratio was US$14,357 per life-year gained for PM, US$104,210 per life-year gained for chemotherapy, and US$51,159 per life-year gained for PM and chemotherapy. Compared with PM, the incremental cost effectiveness ratio of PM and systemic chemotherapy was US$108,036 per life-year gained. The authors concluded that PM was the more cost effective management strategy, even with favourable assumptions regarding the benefit of chemotherapy.

Repeat pulmonary metastasectomies

Sixty nine per cent of patients having PM for STS will develop recurrent lung metastases following complete resection.[2] Repeat thoracotomies are considered for subsequent pulmonary recurrence if all the disease can be resected. Most series report a favourable prognosis for repeat resection, with five year survival after the second operation up to 36%,[54] and a median survival of approximately 25 months.[55] Complete resection is the most important prognostic factor.[54-57]

Similar survival outcomes after a second PM have been reported in osteosarcoma. In 94 patients having a second PM, three and five year event-free survival probabilities were 33% and 32%, respectively.[58]

In an unselected cohort series of 249 patients with second osteosarcoma recurrences of any site, five year actuarial overall and event-free survival rates were 16% and 9% respectively.[6] As for first osteosarcoma recurrences, longer DFI and solitary lesions at recurrence correlated with better outcomes.[19] Among the 119 patients who achieved a second surgical remission, the five year actuarial overall survival rate was 32%.[6] Even after subsequent recurrences, the five year survival estimate for patients who again achieved surgical remissions was approximately 25%. As reported by others, there was almost no long-term survival without surgical clearance, re-enforcing the importance of surgery in the curative therapy of recurrent osteosarcoma.[9]

Research priorities

Health related quality of life is an important consideration after any medical intervention, particularly when the intervention is performed in the setting of advanced cancer and where the evidence of survival benefit is uncertain. Health related quality of life has not been measured prospectively in patients undergoing PM for metastatic sarcoma. During 2010, a new study will commence, titled “A prospective longitudinal cohort study describing quality of life in patients undergoing pulmonary metastasectomy for metastatic sarcoma”, supported by the Australian Sarcoma Study Group and Psycho-oncology Cooperative Group. This study will collect clinical and quality of life data in patients undergoing PM for lung-only metastatic sarcoma from around Australia and New Zealand.

The optimal treatment strategy using surgery and chemotherapy in relapsed sarcoma is unknown due to the absence of prospective trials. A European Organisation for Research and Treatment of Cancer randomised trial of PM and peri operative chemotherapy was closed due to poor accrual in the mid-1990s. More recently there has been renewed interest in this unresolved question. One of the most important aspects of the Australian Sarcoma Study Group and Psycho-oncology Cooperative Group study is that it will provide information about the frequency, nature and timing of systemic therapy used in combination with PM. It is envisaged that these data will inform a multi-site randomised trial of PM and/or systemic therapy. The challenges of such a study include the rarity of sarcoma and the heterogeneity of sarcoma pathology and biology. With international collaboration these difficulties can be overcome and provide worthwhile data to improve the outcomes of sarcoma patients with lung-only metastases.

Conclusion

All patients with osteosarcoma or STS and potentially resectable lung metastases should be evaluated for PM. PM is a procedure with low operative mortality and morbidity which may improve survival, and even cure some patients. Patients with a lung recurrence after PM should also be assessed for PM if complete resection can be achieved. The role of peri operative chemotherapy is uncertain and is a priority for future research to improve the outcome for these patients.

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IMPORTANCE OF MOLECULAR GENETICS OF SARCOMAS

David M Thomas
Research Division, Peter MacCallum Cancer Centre, Victoria.
Email: david.thomas@petermac.org

Abstract

Sarcomas represent a paradigm for rare cancers. Rare cancers have historically presented significant challenges, because traditionally clinical trials require significant numbers of patients to achieve adequate statistical power. In part, this was due toe the lack of efficacy of the treatments used for sarcomas, and in part to the sheer heterogeneity of subtypes within this uncommon group of cancers. It is arguable that recent developments in molecular genetics are transforming the outlook for patients with rare cancers. Since the sequence of the human genome was published in 2001, the landscape of cancer genetics has changed forever. A combination of the accelerating progress in genomic technologies, together with the raft of molecularly targeted therapeutic agents, is fundamentally altering the face of clinical trials in sarcomas. These developments in molecular genetics of sarcomas, and their current and future impact on clinical care will be reviewed. These changes throw out a new challenge to clinicians treating rare diseases, and those responsible for health care systems to avoid being rate-limiting in translating science into clinical benefit.

Sarcomas are rare cancers, which are increasingly treated by a handful of experts in remote ivory towers. There are so many sarcomas, each more individually rare than the last! Many of them have dreadful consequences, and nothing has really changed, has it? Moreover, what earthly use is molecular genetics to a clinician at the coalface? The litany of unintelligible acronyms that constitute many papers on the molecular genetics may be enough to turn even the boldest off an article - even in *Cancer Forum.*

Let me persuade you to read on. In return, I will provide a satellite level overview of the genetics of sarcoma, pointing out key areas of interest and putting our patients right at the heart of the matter. I promise to avoid jargon as much as I can; if I do weaken, it will be to make an important general point. I do not intend to delve into each of the 70+ subtypes of sarcoma, but to illustrate my messages with examples that will make my meaning clear.

The rarest diseases can have the most important consequences - nowhere is this more true than for the collection of diseases collectively called sarcomas. That the future of modern cancer care is fundamentally changing, so fast that it is bewildering. However, it is increasingly critical for our patients that we bring the emerging world of molecular cancer genetics into our consulting rooms.

Molecular genetics, histopathology, and cancer classification

Do rare cancers like sarcomas really matter? With limited resources, utilitarians teach us that the greatest good for the greatest number should guide difficult decisions. It is arguable that we should place our money not only where the need is, but where it can make a difference. However, the question is cruel. No patient has ever been cheered by the thought that their cancer is rare; to the patient, rare cancers are life itself. But rare cancers do matter to all of us, because one in five cancers lies outside the top 10 (bowel, breast, prostate, lung and so on), and they cause one in three cancer deaths.[1] Rare cancers also have been traditionally neglected, because up until the past decade, we haven't really known how most of our treatments work. If you use a blunderbuss, the details don't matter. 'Treatment' or 'therapy' - in this context I mean drug treatments, unless otherwise stated.

A recent survey showed that there was an inverse relationship between the incidence of a cancer and the likelihood of approval of new drugs,[2] drugs that have fundamentally changed the outlook for affected individuals. Why is this so? It is because of something called genotype-phenotype relations. I am using this term (genotype-phenotype relations) to mean that a given pattern of genetic changes yields a defined, identifiable appearance. This concept is important, because it seems that the new treatments are mostly based on the underlying genotype, regardless of the appearance. Let me explain how this works, and how it applies to sarcomas.

It is increasingly accepted that the common cancers are genetically heterogeneous. For example, the entity formerly known as 'breast cancer' is rapidly evolving under the influence of molecular genetics into more than half a dozen different subtypes of cancer, according to oestrogen and progesterone receptor status, HER2 status, luminal A, luminal B, BRCA1/2 mutant, and so on. Some of these distinctions already have clinical significance. This situation will likely get more complex with time. Sequencing of cancer genomes reveals that there may be about 50 different mutations in each cancer, and that many of these mutations occur in less than 5% of what we previously considered one disease.[3] Thus, there is a poor genotype-phenotype relationship in many

common cancers. This is the reason that the epidermal growth factor receptor (EGFR) inhibitors failed to work in more than 10% of lung cancers, until we realised that we needed to target the underlying genotype (EGFR mutation positive lung cancer), after which our response rates increased dramatically.[4] In summary, where the phenotype does not reflect the underlying genotype, genotype is increasingly likely to trump phenotype in clinical importance.

For sarcomas, by contrast, genotype-phenotype relations are often (but not always) much more reliable. Sarcomas may be divided into several broad groups - those with defined molecular genetic abnormalities and those that more closely resemble the common epithelial cancers.[5] The latter (leiomyosarcoma, malignant fibrous histiocytoma (MFH), pleomorphic liposarcoma, osteosarcoma and so on) lack a characteristic genetic change. I will come to these later. The group of connective tissue tumours with defined molecular genetic abnormalities is increasing in number. It includes Ewing sarcoma, gastrointestinal stromal tumours (GIST), dermatofibrosarcoma protuberans, well/dedifferentiated liposarcoma, myxoid liposarcoma, pigmented villonodular synovitis and many more. These tumours have quite distinct appearances under the light microscope. This means that, for these diseases, the light microscope appearance of the cancer is predictive of an underlying genetic defect, and therefore may be used to guide treatment in many cases.

Know thy enemy

The impact of molecular genetics on the classification of sarcomas cannot be overstated. In the early 1990s, the misclassification rate in sarcomas based on histopathology (phenotype) was formally shown to be 15-20%.[5] This remains true today, with potentially devastating consequences. The problem is that sarcomas are rare and the subtypes are rarer, the clinical implications are not always immediately obvious, and molecular pathology is still not routinely available to back up the diagnosis.

For the so-called 'pleomorphic' sarcomas (leiomyosarcoma, MFH and so on), there is generally no clinically effective, targeted therapy (leaving out for a moment osteosarcoma). One consequence of this has been the creation (and imminent demise) of an entire category of sarcomas - MFH. The category of MFH (sometimes known as pleomorphic sarcoma, not otherwise specified) was created to allow pathologists to classify sarcomas without an obvious line of differentiation. Struggling to make out the line of differentiation did not appear to matter - there is still no underlying genotype identified and our chemotherapy treatments still do not really work well. A fine pathologist (Chris Fletcher, in Boston) showed that it is possible to reclassify MFH in almost 70% of cases,[6] and it is likely that MFH will be dropped as an entity from the next edition of the World Health Organisation atlas on the Pathology and Genetics of tumours of soft tissue and bone. The distinctions may not impact upon clinical care immediately, but there is every chance they will matter soon.

The distinction between leiomyosarcoma and MFH may not be critical (yet), but this is not the case for the distinction between synovial sarcoma (carrying a translocation between chromosomes X and 18) and Ewing sarcoma (translocation between chromosomes 11 and 22).[5] Although our treatments are not targeted (blunderbuss), they seem for unknown reasons to be particularly effective in these cancer types. In the case of Ewing sarcoma, an intensive and prolonged course of chemotherapy, combined with surgery and perhaps radiotherapy, is critical to cure. The tests we use to diagnose these cancers are based on the light microscope and cytogenetics. The appearance under the light microscope is fallible, as reported in the literature. The consequences of a misdiagnosis of Ewing sarcoma are very great for our patients. If we wrongly call a tumour 'Ewing sarcoma', the patient will receive nine months of intense chemotherapy, itself carrying a significant risk of mortality. If we wrongly fail to diagnose this cancer, the patient may not receive potentially curative treatment. Yet there is no government rebate for the cytogenetic test required to demonstrate the Ewing translocation, which is technically relatively simple and commercially available. Nowhere is a clinical need for molecular pathology more important than among the 70 or more diseases called sarcoma.

The clinical development of targeted therapeutics makes the need for good molecular pathology even more pressing, a point strikingly illustrated by GIST. Gut leiomyosarcoma and GIST were routinely conflated in the early 1990s, and GIST was thought to be relatively rare. These cancers were collectively unresponsive to drug treatments. In 1998, a Japanese group showed that GIST was due to mutations in the KIT gene, which encodes a growth receptor on the surface of that mysterious entity, the interstitial cell of Cajal.[7] In parallel with this, Novartis was developing a targeted drug (imatinib), whose targets include the platelet-derived growth factor receptor (PDGFR), the ABL kinase and the colony stimulating factor 1 receptor (CSF1R). When it became apparent that imatinib had a dramatic effect on GIST through its inhibition of KIT, not only did centres accessing the drug through clinical trials rapidly become inundated by patients, but the incidence of GIST mysteriously rose. A recent survey in France has shown that GIST is one of the single most common subtypes of soft tissue sarcomas.[8] It is now considered routine standard of care to test for mutations in KIT, in part because it is clear that different mutations respond differently to treatment.[9] The discovery of mutations affecting other imatinib targets has expanded the therapeutic applications of imatinib to dermatofibrosarcoma protuberans and possibly other connective tissue tumours.

Changing times: clinical trials as standard of care

An important theme is that the time from target discovery to proof-of-principle in cancer care is accelerating.[7,10] One implication is that the clinical classification of cancers needs increasingly to take into account the underlying genotype, for consideration of access to therapeutic

trials of novel agents as they become available. The standard of care is shifting rapidly, and the clinician is right at the centre of this trend. This is true for perhaps the most common soft tissue sarcoma, well-dedifferentiated liposarcoma. This disease is characterised by the near obligate amplification of two oncogenes, MDM2 and CDK4. While well-differentiated liposarcoma is generally a slow growing cancer, there are currently no effective drug treatments. In cases where complete surgical removal is difficult, like the retroperitoneum, recurrence rates and eventual lethality may approach 90%.[10] The development of agents that target CDK4 and MDM2 is proceeding rapidly, with clinical trials of both underway in the US and elsewhere. It is highly likely that the first access to these agents over the next five years will be through clinical trials, which will become a de facto standard of care.

The eligibility criteria for clinical trials are also changing, with an increasing emphasis on the molecular genetics of cancer. Not only does this define potential suitable cancers that have a high a priori chance of benefit (eg. using imatinib in cancers with KIT mutations), but also may help to screen cancers unlikely to benefit. Sarcomas illustrate this point. The p53 pathway is probably the single most commonly mutated in all cancers. Parenthetically, the discovery of TP53 as a tumour suppressor gene was in part made through the study of inherited cancer syndromes (the Li-Fraumeni syndrome). Sarcomas comprise the single most common cancer observed in these unfortunate families, 70% of whom carry in their germline mutations in the TP53 gene.

The p53 pathway has three main components: p14ARF, MDM2 and p53 itself. Different components are inactivated in different cancers. As noted above, MDM2 is amplified in almost all well-dedifferentiated liposarcomas. It appears that MDM2 inhibitors may not work in cancers with mutant p53, because they depend on this gene being functional in order to work.[11] Similarly, in colorectal cancer, KRAS mutations predict for poor response to EGFR inhibitors.[12] Thus an understanding of the molecular genetics of sarcomas will increasingly be critical to understanding who should go on what trial and why some people unexpectedly don't benefit.

Sarcoma and the genetic tsunami

The past decade has seen astonishing developments in our understanding of the molecular genetics of cancer. In 2001, the publication of the human genome sequence heralded a new era in the depth of our mapping of human genetics.[13] This herculean effort, led by Francis Collins of the National Institutes of Health, involved hundreds of scientists across several continents, is estimated to have cost $2.7 billion, and took over a decade to come to fruitition. In the past 10 years, technologic advances in sequencing have resulted in the ability to sequence an entire human genome for under $50,000 and within one month. The genetic mapping of cancer is now being accelerated through 'Big Science' consortia, exemplified by the International Cancer Genome Consortium, whose objective is to fully sequence 500 tumours of each cancer type, beginning with common cancers. Inevitably, the generation of data from such studies will strip away the simplicity of long-held concepts of human genetics. Already, so-called 'junk' DNA is known to be actively transcribed, and to play important roles in development, physiology and disease. The loss of innocence can only continue.

It is highly likely that we will discover new opportunities for therapeutic intervention. These opportunities will include the development of novel agents and strategies for drug development, but they will also include the unexpected discovery of opportunities for application of existing drugs. In this way, the wave of molecular genetics that will emerge in the next decade or more will radically change the textbook treatment of many subtypes of sarcomas. The challenge will be to translate these opportunities into clinical benefit for our patients as quickly as possible. I believe that the rate limiting component of translation of genetics and therapeutics of cancer into clinical benefit will be reform of the health care system, including ethics, processes for clinical trials development, approval and funding of new drugs, and access in the public and private health care systems across our community.

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NEW DRUGS IN THE MANAGEMENT OF SARCOMA

Maggie Moore and Jayesh Desai
Sarcoma Service, Peter MacCallum Cancer Centre, Victoria.
Email: jayesh.desai@ludwig.edu.au

Abstract

Sarcomas are a rare group of malignant mesenchymal tumours arising from bone and soft tissue. The diversity of this group of tumours and the rarity of each subtype poses significant challenges in the search for effective therapeutic agents. While recent advances in the molecular characterisation of these tumours has lead to the development of some promising agents targeting critical steps in the neoplastic process, it has also highlighted the true heterogeneity of sarcoma subtypes. These tumours can no longer be 'lumped' together for the purposes of research or treatment, but rather collaborative effort and novel clinical trial design are required to allow for accurate and timely assessment of emerging agents in specific sarcoma subtypes. New and emerging drugs and drug combinations for the treatment of advanced sarcoma will be discussed in this review.

Sarcomas are a rare group of malignant mesenchymal tumours arising from bone and soft tissue. Approximately 800 new cases of sarcoma are diagnosed in Australia each year, comprising <1% of cancer diagnoses overall, although a significantly greater proportion of those diagnosed in childhood and adolescence.[1]

There are more than 50 different histological subtypes of bone and soft tissue sarcoma (STS) and recent advances in molecular characterisation have brought with them with an increased understanding of the true heterogeneity of this group of neoplasms. Whereas previously these tumours were often 'lumped' together, both in the research and clinical context, modern practice dictates the tailoring of treatment strategies based not only on histology, but identified molecular mechanisms of tumourigenesis.

With rare exception, the prognosis of patients with unresectable metastatic sarcoma remains poor, however significant advances have been made over the last decade in the treatment of some sarcoma subtypes. This has been most notable in tumours where cell signalling pathways critical to the neoplastic process have been identified and specifically targeted by therapeutic agents. The most impressive example to date has been seen in the treatment of gastrointestinal stromal tumours (GIST) by imatinib, a protein tyrosine kinase inhibitor targeting c-KIT, a proto-oncogene mutated in the majority of these tumours.[2-4]

This review outlines the new drugs and drug combinations that have shown promise in the treatment of advanced sarcoma. A detailed description of the tumour biology and genetics that underlie the mechanism of action of many of these agents has not been undertaken, and can be found in the companion article 'Importance of molecular genetics of sarcomas'.[5]

Trabectedin

Doxorubicin as a single agent or in combination with ifosfamide has been the standard of care for patients with advanced or metastatic STS for two decades. With objective response rates ranging from 9-34%, [6-9] and no standard treatment option following failure of these two agents, it is clear that new active drugs are urgently required.

Trabectedin (ecteinascidin-743; ET-743) is a novel compound originally derived from the Caribbean tunicate ecteinascidia turbinate and now manufactured synthetically. Although the exact mechanism by which trabectedin exerts a cytotoxic effect is incompletely understood, it is known to bind to the minor groove of double stranded DNA, bending it towards the major groove.[10] This interferes with the transcription coupled nucleotide excision repair pathway, inducing lethal DNA strand breaks.[11] Trabectedin has also been shown to selectively inhibit activated gene transcription and lead to G2/M phase cell cycle arrest.[12]

Following promising pre-clinical data,[13-15] phase I trials of trabectedin were undertaken, with tumour responses seen in a number of heavily pre-treated patients with advanced soft tissue sarcoma.[16-19] This led to the initiation of three simultaneous phase II trials conducted in France, the United States and Europe assessing the efficacy and safety of trabectedin in this group of patients.[20-22] A further phase II trial designed to compare two different schedules of administration was limited to pre-treated patients with advanced or metastatic leiomyosarcoma or liposarcoma.[23] Trabectedin was subsequently assessed in the first-line setting.[24] The results of these trials are summarised in table one.

Although the objective response rates could be considered low for a cytotoxic agent (5-17%), it is widely acknowledged within the sarcoma community that duration of response and disease stabilisation in patients known to be progressing prior to study entry are also relevant when assessing the clinical activity of a new treatment. The European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue Bone and Sarcoma Group conducted a retrospective analysis of their database looking at the three and six

month progression free rates for chemotherapy in patients with STS. Active agents had progression free rates at six months of 30-56% in the first line setting and 14% in the second line setting.[25] The six month progression free rate for trabectedin in the phase II first line trial was 24.4%, and between 20 and 35% in the four second line trials, indicating clinically relevant activity of this drug. Retrospective review and pooled analysis suggest that leiomyosarcoma and liposarcoma (especially the translocation related myxoid liposarcomas) may be particularly sensitive histological subtypes.[26,27]

In addition to being active, trabectedin appears to have an acceptable safety profile with the main toxicities being an asymptomatic transaminitis (grade 3-4 in 34-57% of patients) and neutropenia (grade 3-4 in 33-61% of patients), with the 0-7% rate of febrile neutropenia comparing favourably to that seen with doxorubicin and ifosfamide.[20-24] Importantly, in contrast to the cardiac and renal toxicities that limit prolonged administration of doxorubicin and ifosfamide respectively, no cumulative dose limiting toxicities have been identified in studies of trabectedin allowing for prolonged treatment in responding patients.

Although not approved in Australia, the efficacy and tolerability of trabectedin in STS has led to the drug being approved in Europe and 21 other countries for the treatment of this group of tumours after failure of doxorubicin and ifosfamide. It currently holds orphan drug status in the United States for the treatment of STS and ovarian cancer, however is not FDA approved for either of these indications. Further clinical trials are currently underway assessing trabectedin in combination with other chemotherapeutic agents and in specific histological subtypes of STS, including a phase III trial comparing doxorubicin with trabectedin in the first-line treatment of patients with translocation related sarcomas. The results of these studies will further define the role of trabectedin in the treatment of this challenging group of tumours.

Table 1: *Results of published Phase II trials of trabectedin in the treatment of soft-tissue sarcoma. (NR- not reported; PFS - progression free survival; OS - overall survival).*

Reference	Study population	Number	Regime	Response rate	Median PFS (months)	Six-month PFS	Median OS (months)
Yovine et al 2004[22]	Pre-treated soft tissue sarcoma	54	1.5mg/m2 24hr q3w	3.7%	1.9	24.1%	12.8
Garcia-Carbonero et al 2004[20]	Pre-treated soft tissue sarcoma	36	1.5mg/m2 24hr q3w	8.0%	1.7	20.0%	12.1
Le Cesne et al 2005[21]	Pre-treated soft tissue sarcoma	104	1.5mg/m2 24hr q3w	8.0%	3.4	29.0%	9.2
Demetri et al 2009[23]	Pre-treated liposarcoma and leiomyosarcoma	136	1.5mg/m2 24hr q3w	5.6%	3.3	35.5%	13.9
		134	0.58mg/m2 3hr qwk for 3 wk in 4wk cycle	1.6%	2.3	27.5%	11.8
Garcia-Carbonero et al 2005[24]	Chemotherapy naïve soft tissue sarcoma	36	1.5mg/m2 24hr q3w	17.1%	NR	24.4%	NR

Recent studies have explored the use of the cytotoxic agents gemcitabine and docetaxel in combination for the treatment of metastatic STS. Promising results have been seen in some sub-types, including leiomyosarcoma and undifferentiated high grade pleomorphic sarcoma (UPS).[28-31]

Gemcitabine is a pyrimidine antimetabolite that inhibits DNA synthesis by inhibition of DNA polymerase and ribonucleotide reductase. Pharmacodynamic studies performed in patients with sarcoma and pancreatic cancer have shown improved clinical efficacy of the drug when administered as a fixed dose infusion (FDI) compared with bolus dosing, thought to be due to optimisation of intracellular accumulation of the drug.[32,33] Phase II trials of single agent gemcitabine for first or subsequent line treatment of metastatic soft tissue sarcoma have yielded response rates of 3-18% (median 6.5%), with many of these studies identifying leiomyosarcoma as a histological subtype associated with a better response.[33-39]

Docetaxel is a taxane drug which promotes microtubule assembly and stabilisation in the cell leading to inhibition of DNA, RNA and protein synthesis. Despite an initial phase II trial conducted by the EORTC reporting a 17% (five of 29 patients) response rate to docetaxel as second line therapy in patients with advanced soft tissue sarcoma40, a subsequent larger phase II trial by the same group, comparing sequential therapy with doxorubicin then docetaxel on progression or the reverse, showed a 0% response rate to docetaxel in both lines of treatment.[41]

Although the findings of pre-clinical studies evaluating potential synergy between gemcitabine and taxanes have been inconsistent,[29,42-44] the results of four clinical trials assessing the activity of gemcitabine and docetaxel in advanced sarcoma have been promising.[28-31] Hensley et al evaluated docetaxel and gemcitabine (as a FDI) in a phase II trial of 34 patients with leiomyosarcoma, the majority of which (29 patients) were of uterine origin.[31] They reported a response rate of 53% (including three complete responses), time to progression of 5.6 months and a median overall survival of 17.6 months in a population where 47% (16 patients) had received prior treatment with a doxorubicin based regime.

Two subsequent retrospective reviews support the activity of this combination in a broader spectrum of sarcoma histologies. In a study from the University of Michigan, an overall response rate of 43% was reported in 35 patients with a variety of advanced bone and soft tissue sarcomas, including 7/12 (58%) of patients with leiomyosarcoma.[29] A French study assessing 133 patients with advanced soft tissue sarcoma treated with docetaxel/gemcitabine found an overall response rate of 18.4%, with a higher response rate for patients with leiomyosarcoma than other histological subtypes (24.2% v10.4%; p = 0.06).[30]

The activity of the docetaxel/gemcitabine combination was then compared to gemcitabine alone in a multi-centre randomised phase II clinical trial conducted by the Sarcoma Alliance for Research.[28] In this study, 122 patients with metastatic soft tissue sarcoma were adaptively randomised to receive gemcitabine alone (1200mg/m2 by FDI D1, D8 every 21 days) or a reduced dose of gemcitabine (900mg/m2 by FDI D1, D8 every 21 days) in combination with docetaxel (100mg/m2 D8 every 21 days). The response rate was 8% for single agent gemcitabine and 16% for the combination. The response rate for the 29 patients with leiomyosarcoma treated with docetaxel/gemcitabine in this study was 17% (compared with 11% for gemcitabine alone). Notably, amongst the 11 patients with UPS enrolled on this trial, four patients (36%) responded to combination treatment including one complete response. Response for this histology in the single agent arm was also higher (25%) than the average suggesting a particular sensitivity of UPS to gemcitabine alone and in combination with docetaxel.

It should be noted that patients receiving treatment on the combination arm in this trial experienced significantly more toxicity than those on the gemcitabine alone arm, with more than 40% of patients discontinuing therapy due to non-hematologic toxicities. These were predominantly constitutional symptoms such as myalgias and fatigue. The authors acknowledge that the dose and scheduling used in the study is probably too high for long-term use and this should be borne in mind when considering this combination in routine practice.

Denosumab

Denosumab is a fully human monoclonal antibody that specifically inhibits Receptor Activator of Nuclear Factor Kappa B ligand (RANKL), an important mediator of osteoclast activation. Under normal conditions RANKL is expressed on a number of different cell types including lymphocytes and stromal cells.

Giant cell tumour (GCT) of the bone is a rare osteolytic bone tumour seen predominantly in young adults. Although it is considered benign, GCT can be locally aggressive and in rare cases metastasise to the lung.[45] Surgery forms the mainstay of treatment, however there are limited options for patients with unresectable primary or recurrent disease.

It has been suggested that the RANKL expression, observed in the mononuclear stromal cells of GCTs in several studies,[46-48] stimulates the recruitment of osteoclast-like giant cells from their normal monocytic precursors.[49] This overpopulation of giant cells then causes the osteolysis associated with these tumours.

In an open label phase II study, 37 patients with recurrent or unresectable GCT were treated with subcutaneous denosumab 120mg every 28 days after three initial weekly loading doses.[50] In this trial 30 of the 35 assessable patients (86%; 95% CI 70-95%) had a tumour response including all of the 20 patients who were assessed by histology, with response defined as elimination of at least 90% of the giant cells on repeat biopsy.

In view of these very promising results, further investigation of denosumab as a treatment for GCT is justified, with specific attention to the optimal duration of treatment with this agent and the safety profile of denosumab required. An international open label phase II study is currently underway in an attempt to address the latter point and is recruiting at sites within Australia.

mTOR Inhibitors

The phosphotidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway is a cell signalling pathway which plays a central role in the control of cell proliferation, survival, mobility and angiogenesis.[51-54] This pathway is abnormally activated in a range of cancers, including sarcomas, which has led to its evaluation as a therapeutic target.[54-56]

A number of mTOR inhibitors are being assessed in clinical trials against a variety of tumour types. Of these, the most data concerning activity against non-GIST sarcomas has been reported for ridaforolimus.

In a phase I dose escalation trial of ridaforolimus administered to patients with advanced malignancies, all seven patients with sarcoma were noted to have a partial response (two patients), minor response or stable disease for more than three months.[57] This led to a phase II study of ridaforolimus in patients with advanced soft tissue or bone sarcoma with a primary endpoint of clinical benefit response, defined as complete or partial response or stable disease for ≥16 weeks. The results were presented in abstract form at the American Society of Clinical Oncology Annual Meeting in 2006 and updated in 2007.[58,59] Of the 212 patients enrolled on this trial, 61 patients (29%) had a clinical benefit response, including five partial responses. The most frequent toxicities were mucositis, fatigue, rash, thrombocytopenia and hyperlipidemia, most of which were mild to moderate in severity.

In light of this promising clinical activity and acceptable safety profile, this agent is now being evaluated in the phase III clinical trial 'Ridaforolimus in Treatment of Sarcoma-SUCCEED (Sarcoma Multi-Center Clinical Evaluation of the Efficacy of Ridaforolimus)'. This study is a randomised double-blind placebo-controlled trial assessing the safety and efficacy of ridaforolimus administered as maintenance therapy to patients with metastatic sarcoma who have achieved a favourable response to chemotherapy. The study has completed enrolment, with results expected in early 2011.

Insulin–like growth factor-1 receptor (IGF-1R) inhibitors

The insulin-like growth factor (IGF) signalling pathway is another potential therapeutic target currently being explored. This pathway is involved in the regulation of cell growth and survival,[60] with preclinical data suggesting it plays an important role in tumourogenesis.[61,62]

The IGF-1R is an important positive regulator of this system and the potential utility of blocking this receptor has been demonstrated in pre-clinical studies in a range of cell lines, including several sarcoma subtypes.[63-66] A number of monoclonal antibodies targeting the IGF-1R are currently being evaluated in clinical trials in sarcoma AMG 479, R1507 and figitumumab (CP-751,871). Results have been reported for a phase I trial of figitumumab and in abstract form for Phase II trials of AMG 479 and R 1507.[67-69] These are summarised in table two.

Future trials of these agents in the treatment of the Ewings family of tumours and other sarcomas are likely to be in combination with chemotherapy and other targeted therapies, with a strong rationale for this approach. One effect of IGF-1R signalling is to protect the cell from apoptosis, so inhibiting this pathway may sensitise the cells to the effects of anti-cancer drugs, a theory that has been borne out in several pre-clinical models.[70, 71] The lack of overlapping toxicities with conventional cytotoxic agents used to treat sarcoma adds further merit to this approach.

Table 2: *Results of phase I and II trials of IGF1-R inhibitors in the treatment of advanced sarcoma (DSRCT- desmoplastic small round cell tumours; CBR- clinical benefit rate; MOS- median overall survival; PFR- progression free rate).*

Drug	Phase	Population	Number of patients	Efficacy	Grade 3/4 adverse events
AMG 479[67]	II	Pre-treated EFT and DSRCT	35	RR 6% CBR 20%	37% (thrombocytopenia, neutropenia, hyperglycemia)
R 1507[68]	II	Pre-treated EFT	125	RR 14% MOS 17.6M	13% (diarrhoea, anaemia, thrombocytopenia)
Figitumumab[69]	I	Pre-treated EFT and other sarcoma	29	RR 7% 6M PFR 28% (6M PFR 40% EFT)	17% (deep venous thrombosis, back pain, vomiting, abnormal liver function tests, raised uric acid)

Multi-targeted Kinase Inhibitors and c-MET Inhibition

Sunitinib and cediranib are multi-targeted kinase inhibitors which have shown promising signs of activity in the treatment of metastatic alveolar soft part sarcoma (ASPS). ASPS is a rare sarcoma, characteristically affecting the soft tissues of the extremities in young patients. It has a relatively prolonged natural history, however the presence of metastatic disease dictates a poor prognosis.[72,73] No chemotherapeutic agents have demonstrated activity in the treatment of this disease.[73,74]

ASPS is characterised by an unbalanced translocation t(X;17)(p11.2;p25), which leads to dysregulated expression of the transcription factor TFE3.[75] This activates MiT (Micropthalmic transcription factor) and results in the overexpression of the c-met receptor tyrosine kinase. In tumour cells, c-met activation is known to promote tumour growth, angiogenesis and metastasis.[76,77]

Sunitinib is an orally administered tyrosine kinase inhibitor, with activity against a range of targets including VEGFR, PDGFR, c-KIT and RET.[78,79] It is currently licensed for the treatment of renal cell carcinoma and imatinib resistant gastrointestinal stromal tumour. In a case series of 10 patients with unresectable progressive ASPS, treated with sunitinb 37.5mg daily continuously via a compassionate access scheme, five of eight (63%) assessable patients demonstrated a partial response by RECIST criteria with a further patient exhibiting stable disease for >6 months. No grade 3-4 toxicity was seen.[80]

Cediranib is a once daily oral tyrosine kinase inhibitor that targets vascular endothelial growth factor receptors 1, 2, and 3. Efficacy and safety data has been reported for seven patients with ASPS treated on two phase II trials assessing activity of this agent. There were four partial repsonses (57%), two minor responses and one patient with stable disease. Fatigue, diarrhoea and stomatitis were the most common adverse events, but were generally grade 1-2.[81]

Given the lack of therapeutic options for patients with advanced ASPS and the promising activity reported for these two agents, further evaluation in dedicated phase II trials is warranted. A phase II trial of cediranib is currently recruiting for this indication in the United States.

ARQ 197, an agent which directly inhibits c-met, has also shown some promise in the treatment of ASPS, as well as two other MiT associated tumours, clear cell sarcoma and translocation associated renal cell carcinoma (RCC). The activity of ARQ 197 in these tumour types is currently being assessed in a multi-centre phase II trial. Preliminary results, presented in abstract form at the American Society of Clinical Oncology Annual Meeting in 2009, were of a partial response in one of 28 assessable patients (CCS) and stable disease of >29 weeks in 17 patients (13 ASPS, 2 CCS, 2 RCC), giving a disease control rate of 64% overall and 81% for ASPS. Four grade 3-4 events were reported (two anemia, one febrile neutropenia, one thrombocytopenia.).[82]

Additionally, pazopanib, an oral kinase inhibitor targeting VEGFR, PDGFR and c-KIT, has shown promising activity in a large randomised phase II trial of soft tissue sarcomas conducted by the EORTC.[83] In an effort to differentiate activity across a spectrum of STS, this trial stratified patients into four different arms, with activity (defined as progression free rate at 12 weeks (PFR12 weeks)) seen in three (leiomyosarcoma, synovial sarcoma, other STS subtypes) of the groups; but not in the adipocytic group. These results have lead to the conduct of an international randomised phase III trial (the PALLEtte study) in patients with STS refractory to conventional chemotherapy. In this trial patients are randomised to pazopanib 800mg/day or placebo, with a primary endpoint of progression free survival. Enrolment has recently been completed with results expected in early 2011.

Conclusion

An improved knowledge of the molecular alterations driving specific subtypes of sarcoma has lead to the rational development of a number of promising therapeutic agents in bone and soft tissue sarcomas. However, developing these relatively small proof-of-concept studies into the larger randomised trials that are usually required by regulatory and funding agencies to demonstrate efficacy against current standards of care remains a significant challenge.

It is vital that the sarcoma research community works closely with the pharmaceutical industry and regulatory agencies to develop new, more efficient trial designs which allow accurate and timely assessment of the benefit of an intervention for specific patient groups even if the tumour subtype is very rare. The formation of sarcoma specific collaborative international networks (such as the World Sarcoma Network) has been an important step in enabling such trials.

Finally, with the majority of recent advances in the treatment of sarcoma patients stemming from progress in the understanding of important molecular mechanisms driving these cancers, a continued focus on basic research and the integration of molecular pathology into sarcoma trial design is essential to improving outcomes for patients with bone and soft tissue tumours.

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Biopsy of bone and soft tissue sarcoma: pitfalls

Paul D Stalley,[1] Kirsten Coggins,[2] Jo-Anne Cato[1]
1. Bone and Soft Tissue Sarcoma Service, Royal Prince Alfred Hospital, New South Wales.
2. Royal Prince Alfred Hospital, New South Wales.
Email: pdstalley@optusnet.com.au

Abstract

The biopsy of bone and soft tissue sarcoma is an integral part in the management of patients with these disorders and inadequate, inappropriate or inaccurate non-representative biopsies do lead to poorer outcomes for patients in terms of survivorship and limb salvage. We have conducted a review by comparing results of an audit conducted in 2002 with a repeat audit in 2009 of all biopsies performed in our department and biopsies performed on patients prior to referral for treatment. The results of that review clearly show that the method of biopsy is important in establishing a correct diagnosis and that inadequate or poorly performed biopsies compromise patient outcomes. It is clear that there is a significantly higher incidence of the need to change treatment to a more radical procedure than would originally have been necessary or to convert to palliative rather than curative intent on patients biopsied outside a specialist unit. Patients biopsied elsewhere were more likely to have an incomplete excision requiring re-excision, more likely to require amputation and more likely to require adjuvant radiotherapy. Sarcoma patients are best served by early referral to a specialist centre where staging investigations including biopsy can be performed with minimal morbidity.

Bone and soft tissue sarcomas are rare tumours accounting for 0.7% of all new cancer notifications in NSW per annum (soft tissue sarcoma 0.5%, bone sarcoma 0.2%). Within this group of tumours are a large number of diagnoses and it is necessary to have adequate tissue samples to establish not only cytology, but tumour structure to enable accurate diagnosis.[1] Adequate specimens must be available for immunohistochemistry, cytogenetics, flow cytometry and progressively more complex molecular biological assessment. Careful planning of the biopsy is essential. An adequate volume of representative tissue must be obtained while avoiding contamination of adjacent tissue.[2-4] The location of the biopsy tract must be noted to allow accurate excision at the time of the definitive surgery. Furthermore, the specimen should be examined by a pathologist with experience in the area.[2,3,7]

It was first noted in 1982 by Mankin et al, that biopsy-related problems occurred up to five times more frequently if the biopsy was not performed by a specialist sarcoma surgeon.[2,3] It was also recommended that if the surgeon or institution was not equipped to investigate the patient appropriately, perform definitive surgery and administer adjuvant therapy, then the patient should be referred to a treatment centre before biopsy. There are numerous papers that concur with this advice.[8,9-12]

Despite this extensive literature, it is apparent from our audit that inappropriate and inaccurate biopsies are performed by non-specialist practitioners, resulting in poorer outcomes.[2-6] In the case of malignant tumours, the most destructive of biopsies in our audit involved an open biopsy performed inaccurately with contamination of the surgical field, resulting in the need for extensive re-excision or more mutilating surgery than otherwise would have been necessary. As a result there was a demonstrable reduction in five year survivorship.[2,3,8,13-18]

Data acquisition

An audit was performed initially, in 2002, at Royal Prince Alfred Hospital of all patients referred to the Bone and Soft Tissue Sarcoma Service. We excluded patients with metastatic lesions from unknown primary tumours at the time of presentation, infection or non-tumourous conditions. Patients staged elsewhere and referred purely for a second opinion, rather than ongoing management, were also excluded. Only those patients who had biopsy either prior to referral to our service, or after referral, and then subsequent definitive treatment were included. Staging investigations were completed as recommended by the Musculoskeletal Tumour Society.[1] We recorded who performed the biopsy, the type of biopsy, the choice of biopsy site, whether or not adequate material was obtained and whether or not a poorly performed biopsy compromised or altered the definitive treatment. All histological diagnoses were recorded with the site of the tumour and stage. All referring surgical biopsies performed externally were examined by our own pathologists to confirm the diagnosis.

The most important part of the review was to make a comparison between the results of biopsy and the final resected specimen to confirm the accuracy of diagnosis. Complications of inappropriate or inaccurate biopsy were also recorded.

Following this initial audit being published and the information widely disseminated within the orthopaedic community in NSW, a similar audit was performed in 2009, to establish if there had been any general change in practice over the subsequent seven years.

Analysis

In the initial audit, 142 patients satisfied inclusion criteria, 72 men and 70 women, with a mean age of 40 years (6-88 years). Eighty-three tumours arose primarily in bone, of which 48 (58%) were malignant. Fifty nine tumours arose in soft tissue sites, of which 29 (49%) were malignant. Overall there were 77 primary malignant tumours and 65 benign tumours, of which 14 were benign-aggressive. The distribution of the histological tumour types is shown in table 1.

The referring surgeon performed biopsies in 29 cases, of which 20 were malignant. The senior author (PDS) biopsied the remaining 113 cases, of which 57 were malignant. The diagnostic distribution of types of biopsy performed between these two groups is shown in table 2. Adequate diagnostic material was obtained in 21/29 (72%) of patients biopsied elsewhere, compared to 110/113 (97%) in the service at RPA (P<0.0001). The biopsy site was suboptimal and hindered definitive treatment in 11/29 (38%) performed externally, compared to 2/113 (1.8%) performed internally. Fine needle

Table 1: *The distribution of histological types in 142 patients with musculoskeletal tumours – 2002.*

	Malignant		Benign	
Bone	Osteosarcoma	23	Giant cell tumour	10
	Chondrosarcoma	6	Osteochondroma	8
	Ewing's	5	Osteoid osteoma	4
	Lymphoma	4	Geode	3
	Malignant fibrous histiocytoma	3	Eosinophilic granuloma	2
	Myeloma	3	Fibrous dysplasia	2
	Chordoma	1	Osteoblastoma	2
	Synovial-cell sarcoma	1	Osteofibrous dysplasia	1
	Leiomyosarcoma	1	Aneurysmal bone cyst	1
	Plasmacytoma	1	Benign fibrous histocytoma	1
			Chondroblastoma	1
Subtotal		**48**		**35**
Soft tissue	Malignant fibrous histiocytoma	6	Lipoma	6
	Fibrosarcoma	6	Neurofibroma	3
	Synovial-cell sarcoma	5	Bursa	3
	Liposarcoma	4	Haemangioma	3
	Rhabdomyosarcoma	2	Arterio-venous malformation	2
	Haemangioendothelioma	2	Nodular fasciitis	2
	Haemangiopericytoma	1	Schwannoma	2
	Myxosarcoma	1	Angiomyxoma	1
	Leiomyosarcoma	1	Myolipoma	1
	Post irradiation sarcoma	1	Angiolipoma	1
			Fibrokeratoma	1
			Pigmented villo-nodular synovitis	1
			Myxoma	1
			Myofibroma	1
			Ganglion	1
			Desmoid	1
Subtotal		**29**		**30**
Total		**77**		**65**

Table 2: *Distribution of types of biopsy performed by referring surgeons compared to the senior author in 2002.*

	Referral biopsies (29)	Senior author (113)
Fine needle aspiration	7 (24%)	0
Trucut core biopsy	2 (7%)	64 (57%)
Incisional biopsy	7 (24%)	18 (16%)
Excisional biopsy	13 (49%)	31 (27%)

aspiration had been performed in 7/29 patients biopsied elsewhere, with the important observation that only two of these patients were able to generate significant diagnostic material to plan further management.

Of the malignant lesions alone, 8/20 (40%) of patients biopsied by the referring surgeon required re-excision of an incompletely excised tumour, compared to 2/57 (3.5%) of patients biopsied by the senior author (P<0.0001). Adjuvant radiotherapy was required 4/20 (20%) compared to 3/57 (5.3%) (P<0.05). The amputation rate was 5/20 (25%) for external patients and of these, three were thought to have been unnecessary had the biopsy been performed differently. The amputation rate in those patients treated in the specialist service was 4/57 (7%) (P<0.03).

Errors relating to biopsy had significantly altered the definitive management of 11/29 (38%) patients. An example of this

Table 3: *The distribution of histological types in 144 patients with musculoskeletal tumours – 2009.*

	Malignant		Benign	
Bone	Osteosarcoma	18	Giant cell tumour	9
	Chondrosarcoma	8	Osteochondroma	4
	Ewing's	8	Fibrous dysplasia	4
	Lymphoma	8	Aneurysmal bone cyst	4
	Chordoma	3	Epidermal cyst	2
	Plasmacytoma	2	Chondroblastoma	1
	Malignant fibrous histiocytoma	2	Chondromyxoid fibroma	1
			Osteoid osteoma	1
			Geode	1
			Eosinophilic granuloma	1
			Fibromatosis	1
			Paget's Disease	1
			Simple bone cyst	1
Subtotal		**49**		**31**
Soft Tissue	Malignant fibrous histiocytoma	7	Pigmented villo-nodular synovitis	10
	Synovial cell sarcoma	6	Haemangioma	5
	Myxofibrosarcoma	4	Lipoma	4
	Fibro myxoid sarcoma	4	Desmoid	3
	Liposarcoma	3	Schwannoma	3
	Myxoid liposarcoma	3	Myolipoma	3
	Rhabdomyosarcoma	1	Angiolipoma	1
	Leiomyosarcoma	1	Neurofibroma	1
	Angiosarcoma	1	Myxoma	1
	Fibrosarcoma	1	Angioleiomyoma	1
			Fibro osseous pseudo tumour	1
Subtotal		**31**		**33**
Total		**80**		**64**

is a 72 year-old woman who presented with a two month history of a rapidly enlarging and painful mass in the calf. The attending surgeon diagnosed an abscess and performed an 'incision and drainage' of the lesion without prior imaging.

Histological examination revealed a malignant fibrous histiocytoma. Staging investigations revealed a stage IIb tumour that would have been resectable with good margins. However, due to the extensive soft tissue and skin contamination, a below knee amputation was the sole alternative treatment.

These results were published in Australian literature[19] and widely disseminated among the orthopaedic community. We have subsequently performed a further audit using the same criteria as in 2002 in an attempt to ascertain whether there has been any change in practice and therefore in outcome for patients with bone and soft tissue sarcoma.

The second audit was performed in 2009. Of the 144 patients, there were 81 males and 62 females with a mean age of 43 years (8-83 years). Sixty nine tumours arose primarily in bone, of which 45 (31%) were malignant. Seventy four tumours arose in the soft tissues, of which 33 (23%) were malignant. The distribution of histological tumour types is shown in table 3. One hundred and ten tumours were located in the extremities; 14 were in the pelvis, 14 in the trunk and five spinal.

The referring surgeon performed biopsies in eight cases, of which six were malignant. The senior author biopsied the remaining 138 cases, of which 72 were malignant. The distribution of the types of biopsy performed in both groups is shown in table 4. There were five fine needle aspirations within the group where the biopsy was performed by an external referring surgeon, all of which were non-diagnostic to a necessary level to determine appropriate treatment of the patient. The one excisional biopsy was incomplete and resulted in wide spread subcutaneous contamination, which ultimately could not be salvaged and the patient died.

There were no fine needle aspirations performed by the senior author. All biopsies, but one, were correct when compared to the final resected specimen. The one incorrect diagnosis was of an angiosarcoma overlying the sacrum. Multiple surgeries were necessary until the diagnosis became apparent. Even after repeat review of previous resected specimens, the histopathological diagnosis could not be made retrospectively.

Table 4: *Distribution of types of biopsy performed by referring surgeons compared to the senior author in 2009.*

	Referral biopsies (8)	Senior Author (141)
Fine needle aspiration	5 (50%)	-
Trucut core biopsy	2 (20%)	40 (28%)
Incisional biopsy	-	16 (11%)
Excisional biopsy	1 (10%)	85 (60%)

Interpretation and recommendations

It would appear that there has been a reduction in the number of biopsies performed externally to the Bone and Soft Tissue Sarcoma Service. We presume that this is due to wide-spread dissemination of the concepts to referring surgeons that poor biopsy leads to poor results. Stratification of which surgeons have performed those biopsies clearly shows that orthopaedic surgeons are much more likely to refer a patient for biopsy than other specialties. As the method of biopsy appears to have a significant impact on patient survivorship and morbidity, it seems incumbent on those specialising in the area to draw up guidelines for biopsy algorithms to improve patient outcome.

In the initial audit of 2002, 38% of patients' definitive treatment was hindered by a poorly performed external biopsy. In 25% of patients, definitive treatment had to be changed to a more radical procedure or led to a palliative rather than curative procedure than would have been originally possible.[8,13,17,20] It is also important to note that in the first audit, patients biopsied elsewhere had a much higher incidence of fine needle aspiration biopsy and non-diagnostic biopsy than those done in a specialist centre. In the subsequent audit, in 2009, there was a significant drop in the number of inappropriate biopsies being performed, however, numbers and examples of poor results still plague us.

One such example, perhaps, can be mentioned as it illustrates clearly the multiple steps required in the biopsy and treatment of a tumour in a young woman that needed to be addressed for appropriate management. A 17 year-old girl presented to a non-specialist sarcoma surgeon with a five x three centimetre mass in the subcutaneous tissue over the spinous processes in the mid-thoracic spine. An ultrasound examination was performed that demonstrated a "solid tumour". Without further imaging and with a clinical provisional diagnosis of an epidermoid cyst, having been made, an excisional procedure was performed in a marginal fashion. The treating surgeon stated that during the procedure it was clear that the lesion was a solid tumour and not an epidermoid cyst, and yet a marginal excision was performed. The result was a cavity with contaminated margins from an infiltrating pleomorphic sarcoma, with considerable haemorrhage in the subcutaneous tissues five to seven centimeters in most directions.

The patient was then accurately staged and although initially without metastatic disease, resulted in both local recurrence and ultimately fatal metastatic disease, despite wide excision of the primary bed with over five centimetres margins radially.

This case demonstrates several inappropriate actions.

1. The performance only of an ultrasound examination of an unusual tumour in an unusual location is inadequate pre-operative imaging before biopsy. Had a magnetic resonance image (MRI) scan been performed, it is highly likely that the misdiagnosis provisionally of an epidermoid cyst could have been avoided and a core biopsy performed to allow a diagnosis without contamination.

2. Upon encountering a mass different to what was expected and having made the decision to proceed to excision of the lesion, the courageous decision would have been to stop at that point and not proceed. A formal incisional biopsy or frozen section could have been made, which would have allowed for the diagnosis of a pleomorphic sarcoma and hence the need for a different and appropriate plan of management.
3. The worst option was that of marginal excision, leaving circumferentially positive margins, haemorrhage and an ultimate inability to obtain a safe excision.

While the literature unambiguously stresses the need for correct, adequate and careful biopsy by someone skilled in this process, there will still be occasions when an incorrect course of action is embarked upon. Any treatment algorithms should acknowledge this and allow salvage of the situation as safely as possible.

The following suggestions are made:

1. Any mass of sufficient size, where the diagnosis is in doubt and histology will be sought, requires adequate imaging prior to biopsy. This imaging almost always will involve MRI scanning. Ultrasound imaging is historically inaccurate in terms of the demands of biopsy for soft tissue sarcomas and should not be relied upon. It can accurately demonstrate the presence of a lesion and some of its characteristics, but cannot describe to the biopsying surgeon variability within the lesion and thus the location for biopsy for the most representative samples to be obtained. It is important in sarcoma biopsy to avoid necrotic areas and obtain viable material and the MRI scan is very helpful in this aspect. Failure to perform an MRI investigation on the patients in this audit and to rely on ultrasound was the single largest group of patients who have had inappropriate or inadequate biopsy.
2. An adequate volume of tissue must be obtained representatively from the tumour without contamination of the surrounding surgical field. Fine needle aspiration simply does not deliver adequate material in most cases for confident and accurate diagnosis and should be avoided.[21,22] Core biopsy should remain the minimum standard of volume of tissue for histological analysis. Where an open biopsy is performed, it should be direct on to the tumour and through the pathway that would subsequently be used by a treating surgeon attempting limb salvage or excision of the tumour. There must be a frozen section performed at this stage to confirm the diagnosis prior to proceeding to either marginal or wide excision. In our audit, the performance of an inadequate marginal excision as the biopsy, without frozen section, has resulted in a large percentage of poor outcomes. If frozen section at this stage is not available, then the procedure should be abandoned and converted to a two-stage process allowing for laboratory analysis of the biopsy before definitive surgery.

The rareness of musculoskeletal sarcoma means that most treating surgeons will see few in a practice lifetime. The temptation for marginal excision is there, but should be resisted. In our audit, the most common point of re-referral to the Bone and Soft Tissue Sarcoma Service was when the treating surgeon was informed of positive margins on the resected specimen. Re-excision after positive margins is necessarily a more radical and mutilating process than a primary wide excision.

It is clearly shown that local recurrence is more likely and that five year survival is reduced despite wide re-excision. Thus, avoidance of inadequate primary resection is of paramount importance in the appropriate management of these rare tumours. Fine needle aspiration for sarcoma surgery has many disadvantages: it does not deliver the volume of specimen the pathologist often needs for the diagnosis of sarcomas; and the tract produced is often unidentifiable at the time of definitive surgery and may therefore be difficult to be excised. For these reasons, fine needle aspiration is not encouraged.

CT guided biopsy is widely used for tumours, particularly in difficult locations. For example, in the pelvis, the biopsy of a mass through an open procedure may be counterproductive as it would mean a huge exposure. There are always exceptions to the rule and particularly in locations such as the pelvis, a CT guided core biopsy is likely to produce less contamination than would an open procedure and is therefore appropriate practice. It is, however, recommended that the radiologist performing the procedure should discuss with the treating surgeon the best approach in an attempt to minimise contaminated biopsy tracts.

Recommendations from the Bone and Soft Tissue Sarcoma Service are that biopsy of tumours that could be sarcoma require the following:

- appropriate pre-biopsy imaging
- adequate and accurate biopsy by an experienced surgeon
    - if the above is not available, then communication with a skilled surgeon to discuss the biopsy prior to it being performed
- adequate volume of representative tissue must be obtained while avoiding contamination of adjacent tissue, with the specimen examined by a pathologist with experience in the area
- if intra-operative frozen section of an adequate standard is not available after an open biopsy then definitive surgery should be delayed to a second procedure

The most commonly made mistakes remain the:

- inadvertent marginal excision of a primary malignant soft tissue sarcoma
- inappropriate biopsy of primary bone sarcomas.

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FUNCTION FOLLOWING LIMB SALVAGE PROCEDURES FOR BONE SARCOMA

Peter Steadman
National Secretary, Australian Sarcoma Group, Victoria.
Email: petersteadman@mc.mater.org.au

Abstract

Bone sarcomas are the fourth most common cancer in individuals under 25 years. Osteosarcoma is the most common form of sarcoma in this population, with distal femur the most common tumour location. Before chemotherapy protocols were instituted, a 20% overall survival with limb amputation was quoted, however with chemotherapy and limb salvage or limb preservation surgery that figure has improved dramatically to 60-75% at five years. This paper looks at the functional outcome of limb salvage surgery around the knee. It shows that after a tumour resection with prosthetic reconstruction, the oxygen demands on the body are significantly raised by muscular co-contraction activity in both legs as an adaptive gait.

Bone sarcomas are the fourth most common cancer in individuals under 25 years.[1,2] Osteosarcoma is the most common form of sarcoma in this population and is commonly observed in the rapidly growing metaphyseal areas of extremity long bones.[3]

The primary consideration is always the capacity to achieve a wide resection with clear surgical margins, leaving the different modalities of reconstruction to be practised as secondary considerations. Some prostheses function better than others in different joints leading to favoured techniques for different resections types. The distal femur is an obvious case of an excellent functional reconstruction compared with amputation. As time progresses the two recent major surgical voids of the proximal tibia and the shoulder joint are also improving with prosthesis and encircling mesh attachments. In general the lower limb is much more amenable to prosthetic reconstruction and allows good ambulation with some limitations, albeit vastly better than amputation. The upper limb, although not quite as readily reconstructed with a good outcome functionally by contemporary standards, does better due to the fact that "any arm is a good arm" to allow limited grasp and pinch either in the hand or the against the chest wall.

Pelvic resections and the required reconstructions pose major long term viability problems with many of the available reconstructive options, all of which have an initial

success rate of approximately 30%, requiring further reconstructions. There has been a recent groundswell of activity with regards to non-reconstruction and production of a pseudoarthrosis, due to the long-term failure of most of these options. Diaphyseal resections of mid segments of bone generally do well with availability of fibula direct transfer, prosthetic segments, or bone distraction techniques such as the Illizarov frame, allowing for a diverse array of treatments. Below the mid tibia very few simple options exist except amputation, although the aggressiveness of the disease and the advent of plastic surgical soft tissue flaps have widened the reconstructive options and helped with avoidance of amputation. Current options for limb reconstruction after sarcoma include amputation, rotationplasty, arthrodesis and arthroplasty.

Rotationplasty is an operation where the foot is placed backwards on the knee and is ideal for the ages of six to nine. It is not well accepted in western society, however, is still popular in low resource countries that struggle to afford contemporary prosthetic options. See figures one and two.

Figure 1: *Rotationplasty intraoperative surgical technique.*

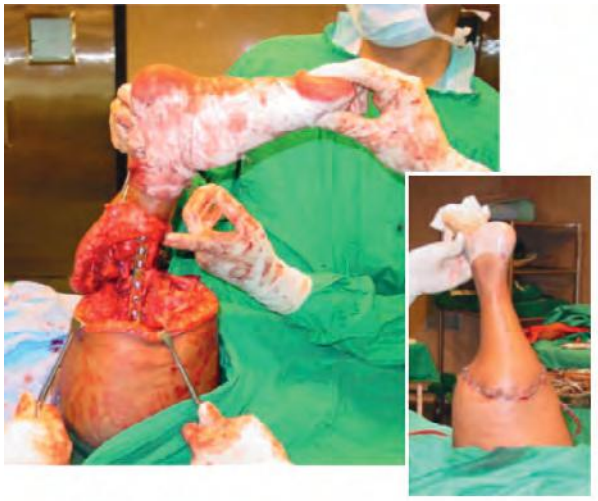
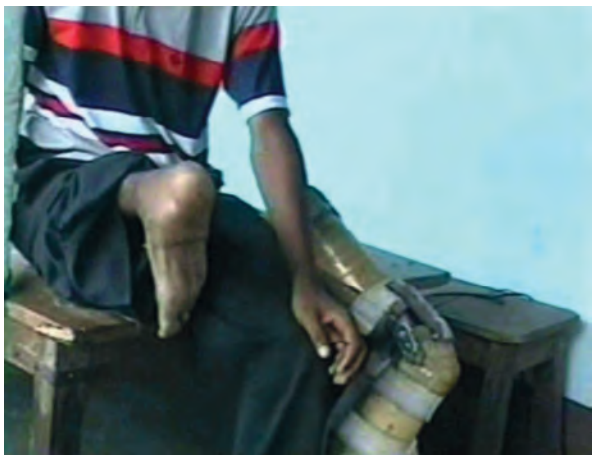


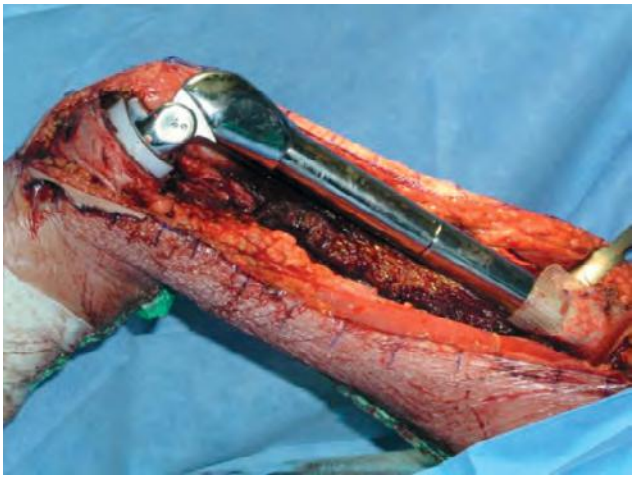
Figure 2: *Final result Rotationplasty with below knee prosthesis.*



Arthrodesis, or fusion of the affected joint, is practised less and less, however is still popular for the shoulder and the pelvis where prosthetic options are limited.

Arthroplasty or joint replacement is most popular with the use of a mega-prosthesis, either in isolation or with allograft. Reconstruction of a limb to near normal physical appearance is possible, but there are ambulatory functional limitations. See figure three.

Figure 3: *Distal Femur prosthetic replacement intraopertaively following tumour resection.*



Limb-salvage procedures have become increasingly popular for the treatment of osteosarcoma due to functional and physiological benefits over traditional amputative procedures.[4,5] A low recurrence of osteosarcoma (< 10%) has been reported following limb salvage procedures for high grade sarcomas.[6,7] Previous locomotor research has shown that limb salvage patients often adopt a 'stiff-legged' gait pattern post-surgery, that is characterised by muscular co-contraction.[8-12] The stiff-legged pattern has been attributed to a number of factors including: proprioceptive impairment; quadriceps weakness; avoidance of shear forces; disruption of the mechanical advantage mechanism (ie. patella and patella tendon); instability; pain; and habit.[13,14,10,15,12,16]

The purpose of this paper was to apply three dimensional gait analysis methods to a group of intra-articular knee osteosarcoma patients greater than one year post surgery. A retrospective subjective outcome study was undertaken on 20 limb salvage patients (10 female, 10 male) recruited from the Queensland Bone Tumour Registry. Kinematic data were collected using an eight camera real time motion analysis system. Foot ground reaction forces were recorded with the use of three force platforms. Loading response knee flexion in the affected lower limb was reduced compared to the unaffected lower limb ($P < 0.001$) and the control group ($P < 0.001$). Multiple regression analysis revealed that the amount of soft tissue removal was the most predictive factor of function following limb salvage surgery; this was followed by knee extension strength, knee flexion range of motion, time from surgery and length of bone resection. The results of this study suggest that following limb salvage patients use a variety of techniques aimed at reducing the movement

demand at the knee and hip. These techniques appeared to be a compensation for pain, stability and/or weakness.

Findings

Limb salvage patients demonstrated prolonged rectus femoris activation in both their affected and unaffected lower limbs when compared with the control participants. Limb salvage participants also displayed significantly prolonged activation of the medial hamstrings and the medial gastrocnemius in their affected lower limb when compared with the control subjects. The medial hamstrings activity was observed to be significantly longer in their affected lower limb when compared to their unaffected lower limb. Assessment of rectus femoris/medial hamstring co-contraction showed that limb salvage participants had a higher quadriceps to hamstring co-contraction index in both lower limbs when compared to the control subjects, with their affected lower limb showing a trend for a higher index compared to their unaffected lower limb.

There were no group differences in free walking velocity or relative velocity. Gross energy expenditure, net energy expenditure and energetic cost measurements were all significantly higher in the limb salvage participants. Furthermore, mass specific values of energy consumption and cost of transport were significantly higher in the limb salvage participants.

Relative walking efficiency for the limb salvage population was calculated as 80%. Mass-specific net cost of transport was higher in the limb salvage participants compared to the control participants, for a given relative velocity. The ANOVA test analysis (Analysis Of Variance) confirmed the difference between the heights of the two slopes ($p < 0.001$) but not the gradient.

Pearson correlations showed negative relationships between knee extension strength ($R = -0.5$, $p < 0.5$), knee flexion range of motion ($R = -0.46$, $p < 0.05$) and energy cost. Furthermore, Pearson correlations showed positive relationships between knee extensor strength and rectus femoris activation time ($R = 0.39$, $p < 0.05$) and between knee extensor strength and rectus femoris to hamstring co-contraction percentage ($R = 0.43$, $p < 0.5$). Time from surgery was not related to any of the electromyographic or energetic parameters assessed. Finally, Pearson correlations revealed that there were small but insignificant relationships between the electromyography findings and the energetic results.

Conclusion

Prolonged activation patterns were observed in muscles surrounding the knee in total knee replacement patients. As a typical total knee replacement stiff-legged gait pattern was adopted, the prolonged activations were not related to increased moment requirements, suggesting that the activity patterns were related to knee stability and may have reflected proprioceptive deficits at this site.

Electromyographic patterns in the unaffected lower limb suggested that alterations in gait involved higher neuronal centres. These results are important for the development of rehabilitation programs, as they suggest that an overall reprogramming of the gait pattern occurs post-operatively, thereby limiting the impact of conventional strength and stretching interventions.

On consideration of quality of life factors, limb salvage alone versus amputation has significant value in allowing the person to maintain their ambulatory independence. On a low functional level with activities of daily living, ambulatory independence has returned without crutches and the ability to walk up and down stairs and long distances. At a higher functional level many return to sport with an appropriate disability grading for active competition.

Prosthetic reconstruction is not a normal limb, but much closer to normality in any other reconstructive option, with some added increased physical oxygen demands due to heightened muscle activity.

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Cancer Council Australia's student essay competition

Cancer Council Australia's annual essay competition is open to Australian residents enrolled in a medical course in an Australian university. Students are required to submit an essay on an issue related to cancer control. In 2010, the topic was 'Cost and value of cancer care'. The essays are judged by members of Cancer Council Australia's Oncology Education Committee.

This article is the winning essay by Catherine Tang. As the winner, Catherine attended the 13th International Summer School 'Oncology for Medical Students' in Groningen, Netherlands (5 – 16 July, 2010).

Cost and value of cancer care in Australia: a medical student's perspective

Catherine Tang
6th year medical student, University of New South Wales.
Email: catherinewytang@gmail.com

Given that cancer directly affects one in three Australians,[1] it is inevitable that the costs of cancer prevention and care are borne by us all. However, appraising the value of such care is fraught with difficulty. Too often outcomes are assessed through mortality and financial costs alone – two finite ends of a spectrum that fail to take into account factors such as disability adjusted life-years (DALY) and the even less tangible psychosocial aspects of care.

This report will examine the cost and value of cancer care, starting from the rewards of investing in prevention and early detection, to the burden of resourcing treatment and allowing equitable access to cancer treatment across Australia. Furthermore, it will explore the implications of both increasing cancer burden and improving cancer survival upon care of cancer survivors. In the context of current and future reforms in Australian cancer care, all these areas are of relevance to medical students as the next generation of doctors dealing with the rising burden of cancer.

Investing in prevention and early detection

The adage of "prevention is better than cure" is manifest in our current approach against cancer, where the value of upstream investment is judged by morbidity and costs averted through early prevention and detection. As Australia has the highest incidence of skin cancer worldwide,[2] our efforts in its prevention form a compelling case in point. Although the absolute number of lives lost to both melanoma and non-melanoma skin cancers is low in comparison to other cancers,[1] it is the most expensive when considering direct costs of skin cancer diagnosis and treatment exceed $294 million.[2] This has yet to account for the loss of productivity incurred. Australian SunSmart campaigns since the 1980s have aimed to stem these costs by modifying public attitudes towards sun exposure. Recent research suggests these campaigns have been a cost-effective exercise with $2.32 returned for every $1 invested.[3] Furthermore, the penetration of this 'SunSmart' message is evidenced by the decreased rates of skin cancer in younger age groups, who have been brought up with improved awareness of skin cancer prevention.[2,4] Thus, the true value of such preventive strategies extends beyond simple monetary returns, as it also addresses fundamental health behaviours that place the population at risk of cancer from the outset.

Similarly, the potential of screening to limit the high socioeconomic and human costs of treating advanced cancers is dependent on how the population values participation. The substantial reduction in breast cancer mortality by 28% in the past decade may be largely accorded to the effectiveness of Australia's national BreastScreen program.[1] Besides the organisational merits of this program, its success is also derived from cultivating a strong public awareness of the value of screening.[5-6] In contrast, similar levels of acceptance have yet to be procured for the recently initiated National Bowel Cancer Screening Program. Given that

bowel cancer is the second most common cancer in both sexes,[1] the demonstrated potential of biennial screening to reduce mortality rates by 13-17% should tackle a substantial portion of Australia's future cancer burden.[7] Indeed, considering costs alone, removal of a precancerous polyp detected on screening may save 18 times the cost of treating the cancer that subsequently develops from such a polyp.[8]

Although cost-effective, the value of this approach may be limited if participation rates remain below 50%.[9] Factors such as poor awareness of screening benefits and damaging reports of defective kits being used in 2009 need to be combatted by concerted efforts to raise public perception of bowel cancer screening as a valuable health exercise.[10-11] This should involve targeting groups identified to have lower participation in bowel cancer screening, such as migrants, Aboriginal and Torres Strait Islanders and males in general.[11-12] With the rising costs of expanding this program to all persons aged 50-74 years,[7-8] it will be vital to build public confidence in the value of participation if the benefits of screening are to be realised.

The 'cost' of advances in care

With an ever expanding array of new therapeutic modalities in the context of resource limitations, cancer treatment is perceived to come at great expense. Yet this needs to be considered in the context of the substantial morbidity, productivity loss and psychosocial costs borne by cancer patients and their carers. Cancer treatment accounts for 6% of total healthcare expenditure in Australia, despite cancer being the leading cause of disease burden with respect to DALY, not just mortality.[13,14] Nevertheless, the cost of chemotherapy has been particularly contentious in Australia, with some suggesting that "minimal impact of cytotoxic chemotherapy on five year survival" may not justify sustained high level funding.[15] This view has yet to consider the potential value of chemotherapy in addressing symptoms and improving quality of life.[16,17] Furthermore, it is difficult to reconcile a broad "health economics" view of the cost of treatment to an individual patient's perspective on what value that chemotherapy may add to their care regimen. In order to address these uncertainties on impact of new therapies on patient outcomes, there should be greater support for local clinical trials in Australia.[13] Wider patient participation in clinical trials not only improves outcomes, but can also generate evidence upon which the value of investing in newer treatments can be gauged.[18]

Dynamic advances in different treatment modalities also necessitate a multidisciplinary approach to care provision. Despite increased outlay of expenses and time to conduct meetings, a team approach ultimately reduces resource and time costs for patients and team members otherwise incurred by poorly coordinated care.[19-20] Multidisciplinary models can also improve the value of care provided to patients by integrating the developing evidence bases of different fields and applying them to address an individual patient's specific needs. This has consistently been demonstrated to provide greater patient satisfaction and outcomes.[21] Conversely, patients themselves also contribute to improving the overall value of cancer care through greater participation in clinical trials when they are managed in multidisciplinary settings.[22-23] Taken as a whole, Australia's shift toward a multidisciplinary model can ensure that the substantial advances in cancer care are harnessed in the most efficient way possible.

Enhancing the value of care for all Australians

These improvements to provision of cancer care in Australia belie the inequities in access to care for rural and remote communities. The most telling evidence of such disparity is that greater distance from a metropolitan centre correlates to higher likelihood of death for rural/remote cancer patients within five years of diagnosis.[24] While comparatively lower socioeconomic status in remote areas contributes to this difference,[25] the effect of geographic isolation upon costs of providing 'best practice' care to these patients has significant impact on the subsequent quality of care.

As mentioned, a patient centred multidisciplinary approach has increasingly become the benchmark for cancer care, yet less than half of regional hospitals administering chemotherapy provide multidisciplinary clinics.[25] Furthermore, although 50% of cancer patients require some element of radiotherapy, its access by rural patients remains consistently below their metropolitan counterparts[13,26] an issue accorded to significant travel and accommodation costs accrued by rural patients.[27] Rural patients and carers may also have greater psychosocial needs than urban counterparts,[28] yet over 60% of centres servicing rural patients are requesting urgent access to psychosocial services.[25,29] Innovative strategies such as telephone counselling and internet based care may provide feasible alternatives in lieu of resident psychosocial services.[28] These issues reflect how dated efforts to address geographical barriers such as patient assisted travel schemes have failed to match the evolution of cancer care from a linear to multidisciplinary model. Recent funding towards regional cancer centres has the potential to address these access issues, provided adequate multidisciplinary staffing and capacity for patient accommodation can be achieved.[30]

Besides the physical barriers of distance, cultural barriers can also limit the value of care received by certain groups in Australia. Indigenous Australians have comparatively lower cancer incidence yet later diagnosis and ultimately higher cancer mortality.[31-32] Models of care that fail to address strong community taboos surrounding cancer are seen to have limited value by Indigenous patients,[33-34] leading to lower utilisation of services available. Similar findings have also been reported for other culturally diverse groups in Australia.[35-36] As attitudes to health and care seeking behaviour may be largely dictated by cultural beliefs, concerted efforts to address issues of cultural safety are necessary to enhance the value of cancer care for minority groups in Australia.

Cancer care beyond 'cure'

If the value of care were simply considered using 'survival' as an end-point, substantial gains have been made

in the last two decades - relative survival of Australian cancer patients is second only to the United States on an international comparison.[1] Yet a focus on survival alone overlooks both the value of palliative care and the ongoing costs of cancer survivorship in Australia.

Palliative care aims to address the physical, psychosocial and spiritual needs of patients throughout their cancer trajectory.[37] Patients who experience timely referral to specialist palliative care have been shown to require less hospital inpatient treatment and spend more time at home with less stress reported by carers.[38] However, a third of patients who may benefit from specialist palliative care are not referred and others suffer from delayed referral.[13] This may be related to general community and even health professional views that palliation refers only to "terminal care" and control of symptoms at the end of life.[37,39] These misconceptions need to be addressed such that earlier palliative planning may improve the value of care for these patients with complex needs.

Furthermore, cancer care does not end at 'cure'. Cancer survivors face ongoing issues with physical, psychological and functional wellbeing that need to be addressed if care is to be truly holistic. Cancer survivors in Australia have been shown to report comparatively lower physical and mental health status, along with more days out of role than those who have not previously had cancer.[40] Part of this relates to physical consequences of cancer, but also the less anticipated later costs of treatment, such as post-treatment fatigue,[41-42] chemotherapy related cognitive and genitourinary issues,[43-44] and radiation related gastrointestinal sequelae.[45] The move from acute care to long-term follow-up also opens an array of psychosocial issues for patients, including anxiety about cancer recurrence and uncertainty on return to work and family relationships away from the 'sick role'.[40,46] Cancer survivors also have higher rates of co-morbid chronic conditions and non-cancer related death,[47-48] making the transition to long-term care a vital juncture to instigate lifestyle modifications.

These issues of survivorship all highlight that good value care should involve supporting smooth transition to well co-ordinated follow-up. Conventionally in Australia, most follow-up is based on specialist oncology review and episodic communication with GPs, primarily focusing on monitoring treatment effects and recurrence.[49] Increasing numbers of cancer survivors may significantly raise the cost of providing review in specialist settings, while reducing the quality of care for each patient. A possible solution may be to shift toward greater involvement from the primary care sector in survivorship care.[50] Primary care based follow-up may be more comprehensive as other medical and psychosocial co-morbidities can be reviewed simultaneously.[51] Support for such follow-up would be invaluable in extending the focus of care beyond that of cancer alone and back towards patients overall health status.

Education and strategies for the future

With the increasing prevalence of cancer in Australia, it is inevitable that medical students will become involved in the care of cancer patients regardless of their career choices. Preparing students for the challenges of our rising cancer burden not only involves training skills in diagnosis and treatment, but broader understanding extending from preventive principles through to ongoing survivorship issues. However, current student experiences are largely centred on rotations in highly demanding clinical settings where they may only appreciate the acute aspects of cancer care.[52]

Strategies to address these issues may include:

- Increasing screening – Encouragement from healthcare professionals can influence patient attitudes to screening.[11, 53, 54] Involving students in simulated sessions to discuss the implications of screening with patients may help future doctors raise patient participation.
- Building teamwork skills – Medical students should participate in multidisciplinary team meetings to appreciate the role of allied health professionals and the dynamics of coordinating teamwork.
- Rural access – Building on current rural placements for local HECS supported students, rotations in regional cancer centres may attract and increase retention of future doctors in these areas of need.
- Cultural safety and communication – Workshops for medical students covering how cancer is conceived by other cultures may facilitate better engagement of Indigenous and migrant populations by future doctors.
- Other clinical settings – Cancer care is becoming increasingly decentralised from acute hospital care. Medical students should experience care provision in other clinical settings such as palliation at home. This may improve appropriate and timely referral in the future.
- Following the trajectory – To understand the complex issues patients face at different stages of cancer care, students should be encouraged to follow the course of patients as part of the curriculum. Particular emphasis may be given to survivorship issues that students may be unfamiliar with.

Conclusion

The rising burden of cancer in Australia will unavoidably lead to increased costs associated with care. Sustaining the value of cancer care in the face of these pressures will require a co-ordinated approach, from increasing participation in preventive efforts and removing barriers to multidisciplinary care, to providing comprehensive supportive care beyond cure. Medical students need to be made aware of these issues throughout their training and apply this understanding in their future practice.

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Report on the 2010 Cancer Care Coordination Conference: Relationships, Roles, Reality

Alison Evans
ZEST Health Strategies, New South Wales.
Email: alison.evans@zesthealthstrategies.com.au

Abstract

The 2010 Cancer Care Coordination Conference highlighted the considerable progress that has been made in recent years in developing and implementing cancer care coordinator roles across the country. Moving forward, a strategic, national approach to planning, implementation and evaluation of cancer care coordinator positions and activities will be essential to ensure long-term sustainability of these important roles within the multidisciplinary cancer care team. Informed by the conference outcomes, Clinical Oncological Society of Australia will continue to auspice the cancer care coordination Interest Group with a strengthened and formalised committee and working party structure that will support national collaboration and progression of activity in priority areas.

While Australian cancer treatment outcomes are among the best in the world, the challenge of providing coordinated care remains. The complexity of cancer diagnosis and treatment and the broad range of settings in which care is delivered mean that care can often be disjointed. Patients often miss out on much-needed support and sometimes become 'lost' in the system. Cancer care coordinator positions have been established in a number of jurisdictions across Australia in an effort to streamline patient care and ensure that patients and their carers are informed and supported throughout their journey.

As the peak national body representing health professionals whose main work is cancer control, the Clinical Oncological Society of Australia (COSA) has identified cancer care coordination as a priority issue of concern to its members. Workshops conducted by COSA in 2006,[1] 2007,[2,3] and 2009[4] explored and sought to define the issues, purpose and expected outcomes of cancer care coordination in Australia, and worked towards practical outcome measures for evaluating and developing the cancer care coordinator role. COSA has also established a cancer care coordination Interest Group,[5] with national representation to work through priority issues identified during these workshops with a view to developing care coordination as a formal component of multidisciplinary cancer care in Australia. The interest group has access to a web forum for sharing ideas, views and experiences about cancer care coordination.

In 2008, the first national conference on cancer care coordination – 'Sharing, Caring, Daring' – was held in Perth by the WA Cancer and Palliative Care Network. This report provides highlights from the second national conference – 'Relationships, Roles, Reality' – held on 25-26 March 2010 in collaboration with Queensland Health. The conference was attended by almost 200 participants from Australia and New Zealand and provided a clear illustration of the enormous progress that has been made in the field of cancer care coordination in recent years. Presentations highlighted the range of innovative activities being undertaken across the country in an effort to standardise and streamline cancer care coordination activities and measure the impact of the role.

Defining the cancer care coordinator role

A common theme underpinning many of the conference presentations, including plenaries by Chief Nursing Officer Rosemary Bryant and Michael Fitzpatrick from Cancer Australia, was recognition of the importance of the cancer care coordinator role within the multidisciplinary cancer team. A number of presenters, including Cancer Voices Queensland

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representative Aurilea Augustine and Helen Gooden from Cancer Council NSW, also reflected on the value placed on the role by patients and carers.

Updates from New South Wales, Queensland, Western Australia and Victoria highlighted progress and achievements in the area of cancer care coordination at the patient, team and system levels. While it was apparent that the cancer care coordinator role was still evolving, it was clear that there had been a shift in focus from questions about what the role should be to more strategic questions about how to embed the role as an accepted component of best practice.

The broad scope of practice of the cancer care coordinator was demonstrated in an interactive panel session, in which a series of case studies was used to describe how cancer care coordinators can impact on outcomes at the patient, team and system level. Roles described included patient navigator, educator, support provider and team coordinator. The session highlighted the value of the role in both a comprehensive cancer care centre and in regional and rural settings.

Variation in scope of practice for cancer care coordinators has been an ongoing challenge for individuals in these positions and for the health services in which they operate. Presentations from different jurisdictions highlighted the complex and multifaceted nature of the role. Areas of variation included:

- focus: modality-specific v tumour-specific approach
- role: nursing v allied health background
- integration: across public/private and regional/metropolitan settings
- tasks: direct patient care v administrative roles.

Despite this variation, discussions suggested that there is broad acceptance that skills are more important than who undertakes the role. Given the broad range of settings in which a cancer care coordinator may practice, there is clearly a need for flexibility. It was suggested that further work is needed to set some parameters within which the role operates and to continue to promote the message that cancer care coordination should be the responsibility of the entire team, not solely the task of one individual. The broad range of discussions highlighted the fact that progress in this area is no longer being hampered significantly by questions around scope of practice, but rather that evolution of the role has become an accepted part of the implementation process.

Evaluating outcomes

The importance of ensuring sustainability of cancer care coordinator positions by demonstrating the impact of the role on patient outcomes was a key theme of the conference and a priority for future activity. Impacts were discussed at the patient, team/clinic and system/strategic level.

In a highly engaging presentation, Professor Kathy Eagar from the Centre for Health Service Development at the University of Wollongong provided valuable guidance to delegates around approaches to identifying and utilising outcome measures and potential pitfalls that should be avoided. Key messages included:

- Patient and carer outcomes, rather than processes, should be used as the ultimate quality measure
- A patient outcome is a point-in-time measurement; what is important to measure is likely to vary depending on the patient's stage of illness and values
- Outcome measurement is not a 'before and after' question, but a 'with and without' question that should consider what would happen with and without a given intervention or if a different intervention were used
- Outcome measurement should be linked to the goal of the intervention; sometimes no change or an arrest in decline can be a good outcome
- Outcome measurement is not a one-off event, but should be re-assessed at intervals based on a pre-determined protocol
- An intervention will only be sustainable at the system level if it is sustainable at the patient and provider level.

Professor Eagar described the key questions to be considered when developing an evaluation framework:

- delivery: what did you do?
- impact: how did you go?
- capacity: what has been learned?
- sustainability: will it keep going?
- generalisability: is it useful for someone else?
- dissemination: who did you tell?

In describing how the impact of the cancer care coordinator role may be evaluated, Professor Eagar:

- highlighted the difficulties in attributing an outcome to one particular role
- encouraged the use of credible and validated tools
- cautioned against the use of patient satisfaction as an outcome measure
- emphasised the importance of taking a step-wise approach – deciding what is important and how to measure it.

Collecting data

A consistent approach to data collection was identified as a key step in evaluating the impact of the cancer care coordinator role. Approaches to data collection included state-based tools, such as Queensland Oncology Online, and service-level approaches to data collection, such as that used in the Hunter New England Area Health Service. The value of qualitative approaches to data collection, such as the use of patient stories, was also highlighted.

While data collection was seen as important, participants were cautioned against trying to collect data relating to every aspect of their role and were encouraged to select and pilot meaningful data items in a step-wise manner.

Power of patient stories

The power of collecting and sharing patient stories within the multidisciplinary team was demonstrated graphically in a number of presentations, including an interactive session run by the Queensland Cancer Control and Analysis Team. Shoni Colquist described the 'discovery interview' technique[6] being

used by the National Health Service in the UK as a way of generating meaningful consumer engagement.

The importance of patient feedback in driving change was also emphasised by Professor Eagar, who pointed out that health professionals were highly responsive to negative feedback from patients and carers.

Participants were also introduced to new approaches to managing change based around an exploration of the patient experience, rather than a solution based approach to systems and processes. They were given the opportunity to practice using patient stories as a measure of the patient experience and to use the 'five whys'[7] approach to asking questions.

Multidisciplinary team interactions

The central role of the cancer care coordinator in the multidisciplinary team was referred to regularly throughout the conference. In an interactive session, delegates were invited to consider the ability of the cancer care coordinator to influence patient outcomes through their interactions with the broader multidisciplinary team. Through this exercise, delegates were reminded of the importance of considering the patient experience and using this as a way of driving team interactions and decisions around care and support needs.

The multidisciplinary nature of the cancer care coordinator role was a key theme of the conference, with recognition that the role is not limited to individuals with a nursing background, but can be undertaken by other allied health professionals. Examples in which an allied health professional, such as a speech pathologist or radiologist, had taken on the care coordination role, demonstrated the potential benefits in taking a flexible approach. Delegates noted that some allied health professionals should have particularly high involvement in the development and implementation of a patient's care plan, such as speech pathologists for patients with oral cancers or social workers for patients experiencing a high psycho-social burden.

Strategic frameworks

Flexibility around the cancer care coordinator role should also be discussed in the context of work on national care standards and professional accreditation, which are being broadly scoped as part of the federal health reform agenda.

A number of speakers reflected on the potential for cancer care coordinators to act as leaders in change management, and to influence the policy agenda. The need for a strategic framework to drive improvement was highlighted as a priority moving forward.

In considering how to take this strategic framework forward, participants were encouraged to:

- interact with and utilise the advocacy skills of consumer groups such as Cancer Voices
- build relationships with other groups providing cancer support, such as Cancer Council Helpline
- join COSA and contribute to the national agenda by participating in ongoing cancer care coordination forums and activities.

Moving forward

In an interactive strategic planning session, facilitated by Professor Patsy Yates, Professor of Nursing, Queensland University of Technology, delegates were asked to identify key priorities for advancing cancer care coordinator practice.

Common priorities arising from this activity were:

- research to identify a common 'toolkit' of data items and validated tools to measure the impact of the cancer care coordinator role
- further promotion of networking and information sharing by cancer care coordinators across the country
- the need for a strategic, national approach to planning and implementation of cancer care coordinator roles and activities that will ensure sustainability of the role.

Professor Yates emphasised the importance of building on existing networks and formalising approaches to taking forward priority activities in the area of cancer care coordination. Participants were asked to consider how best to structure their professional body or group to drive the progression of activities at a national level.

There was broad consensus that COSA should continue to auspice the Cancer Care Coordination Interest Group, in recognition of the multidisciplinary scope of the role and the work COSA has undertaken in the area to date. It was recognised that a link between this group and the Cancer Nurses Society of Australia would be important given that the majority of individuals practising in cancer care coordinator roles are nurses. However, the importance of not excluding other allied health disciplines who may be practising in these roles was noted.

Delegates generally agreed on the need for the cancer care coordination Interest Group to have:

- national coverage, that includes state/territory representation as well as input from regional, rural and metropolitan areas and from public and private sectors
- multidisciplinary input, recognising nursing and allied health involvement in the role
- an option for state based as well as national meetings/forums
- input from clinical and strategic management leaders
- defined terms of reference, with an agreed term for representatives (who may be appointed voluntarily or by election)
- sub-groups or working parties to work on priority questions or issues of interest
- opportunities to meet and share ideas (ideally an annual meeting)
- other forums for sharing ideas such as a website or shared email folder.

The value of participating in such a group in terms of professional development was highlighted.

6. NHS Improvement. Using the Discovery Interview to improve care. NHS Improvement;2010. Accessed September 22, 2010. Available from: http://www.improvement.nhs.uk/discoveryinterviews/
7. ASQ. Five Whys and Five Hows. ASQ;2010. Accessed September 22, 2010. Available from: http://www.asq.org/healthcare-use/why-quality/five-whys.html

Key recommendations

Key recommendations arising from the conference:

1. COSA should continue to auspice the Cancer Care Coordination Interest Group with a strengthened and formalised committee and working party structure that will support national representation and progression of activity in priority areas.
2. A national collaborative research initiative should be undertaken, as a priority, to develop and implement a national evaluation strategy that will measure the impact of the cancer care coordinator role, including a common 'toolkit' of data items and validated tools.
3. Activities should continue to be implemented to support networking and information sharing by cancer care coordinators across the country, including an annual cancer care coordination conference as well as web-based approaches to sharing resources and experiences.
4. Opportunities should be sought to actively promote the benefits of the cancer care coordination role within the multidisciplinary team and more broadly to the healthcare community to increase awareness of the roles and encourage referrals.
5. An educational strategy should be developed to identify and encourage training in the core skills that underpin cancer care coordination, regardless of who is undertaking the role.

Acknowledgements

COSA gratefully acknowledges the input and support of Professor Patsy Yates, Queensland Health and the Conference Planning Committee. This article is based on the full report, which was prepared by Dr Alison Evans, Director, ZEST Health Strategies. The full report and the presentations from the conference are available on the COSA website at www.cosa.org.au. COSA members can access information about the COSA Cancer Care Coordination Interest Group via the COSA members area.

Towards a safe asbestos free environment summary of presentations at the National Asbestos Summit

Dave Clement[1] and Deborah Vallance[2]
1. Asbestos Disease Society Victoria, Victoria.
2. Australian Manufacturing Workers Union, Victoria.
Email: deb.vallance@amwu.asn.au

Abstract

The importance of asbestos related disease prevention is highlighted by Australian Institute of Health and Welfare predictions that in 2011 there will be 990 new cases of mesothelioma, up from 579 in 2006. Over 3000 asbestos related products have been used or manufactured in Australia. Education about avoiding asbestos exposure and removal of asbestos in a systematic program commencing with sites posing the greatest risk are therefore important prevention strategies. A national summit, jointly sponsored by Cancer Council Australia, the Australian Manufacturing Workers Union and the Australian Council of Trade Unions, called for the establishment of a National Asbestos Authority to extend and implement successful and safe asbestos awareness, control and eradication programs across the nation. The Summit called for the removal of all asbestos from public and private buildings by 2030. A National Asbestos Authority would act as an information hub and coordinate action on education and asbestos removal. The need for such an authority became clear as a range of speakers at the summit highlighted the persistence of poor community awareness, disjointed approaches by national, state and local governments and serious problems of compliance with existing regulations.

On June 29 this year, a national summit entitled Towards a Safe Asbestos Free Environment brought together asbestos disease support groups, health and safety practitioners, asbestos removalists, unions and other groups concerned with the elimination of asbestos-related disease in Australia. The summit was jointly sponsored by Cancer Council Australia, the Australian Manufacturing Workers Union (AMWU) and the Australian Council of Trade Unions (ACTU).

The summit's National Declaration called on the Australian Government to establish a National Asbestos Authority and to ensure the removal of all asbestos from public and private buildings by 2030.[1] A National Asbestos Authority would act as an information hub and coordinate national action on education and asbestos removal. The need for such an authority was clear as a range of speakers explored the persistence of poor community awareness, disjointed approaches

1. Australian Manufacturing Workers' Union [Internet]. National Declaration: Towards an Australian Safe Asbestos Free Environment;2010. Accessed August 18 2010. Avaliable from: http://www.amwu.org.au/content/upload/files/campaigns/Asbestos/asbestos_dec_jun_2010.pdf accessed 17/8/10

by national, state and local governments and serious problems of compliance with existing regulations. A National Asbestos Authority would be able to build on and consolidate existing good initiatives.

Asbestos related disease includes asbestosis (scaring of the lungs,) asbestos-related lung cancer and mesothelioma. Mesothelioma is a rare form of cancer of the lung cavity and abdomen which occurs exclusively due to exposure to asbestos fibres.

Australia has the highest incidence of mesothelioma in the world and this is likely to continue, due to the heavy use of asbestos containing materials (ACM) by the building industry in the 40 years following the Second World War. People currently at risk include workers who are unsure about safe work practices for handling asbestos products and householders who are either unaware of the existence of ACM, or unaware of safe practices in dealing with ACMs in the home. Communities adjacent to asbestos dumps or deteriorating ACM in the environment are also at risk.

Mesothelioma and asbestos related diseases

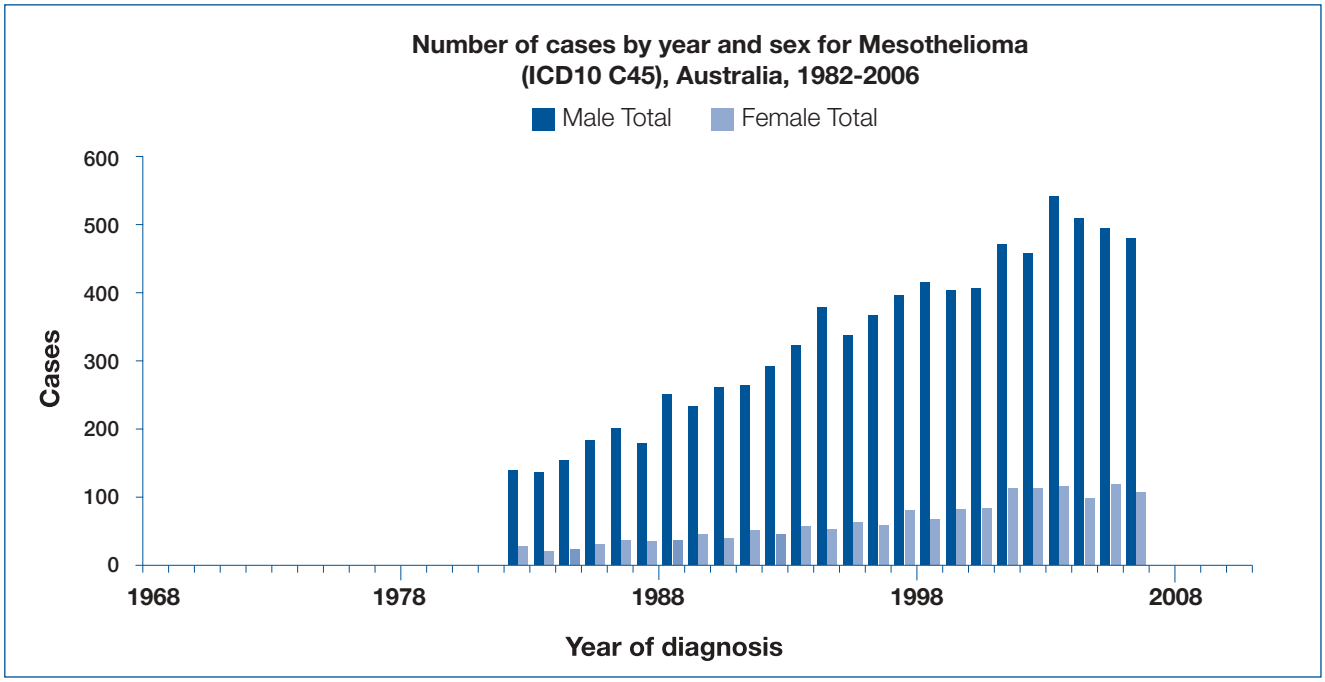
The diseases linked to asbestos exposure develop very slowly, often becoming clinically apparent several decades after the initial exposure. The most serious of these is mesothelioma, a cancer which is almost exclusively due to exposure to asbestos products and affects the pleura and peritoneum. The Australian Institute of Health and Welfare predicts that in 2011, there will be 990 new cases of mesothelioma, up from 579 in 2006. Eight of every 10 cases are in men. The incidence of the disease in Australia has not yet peaked. In 2007, there were 551 deaths, which indicates that mesothelioma should be considered a poor prognosis cancer, where current treatment is not yet effective. Asbestos exposure contributes to other cancers including lung, laryngeal and ovarian cancer, but accurate figures on the other asbestos related diseases are not available.

Relevant statistics highlight the importance of preventing mesothelioma (figure 1). Over 3000 asbestos related products have been used or manufactured in Australia. Education about avoiding asbestos exposure and removal of asbestos in a systematic program commencing with sites posing the greatest risk are therefore important prevention strategies.

Community awareness of asbestos containing materials

Evidence that the dangers of asbestos exposure were not limited to the workplace, but exist in the community and in the home, were emphasised by a National Health and Medical Research Council funded program carried out by a team from the Centre for Behavioural Research in Cancer Control at Curtin University, along with the National Research Centre for Asbestos Disease.[3] The first part of the research involved a national survey of households, with 2811 adults asked about their asbestos exposure. In total, more than 70% of both men and women reported exposure, of which 65% reported exposure in the home. Despite these high levels of reported exposure, the majority of people surveyed thought that their risk associated with this exposure was low (figure 2).

Figure 1: *Number of cases by year and sex for Mesothelioma in Australia 1982-2006.*



2. Australian Institute of Health and Welfare [Internet]. Accessed August 8 2010. Available from: http://www.aihw.gov.au/publications/can/cipa02-11/cipa02-11-c02.pdf
3. Howat P, Jalleh G, Lin C, Reid A , Musk B, de Klerk N, Nola Olsen N, Terry Slevin T, et al. Development of a program to prevent Asbestos exposure in residential settings. National Research Centre for Asbestos Disease, University Western Australia, Curtin University and Murdoch University, 2009.

Figure 2: *Reported exposures to Asbestos National Telephone Survey*

Exposure to asbestos dust or fibres		
	Males % yes	**Females** % yes
Contact in job	36	7
Lived near asbestos processed/used	11	10
Lived near asbestos renovation/ demolition	17	15
Asbestos in home	65	65
Total exposed	**77**	**71**
	(n=2811)	
Metro v country	Higher in country	
Age differences	Exposure more likely if older	

While 40% of those who reported exposure to asbestos through their work said they were involved in safe practices, only one in 10 of those exposed non-occupationally took any precautions. Men in Western Australia who had been exposed participated in focus groups. Themes that emerged from the groups included significant concerns about existing and future community risk and strong support for awareness programs and community interventions.

Twenty years of joint union and community action led to the encapsulation of asbestos roofing on state public schools and TAFE Colleges in Western Australia, and by 2003, its complete removal. Two hundred and fifty school roofs, approximately 400,000 sq metres of asbestos cement sheeting, has been removed at a cost of $25 million dollars. This campaign commenced in the mid eighties and involved teachers, parents and community members. In 2006, a steering committee was set up to review and oversee the management of asbestos in government agencies following enforcement action initiated against the Department of Education and Training, and a subsequent parliamentary inquiry and adverse report from the WA Auditor General. In February 2010, the steering committee report found that there was a serious problem of compliance with eight public sector agencies that were audited. A number of agencies remain non-compliant. The committee has recommended a wide number of measures to ensure compliance in the future.

A coalition of groups and individuals committed to raise public awareness and to campaign about the dangers of asbestos in the community was formed in 2005 in South Australia. Members of the coalition include representatives of two asbestos support groups, unions, MPs, asbestos removal companies, training organisations, state government and local government departments. Meetings, which are informal, are convened by the Secretary of Unions SA. Achievements of the informal group include improved dust disease legislation and innovative real estate legislation for the notification of asbestos when selling a property. Asbestos awareness has also been promoted by governments mailing asbestos information with all household levy notices.

Actions by local government and trade unions

Holroyd is in the “fibro belt” of Western Sydney. Not only is there a very high level of ACM in households, but the future risks to public health are compounded by extensive redevelopment plans over the next 20 years. Holroyd Council policy included a system of approval for asbestos demolition by licensed contractors, neighbourhood notification and receipted evidence of safe disposal. In February 2009, state policy superseded the council control and weakened most of the safeguards to health. This encouraged illegal dumping, the use of untrained people removing asbestos and insufficient neighbour notice. Holroyd Council is campaigning for demolition control to be returned to the council, best practice removal and disposal and the creation of a single independent authority to deal with all asbestos matters.

Asbestos cement products were produced in Tasmania by Goliath Portland Cement in Railton in the North West from 1947 until 1986. Research carried out by Unions Tasmania indicated high rates of mesothelioma, especially in the North West, no compensation claims and ignorance of asbestos regulations. In July 2008, Unions Tasmania wrote to the State Premier asking for a new conversation on asbestos and public health and identified 10 issues of concern. In November 2008, during Asbestos Awareness Week a survey of asbestos registers across 328 sites was carried out. It found 43% of the sites surveyed contained asbestos and in 38% of workplaces employers did not know whether asbestos was present. While 51% of sites had an asbestos register, almost half of these had not been updated in the last three years.

After witnessing many poor workplace practices the AWU has developed a new approach to the management of ACM – the Prioritised Removal Program. This approach tries to address the shortcomings of failed risk assessments and risk management programs, and ineffective or non-existent asbestos registers. The AWU encountered an example of these failings in 2006 after an inspection of the Cement Australia site at Railton, Tasmania, which uncovered deteriorated ACM and poor management practices. Following a ban of certain buildings, a demand that buildings be demolished and that a number of studies be undertaken, the AWU discovered that the previous organisation (Goliath Cement) had produced a range of ACM in the period 1947-1986. Approaches were made to the company and the government to adopt a different management program and policy for the removal of ACM. This resulted in a call for a graded and centralised asbestos register (colour coded at the site of presence by red, amber and green tickets), designating final date of total removal, and the supply of formal plans. To achieve such prioritised removal (a kind of product recall) across Tasmania, the AWU suggested a 20 year period

managed by a dedicated asbestos unit. This has now been adopted by the Tasmanian Government.

Safe Disposal

The Latrobe Valley has the highest incidence of asbestos related disease in Victoria due to the heavy use of asbestos in the energy industry post war. It also has a high level of housing built with ACM. In August 2005, Gippsland Asbestos Related Disease Support and the Gippsland Trades and Labour Council asked the Environmental Protection Agency to form an interagency group to focus on asbestos in the home. A joint project developed two innovative programs.

The first of these was a comprehensive kit to provide residents who wished to carry out home renovations with information and protective equipment to do this safely (figure 3). Home renovators are discouraged from carrying out large asbestos removal projects themselves, but if they do get involved with ACM they are given the necessary training and equipment at subsidised rates.

Figure 3: *What is in Asbestos in the Home Removal Kit*

DVD instruction guide – 11 minutes
2 x 5mx3m 200um black wrap
2 x 60 x450mm printed disposal bags
2 x breathable disposal coveralls
2 x vented flat fold respirators
2 x 100% nitrile gloves made by Pro-Val Disposable Gloves (1 x size 9, 1 x size 10)
4 x disposable overshoes
Roll of duct tape
6m printed barrier tape
4 x wipe down rags
1 lire spray mister
250ml PVA glue
3 x asbestos warning stickers

The second involved the construction of a model Domestic Asbestos Receiving Unit and Transfer Facility. This unit arrives as 3 x 20ft modules (shipping containers) on the back of a semi – tilt slide truck and trailer - requiring 22 metres to deliver and position the unit. It is equipped with all that is needed for the safe decontamination and disposal of ACM. It has its own water supply and electricity generator. Thought to be the first of its kind in the world, it is capable of making a major contribution to the safe disposal of asbestos materials present in the home.

National declaration: Towards an Australian Safe Asbestos Free Environment

All the summit participants endorsed the national declaration, calling on the Commonwealth Government to establish a National Asbestos Authority, which would extend and implement successful and safe asbestos awareness, control and eradication programs across the nation.

Current evidence indicates that despite a general level of awareness about the dangers of asbestos, workers are unsure about specific safe work practices, while many affected householders are ignorant of specific safe work practices for home maintenance and improvement. The concerns raised at the summit were highlighted by Jeff Lawrence, ACTU Secretary, when he noted that: “Buildings with asbestos are deteriorating – creating hazards in our community. Asbestos does not get safer the longer it is left in a building or in a roof. It gets worse.”

The national declaration includes strategies on how to increase awareness on where ACM are located, in environmental, industrial, commercial and domestic settings. It details the mechanisms required for education and regulatory changes to safely remove asbestos from our built environment. This includes:

- auditing of public buildings, particularly in the health and education sectors, with asbestos registers and a target of prioritised removal by 2030
- in the commercial and industrial sectors, asbestos registers that include the program of prioritised removal by 2030 and a requirement for vendors and landlords and/or their agents to notify buyers and tenants of the asbestos register
- for domestic housing stock, a requirement for the disclosure of ACM, at the point of sale, with the purpose of the eventual removal of asbestos from housing stock.

The summit noted that governments must make arrangements for the allocation of funds in a coordinated approach for medical research. In closing the summit, Paul Bastian, President of the AMWU, paid tribute to the efforts being made by those organisations present to ensure that people in the workplace, community and in the home remain free from asbestos related disease. A National Asbestos Authority would build on this further.

Australian Behavioural Research in Cancer

Cancer Prevention Research Centre (CPRC), School of Poulation Health, University of Queensland

Sedentary behaviour, metabolic risk and cancer

Research studies at CPRC, carried out with colleagues at the Queensland University of Technology, the Baker IDI Heart and Diabetes Institute in Melbourne and international collaborators at the US National Cancer Institute, Cambridge University and the Alberta Cancer Board, are examining the role of sedentary behaviour (too much sitting, as distinct from too little exercise). There are exciting new findings that relate to risk of the major metabolic cancers, primarily breast and colon cancer, and with newly-emerging international evidence implicating risk in relation to endometrial and other cancers. Work with cross-sectional and prospective data from the national Study of Diabetes and Its Risk Factors has shown significant relationships of television viewing time with biomarkers (including overweight and obesity and abnormal glucose metabolism) that are known to increase cancer risk. A recent study with Queensland Cancer Registry participants identified significant prospective relationships of TV viewing time with weight gain over three years in colorectal cancer survivors; weight gain in this high risk group is related to co-morbidities, particularly type II diabetes and cardiovascular disease. Having established sedentary behaviour (and particularly prolonged television viewing time) as a major element of the cancer risk equation, studies at CPRC are now proceeding with controlled intervention trials among adults with diabetes and with cancer survivors, designed to gather crucial causal evidence by examining whether reducing sedentary time and weight loss can have beneficial effects on risk biomarkers. CPRC is conducting a pilot study to evaluate a six month telephone delivered weight loss intervention in overweight and obese women who have recently completed treatment for stage I-III breast cancer. This is a behavior based intervention which will assist participants to increase physical activity, reduce sedentary time and reduce energy intake.

Centre for Behavioural Research in Cancer Control, Western Australia

Are current alcohol advertising restrictions working?

Current alcohol advertising restrictions ostensibly shield Australian children and adolescents from exposure. We conducted a simple experiment to measure awareness of Bundy R. Bear, a character frequently appearing on Australian alcohol television advertisements. Children (n=156) were recruited from eight Western Australian primary and secondary schools, with one primary and one secondary school selected from each of the four socioeconomic quartiles of the Perth metropolitan area. An image of Bundy R. Bear was included among seven other distracter images of characters used to advertise various foods and drinks within the popular media. All images were digitally 'cleaned' to remove products and/or trademarks. Children were asked to correctly match images of the eight characters to a collection of products. Twice as many food and beverage images were provided to counteract the possibility of children using a process of elimination to correctly match pairs. Three-quarters (75.4%) of children and adolescents could correctly associate Bundy R. Bear with an image of a generic bottle of alcohol. This included 66.7% of children from the youngest age-group (9–12 years, mean age=11.06, SD=.94) rising to 84.2% of older children (range 13–15 years, mean age=13.76, SD=.70). Our data suggest a large majority of Australian children are exposed to alcohol advertising and current alcohol advertising restrictions clearly are not working as intended *(Three-quarters of Australian children know the Bundaberg Rum Bear: are current alcohol advertising restrictions working? ANZJPH, inpress).*

Evaluation of the Make Smoking History cigarette additives campaign

In May and June 2010, Cancer Council Western Australia ran a Make Smoking History campaign highlighting the additives found in cigarettes, such as sugar and honey, which are commonly added and make the product more palatable by masking the bitter taste of the tobacco. A television advertisement ('Sugar Sugar') featured a range of scenes depicting smokers with various smoking-related diseases, including laryngeal cancer, chronic bronchitis, emphysema and heart disease. The advertisement is set to the well-known song by The Archies, 'Sugar Sugar', and finishes with the words "Additives such as sugar and honey can hide the bitter taste of tobacco. But the damage cigarettes do can't be hidden." The press advertisement ('Deceptively Delicious') shows a cigarette that has been pulled in two, with a caramel-like substance stretching between both ends. It talks about additives like sugar and honey that are commonly added to cigarettes to make them taste better and easier to smoke. Random digit dialling telephone surveys were conducted within the Perth metropolitan area. In total, 200 current smokers or recent quitters aged 25-54 years were surveyed. Analysis of the data is in progress.

Centre for Health Research & Psycho-oncology, New South Wales

Move More for Life

Due to early detection and advances in treatment, the number of women surviving breast cancer is increasing. While there are many positive aspects of improved

survival, breast cancer and its treatment is associated with many long-term health and psychosocial sequelae. Engaging in regular physical activity post-diagnosis can reduce this burden. Despite this evidence, the majority of breast cancer survivors do not engage in regular physical activity. The challenge is to provide breast cancer survivors with appealing and effective physical activity programs in a sustainable and cost-effective way. Our study, 'Move More for Life', is testing in an Australia-wide randomised control trial, whether an individually tailored, distance based behaviour change program increases physical activity in breast cancer survivors. The intervention group receives three newsletters delivered every five to six weeks, tailored on women's personal demographic information, psychosocial information, health status and reported physical activity behaviour. This study improves upon the methodology used in other studies by including an objective measure of physical activity, and is one of the first to promote a pattern of physical activity that addresses the metabolic consequences of unbroken sedentary behaviours. If proven to be effective, the tailoring program developed as part of this study will be made available for use by organisations that have frequent contact with breast cancer survivors. It can also be readily adapted for use in other cancer populations and for primary prevention

General practitioner knowledge, attitudes and practices relating to vitamin D and the sun

Adequate vitamin D is not only important for good bone health, but it is increasingly being recognised as a potential protective measure against various cancers. The most effective source of vitamin D is direct exposure to sunlight. This poses a communications challenge for cancer authorities - how do we recommend a balance of adequate sunlight for vitamin D, but not too much to increase the risk of skin cancer? General practitioners (GPs) have a potentially important role in communicating the balanced approach to receiving sunlight. However, there is little information about GP current practices with regards to giving advice about sun exposure and vitamin D, or about their current levels of vitamin D knowledge and attitudes. In order to address this gap in information, a random sample of over 400 GPs across NSW was conducted. The survey found that although knowledge about vitamin D was generally sound, GPs displayed some confusion regarding the amount of sunlight needed for adequate vitamin D. This result suggests that GPs require tools to assist them in the giving of appropriate sun exposure advice, particularly as it relates to the balance message. This point is made more salient by the finding that most patient enquiries about vitamin D to GPs were for more information about the amount of time they needed to spend in the sun safely.

Viertel Centre for Research in Cancer Control, Queensland

Beating the Blues After Cancer study

There is a well established body of evidence demonstrating that psychosocial interventions increase wellbeing, improve adjustment and coping and reduce psychological distress in people affected by cancer. Cancer helplines provide a potential assessment and referral point for patients and family members for psychosocial intervention both during and beyond their treatment experience within the acute health care setting. The feasibility of Cancer Council Helpline identifying highly distressed individuals within the population of cancer patients and their families is now established. The next logical step has been to utilise this care pathway for the delivery of evidence-based psychosocial interventions for high distress cancer patients and their carers.

To that end, the aim of the 'Beating the Blues After Cancer' study is to assess the efficacy and cost-effectiveness of accessible and affordable psychological interventions for distressed cancer patients and carers who contact the NSW and Queensland Cancer Council Helplines. By comparing two different support options, the study will determine the best possible way to help people affected by cancer. The study began in September 2009 and to date, 676 participants have been recruited and randomly allocated to one of two support options – five tele-based sessions with a psychologist or one tele-based session with a nurse counsellor. In addition, follow up assessment is taking place at three, six and 12 months. It is intended that this research will produce important outcomes for health services planning.

CanChange Study

Colorectal cancer survivors may suffer from a range of ongoing psychosocial and physical problems that negatively impact on quality of life. Improvements in modifiable lifestyle factors (physical activity, diet, overweight/obesity, smoking and alcohol) may improve psychosocial and quality of life outcomes, treatment related declines in quality of life and potentially survival from colorectal cancer and other chronic conditions (diabetes, heart disease). The CanChange study is a randomised control trial of a telephone delivered intervention to improve lifestyle factors and overall quality of life for colorectal cancer survivors.

Recruitment has been conducted through the Queensland Cancer Registry, and a final sample of 410 participants has been randomised to an intervention or "usual care" control condition. The intervention focuses on symptom management, lifestyle and psychosocial support using telephone delivered health coaching sessions from a study trained health professional (Health Coach), additional educational resources, a pedometer and motivational postcards. Control participants receive standard Cancer Council educational materials. Primary outcome variables include physical activity, cancer related fatigue and quality of life. Baseline data collection has been completed and follow-up data collection is ongoing. A cost effective analysis of the costs and outcomes for both study groups will be conducted. Final study results will be available in 2011.

(A randomised control trial of a lifestyle intervention for colorectal cancer survivors CanChange: study protocol. BMC Cancer 2009;9:286)

Centre for Behavioural Research in Cancer (CBRC), Victoria

Norms and built environment: Use of shade in US and Australian city parks

Building quality shade has shown to be a promising strategy for adolescents' sun protection in Melbourne. Purpose built shade can be a costly investment and it is important to understand the context in which shade is sought and used. CBRC has been awarded a five year grant from the US National Institutes of Health ($2.7 million) to conduct an intervention study to examine the effects of societal level norms on people's use of newly shaded areas in parks in Denver and Melbourne. Both cities have similar summer temperatures and UV levels, however Denver has had only sporadic skin cancer education campaigns, while Melbourne has had extensive public education on skin cancer. It is hypothesised that where a positive culture of sun protection is established (Melbourne), people will be much more likely to seek and use purpose built shade. Eighty parks in each city will be recruited to the study, with unshaded passive recreation areas having potential for a shade development monitored within these parks. Twenty in each city will be randomised to receive a shade sail built over winter. Observed use of the passive recreation areas at all 160 parks and other measures will occur in the summers before and after the shade sails are built. The main outcome will examine the use of 'shaded' passive recreation areas versus 'unshaded' passive recreation areas, to determine if there are differences between Melbourne and Denver due to the difference in sun safety culture between Australia and the US. This research will inform policy makers about the potential role of shade development in reducing skin cancer rates and the extent to which public education campaigns are needed to facilitate shade use.

Effects of counter advertising on parent/child susceptibility to junk food promotions

At present in Australia, children and parents are constantly exposed to food industry marketing and promotions aimed at encouraging purchase and consumption of unhealthy child oriented foods. Despite strong community support for tighter restrictions on food advertising to children, efforts to provoke meaningful policy change in this area have been unsuccessful. CBRC has been awarded a two year grant from the MBF Foundation ($280,000) to assess effects on parents and children of exposure to counter advertisements designed to debunk potentially misleading food promotions. Specifically, this research will explore whether counter advertisements can empower consumers to more critically and accurately evaluate advertised foods. Two experimental studies will be conducted. The first will test whether parents exposed to counter advertising can more accurately assess the nutritional content of unhealthy child oriented food which bears sports celebrity endorsement or misleading nutrition content claims. The second study will focus on primary school aged children to determine whether child oriented counter advertising can protect children from the influence of similar front-of-pack marketing techniques. If found to mediate the effects of promotions, these studies would provide evidence that counter advertising could be a potential strategy to reconcile the disproportionate amount of unhealthy food advertising to children through all media, including product packaging.

Behavioural Research and Evaluation, South Australia

Evaluation of the impact of the SA Health Smoke free Policy on SA Health staff

From 31 May 2010, smoking was prohibited at all South Australian public health services, including all buildings, structures, outdoor areas and government vehicles. The policy was applied to all South Australian Department of Health employees, consumers, visitors and all other persons entering Department of Health premises. To determine the impact of this new smoke free policy on SA Health staff, the Tobacco Control Research and Evaluation program will administer surveys to evaluate changes to smoking behaviour, perceived exposure to second-hand tobacco smoke and attitudes towards the policy. The study will compare data collected pre-implementation (baseline data) with responses three and 12 months post implementation of the smoke free policy. The surveys will also give insight into staff satisfaction with support and assistance mechanisms provided to assist in managing nicotine dependence.

Tackling Smoking program

The South Australian Government has recently awarded the Tobacco Control Research and Evaluation program funding over three years to provide an independent and culturally appropriate monitoring and evaluation service for the 'Tackling Smoking' component of the National Partnership Agreement on Closing the Gap in Indigenous Health Outcomes. This work will increase the evidence base in South Australian Indigenous tobacco control.

NEWS & ANNOUNCEMENTS

Election 2010

Cancer Council Australia published its election priorities in July, calling for support from all parliamentarians and candidates for a nine-point plan for the next term of office:

- Implement the National Bowel Screening Program
- Re-introduce the National Skin Cancer Awareness Campaign
- Abolish duty-free tobacco sales and set a minimum floor price
- Support a comprehensive obesity strategy
- Review alcohol taxation, marketing and promotion
- Review gene patent laws
- Fix remote patient travel schemes
- Announce a national cancer research strategy
- Commit to a cancer workforce review.

In an election campaign described by media as light on policy detail, there was no published support from either of the major parties for Cancer Council Australia's priorities. It was the first time in more than a decade that neither of the major parties had released a cancer control plan.

The Australian Greens, however, published a detailed response to Cancer Council Australia's proposals, supporting eight of the nine priorities in principle, along with a commitment to continue to review gene patent policy through the Senate committee chaired by Greens' health spokesperson, Rachel Siewart. The Greens also made separate media statements in support of the National Bowel Cancer Screening Program and greater protection of children from targeted junk food advertising, with Cancer Council Australia welcoming the party's position on these issues with widely published media comments.

Despite the lack of cancer policy detail elsewhere, Cancer Council Australia remains optimistic that it will be able to work constructively with whoever forms the next government to continue to build on Australia's globally strong record in cancer control.

Coalition calls for asbestos free Australia by 2030

The Australian Manufacturing Workers' Union (AMWU), the Australian Council of Trade Unions and Cancer Council Australia convened a national summit on 29 June, to call for coordinated national action on asbestos removal.

The summit aimed to create a coalition involving unions, asbestos disease experts, regulatory bodies and asbestos support groups, who will work towards making Australia asbestos free by 2030. Researchers estimate that the deadly substance is still present in over a million Australian homes, schools and public buildings.

AMWU National President, Paul Bastian, said the aim of the summit was to call for the establishment of an independent national authority on asbestos to work across all jurisdictions.

"We call on the Federal Government to urgently address this issue by creating a dedicated National Asbestos Unit. This unit would act as an information hub and coordinate national action on asbestos removal and education."

Cancer Council Australia CEO, Professor Ian Olver, said Australia would continue to experience an increase in asbestos related disease over the next two decades. "Australia has the highest per capita incidence of mesothelioma in the world and it's estimated that up to 18,000 Australians are likely to die from this disease by 2020," he said.

"It can take 20 to 30 years after exposure to asbestos for the symptoms of disease to appear, so we need to do far more to reduce Australians' exposure to asbestos."

Tobacco industry misinformation further evidence plain packaging would reduce smoking deaths

As a new, big-budget media campaign funded by the tobacco industry sought to roll back the Government's plan to introduce plain packaging of tobacco products, Cancer Council Australia and the National Heart Foundation of Australia called on all political parties to support the important health measure.

Professor Olver, and Heart Foundation CEO, Dr Lyn Roberts, said tobacco industry resistance and misinformation in the nation's media added to evidence that tobacco consumption would decline if branded packs were replaced by plain packaging.

"Glossy, branded packaging is one of the remaining ways for advertising tobacco products in Australia," Professor Olver said. "The industry knows this, which is why it is putting so much money into trying to reverse what is a groundbreaking public health policy commitment."

"We were delighted to welcome the Government's announcement in May to phase in plain packaging for tobacco products from 2012 and the Opposition's tacit support for the proposal.

"So we hope the tobacco industry's campaign, aimed at maintaining profits while thousands of Australians continue to die of smoking-related cancers, will prompt all political parties to voice their support for plain packaging of tobacco products."

Dr Roberts said that despite its self-serving claims about businesses and jobs, the tobacco industry contributed only $1 billion to the Australian economy while costing the community an estimated $31 billion in healthcare expenses, lost productivity and a range of other liabilities.

"The Australian public – and our political parties – should see this big-budget tobacco industry campaign for what it

is - self-interest from an industry that profits from death and disease," Dr Roberts said. "The industry also knows the rest of the world is watching."

Clinical guidelines for advanced prostate cancer now available

Cancer Council Australia has published the nation's first clinical practice guidelines for the management of locally advanced and metastatic prostate cancer.

Developed by Cancer Council Australia's guidelines specialists, the Australian Cancer Network (ACN), and endorsed by Andrology Australia and the Prostate Cancer Foundation of Australia, the guidelines are based on an exhaustive analysis of international research.

According to the Chair of the guideline's working party, Professor Villis Marshall AC, the guidelines assess the quality of evidence for each recommendation, enabling clinicians to assess the risks and benefits of different treatment options.

"Managing prostate cancer is complex and often confusing for the patient, his family and even medical and health practitioners," Professor Marshall said. "These guidelines bring together the best evidence currently available to provide health professionals with evidenced-based treatment recommendations."

ACN's Senior Medical Advisor, Emeritus Professor Tom Reeve, said that one in five men would be diagnosed with prostate cancer by the age of 85.

"Each year, more than 17,000 men are diagnosed with prostate cancer and it causes almost 3000 deaths," Professor Reeve said. "Although we have made significant progress over the past 30 years, there is still uncertainty around managing prostate cancer.

"These clinical guidelines bring together the body of research on prostate cancer and will help health professionals decide on the best care options for their patients, including navigating the various treatment options, psycho-social care, complementary and alternative therapies."

Health professionals can access the clinical guidelines online at www.cancer.org.au/clinicalguidelines or by calling Cancer Council Australia on 02 8063 4100.

New GP guide for cancer screening

Cancer Council Australia has published a quick reference guide to assist GPs and other health professionals in the screening and surveillance of specific cancers.

The guide provides evidence-based recommendations on which cancers are suitable for population screening, methods and frequency of screening and whether a government screening program exists.

According to Professor Olver, in addition to population based screening of breast and cervical cancer, health professionals should be encouraging patients 50 and over to screen for bowel cancer using the faecal occult blood test (FOBT).

According to the guidelines, most women aged 50 to 69 should have a mammogram every two years, and all women aged over 18 and who have commenced sexual activity should have a Pap test every two years. However, women over 70 who have had two normal Pap tests in the last five years do not require further tests.

While the evidence does not support population based screening of ovarian, prostate, testicular or lung cancers, or melanoma, advice is provided on screening in specific cases involving high risk groups.

Cancer Council is distributing the guidelines to GPs and specialists nationally in August. They are also available online at www.cancer.org.au/screeningguide

Michael Clarke opens innings as ambassador for skin cancer awareness

Australian Cricket's Twenty-20 captain and Test vice captain, Michael Clarke, will front Cancer Council's campaign this summer to encourage greater use of sun protection and early detection of skin cancer.

Announcing Michael's appointment as a Cancer Council Ambassador today, Professor Olver, said the cricketer's popularity would help Cancer Council get its messages to a wide audience.

"More than 340,000 Australians get skin cancer each year and 1700 die from it," Professor Olver said. "With Michael's help, we want to reduce this figure by promoting sun protection, as well as getting people to be more aware of changes to their skin and consulting their GP."

Michael, who has had two skin cancers removed from his face, said he was passionate about the issue and was keen to help Cancer Council educate Australians about sun protection and early detection.

"I noticed two unusual moles on my face and got them checked out by my GP," he said. "It was certainly a wake-up call and having them removed prevented what could have been a lot more serious.

"This experience made me realise the importance of protecting myself from the sun, especially because I am outdoors so much in the summer, which is when UV levels are at a peak."

Cancer Council's skin cancer campaign this year will focus on men, who make up two thirds of the skin cancer death toll.

For more information on sun protection and early detection, visit www.cancer.org.au/sunsmart

A true icon in cancer control

Cancer Council Australia's highly esteemed Emeritus Professor, Tom Reeve AC CBE, retired on June 30 from his position as Medical Director of the Australian Cancer Network (ACN).

Following a renowned surgical career, Professor Reeve led the development over 16 years of clinical guidelines for the management of common cancers through ACN, guidelines that were adopted both nationally and internationally.

Professor Reeve was presented with the Australian Cancer Society Gold Medal in recognition of his contribution at a symposium and retirement lunch in July.

Cancer Council Australia and COSA are indebted to Professor Reeve for his unparalleled contribution to cancer control. We extend our warm wishes to Professor Reeve and his wife Mary Jo as they embark on a new phase of their life post retirement.



BOOK REVIEWS

Pieces of Me: Genetically flawed – surviving the breast cancer I may never have

Veronica Neave
Big Sky Publishing (2009)
ISBN: 9780980658200
224 pages
RRP: A$24.99

Pieces of Me is not a self-help book. It is not a structured guide for the general public on surviving a genetic diagnosis. It is certainly not a textbook. It is one woman's account of how she and her family have coped with the discovery that the family history of breast cancer was, in fact, due to an inherited BRCA2 mutation.

Ms Neave is an actor, a creator, and writes with eloquence about her ongoing journey through the complicated world of a diagnosis of cancer predisposition and subsequent decision making about her risk management options.

She begins with painting a vivid picture of her family, covering far more than the facts of the breast cancers that took the lives of her grandmother, great-grandmother and has also affected her own mother. She describes her childhood, her training as an actor and the early years of her career in Sydney. Then there is the story of her mother's original diagnosis and treatment for breast cancer, but quickly the reader is swept back into the highs and lows of Ms Neave's career, love life and then the birth of her son, Kaspar.

About a third of the way into the book, the identification of a familial BRCA2 mutation is made, and the real meat of the story begins. Ms Neave's account of how she received her own genetic result is by no means representative of the usual practice of familial cancer clinics in Australia (and one wonders how much of the story is true or lost to memory and emotion), but nonetheless, she now has to face the questions of what to do about her increased risk of breast and ovarian cancer. She is very honest and up-front about all her decisions and the experience of the surgery she chose. As a health professional working in this world every day, it is refreshing to read a patient's perspective. I found her story to be engaging and accessible.

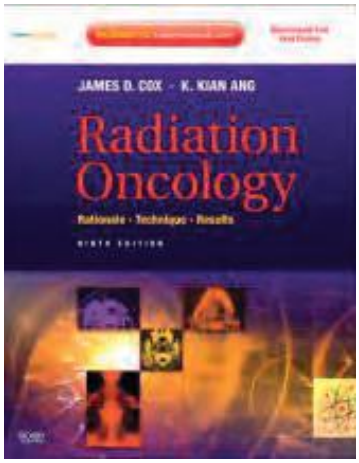
As mentioned, *Pieces of Me* is not a textbook, although Ms Neave has obviously done a lot of research and works hard to present factual information. However, *Pieces of Me* should not be relied on as a source of accurate medical advice, and nor do I expect that Ms Neave wishes it to be used in such a way. As such, I would not recommend this book to a patient facing similar circumstances without making it clear that this is simply one woman's experience and her individual choices; all facts and medical advice should be checked, and possible decisions explored with their own team of experts. I would, however, recommend the book to health professionals who are interested in hearing a quite well written account of "pre-vivorship" in a young Australian woman.

Michelle Bowman, Associate Genetic Counsellor, Familial Cancer Service, Westmead Hospital, NSW.

Radiation Oncology

James D. Cox and K. Kian Ang
Elsevier (2009)
ISBN: 978-0-323-04971-9
1072 pages
RRP: A$283.00

Radiation Oncology is in its ninth edition, and the authors have stated their intention to update and replace chapters from earlier editions that are outdated.



The chapters are well formulated, with the content presented in a logical and sequential manner, allowing for an ease in both reading and sourcing of information. The text flows nicely, outlining changes that have taken place in radiation oncology since the last edition (2003) and builds on these changes to update the reader with advances in radiation oncology techniques, including new developments in intensity-modulated radiotherapy (IMRT) and proton therapy.

Disease sites are covered from aetiology, anatomy and pathology, through to treatment options and outcomes. Recent clinical trials and adjuvant therapies are covered where applicable and this enables the reader to obtain a 'big picture' view of the disease.

Photos and diagrams used in the text provide solid technical support and visual representation of the topics being discussed. Most figures in this ninth edition utilise colour, enhancing the value of the diagrams. The utilisation of selective relevant images allows easier understanding for those unfamiliar with the detail of 3D treatment planning systems and CT cross sectional anatomy.

Patient outcomes are limited to some discussion of the acute and late complications of radiotherapy to some sites, and there is minimal discussion or evidence to justify interventions for patient care. However, this is not the intent of this text, as it is primarily a theoretical textbook of the impact of radiotherapy alone or in combination with other treatment modalities on specific tissues, while minimising the harm to healthy surrounding tissues. If the reader is searching for specific and detailed patient outcomes and evidence for a range of interventions, then they are available elsewhere.

Purchase of this book enables access to the expertconsult.com website. This allows for full text access online and the ability to search on any topic. Links are available to PubMed abstracts for most bibliographical references listed.

This text would be of interest to a range of professions within radiation oncology, and although some of the concepts are advanced reading, generally the language is accessible to most readers with some knowledge of the concepts. This is a useful textbook for a range of health professionals of varying levels of expertise working in radiation oncology, and its logical approach provides guidance for the novice practitioner, as well as detailed, up-to-date information for the advanced practitioner.

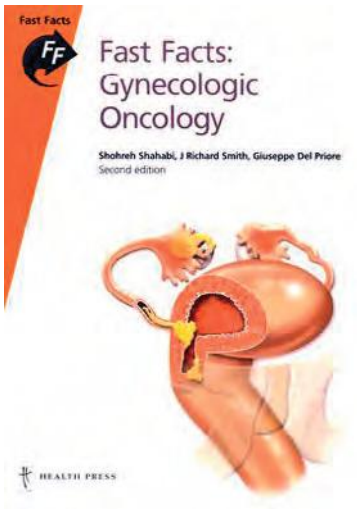
Pauline Rose, Nurse Unit Manager and Simon McQuitty, Director of Radiation Therapy Services, Radiation Oncology, Mater Centre (Princess Alexandra Hospital), Brisbane.

Fast Facts: Gynecologic Oncology

Shohreh Shahabi, J Richard Smith, Giuseppe Del Priore
Health Press Second Edition (2010)
ISBN: 978-1-903734-00-1
RRP: EUR15.00

Within the introduction to this book the authors write that they aim to 'update the primary care provider and non-specialist who see these (gynaecologic) tumours infrequently on current management and prognosis'. The authors also claim, 'it is a useful starting point for medical students and junior doctors on a gynaecologic oncology rotation'.

This book is divided into colour coded sections with matching indexes at the front and back, allowing for quick, easy referral. Each coloured section discusses one area of gynaecologic cancer or a related issue. Topics include cervical, vaginal, uterine, ovarian and vulval cancers, and gestational trophoblastic neoplasia, with sections on pain management and palliation, and future trends to complete the book. At the end of each section there is a box of key points which give a brief overview of the topic discussed. I gave this book to several of our new residents to read. These doctors who had no experience with gynaecologic oncology, reported that they found the book easy to read



and helpful, as they were able to relate what was discussed in the book to what was happening in theatre and on the ward.

Diagrams were simple and easy to follow and pictures were clear, both were placed in logical areas of the book. At the end of the book is a section on useful resources which includes several Australian support services (Cancer Council Australia and National Centre for Gynaecological Cancer) among other international resources.

I found this book very easy to read and a good basic overview as the authors intended. Several others also commented on how well set out this book was. Its compact size made it easy to handle and carry, the main issue being finding it again when you put it down. This book will be a good resource for those who are new to working with women who have gynaecologic cancers.

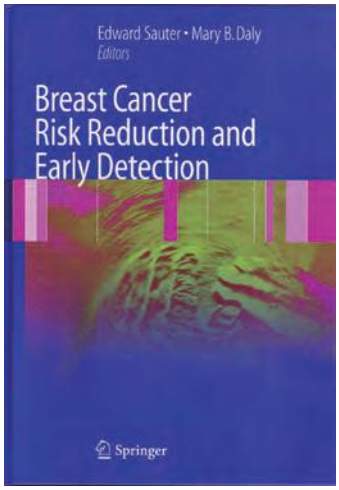
Jennifer Mayne, Department of Gynaecology, Royal Hobart Hospital, Tasmania.

Breast Cancer Risk Reduction and Early Detection

Edward Sauter, Mary B Daly
Springer (2010)
ISBN: 978-0-387-87582-8
RRP: EUR149.75

At first glance this book appeared to be a compilation of graphs and tables based on various scientific findings, however upon further reading, I discovered a very valuable resource which covered a variety of topics related to breast cancer risk factors and methods of early detection.

Editors, Sauter and Daly acknowledge that many texts have been published with a focus on breast disease and treatment. It is therefore refreshing to look at a collection of studies which address other areas in the hope of stimulating further research into "reducing the burden of this disease".



The book is divided into two sections. The first is titled 'Prevention' and covers four areas including risk factors, lifestyle factors, breast cancer chemoprevention,

and surgical management of inherited susceptibility to breast cancer.

Obvious risk factors associated with gender, age and family history are discussed, but more interestingly, factors associated with lifestyle and the use of exogenous hormones were also explored. This chapter highlighted the fact that while some women would be diagnosed with breast cancer regardless of supposed risks, there was evidence that modification of certain lifestyle factors associated with diet and exercise could prevent a substantial proportion of postmenopausal breast cancers.

The chapter on chemoprevention looks at the protective effect of tamoxifen and raloxifine in high risk women with a pre-existing history of atypical ductal hyperplasia or lobular carcinoma in situ. The studies so far have shown significant reductions in the risk of invasive breast cancer and this chapter stimulates the urge for further studies into this area of breast cancer prevention. Similarly, the chapter on surgical management looks closely at prophylactic surgery and associated risk reduction. These include both mastectomy and Salphingo-oopherectomy.

I found part two of the book entitled 'Early Detection', a more 'intense' read. Ideal for those well versed in the language of genetics and molecular targeting. Having said that, it gave a valuable insight to the future of early detection methods and while I found some of the diagrams, graphs and tables a challenge to decipher, the overall discussion and findings whetted my appetite for future developments in this area of early detection. The book highlights various methods of early breast cancer detection, from clinical examination and mammography to PET scanning, MRI, genetic and molecular imaging, and intraductal approaches including both nipple aspirate and ductoscopy and ductal lavage in the diagnosis of breast cancer.

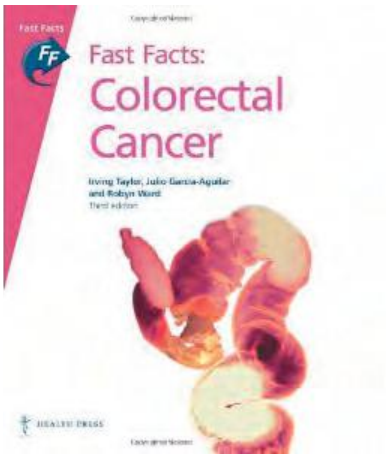
All chapters are widely referenced and the layout of the book is such that it would be an ideal resource for any health professional interested in current research associated with breast cancer risks and detection. I would easily recommend this book for medical and nursing staff alike.

Kathryn Wallace, Breast Care Nurse Specialist, Northern Health, Victoria.

Fast Facts: Colorectal Cancer

Irving Taylor, Julio Garcia-Aguilar and Robyn Ward
Health Press Third Edition (2010)
ISBN: 978-1-905832-02-6
RRP: EUR15.00

Fast Facts: Colorectal Cancer does exactly what it says on the tin. This book is concise, easy to read and easy to dip in and out of in the sections you want to know about. It is easy to comprehend and follows a logical progression if you want to read it from cover to cover. As it is only 94 pages long, it is feasible to read the book from cover to cover in one sitting, and in fact, I did this. It packs a great deal of relevant information into not a lot of pages.



This book would be suited to people new to the area of colorectal cancer including nurses, students, allied health workers and clinicians. It provides a thorough and succinct overview of colorectal cancer. The latest facts and figures are also presented from epidemiology to treatments to future directions. At the end of each chapter references are provided, if you want more in-depth information on a particular subject it is easy to find further resources. A table of 'key points' is also presented at the end of each chapter, providing an easy way to refresh your memory, or a simple way to digest the information presented in the chapter.

Each chapter is colour coded on each page, making it very easy to find the section you are interested in. Chapters are set out as follows:

- Epidemiology and pathophysiology
- Clinical presentation
- Diagnosis and staging
- Screening and surveillance
- Treatment of primary disease
- Large bowel obstruction
- Advanced and recurrent disease
- Multidisciplinary management
- Future trends

The illustrations, clinical photographs, graphs and tables provide extra interest and another dimension in understanding the information presented. The only drawback is that most statistical information is presented from the American or UK perspective, even though the three authors are from US, UK and Australia respectively. However, Australia is represented in the 'useful addresses' section. A glossary is also provided.

Based on the strength of this fantastic small book, I would purchase other 'Fast Facts' titles in areas of interest. Even though the book is small, all the information is pertinent, up-to-date and easily understood. A great read that I will refer to in the future and use when I am precepting students or new staff members.

Renae Grundy, Cancer Care Coordinator, Royal Hobart Hospital, Tasmania.

CALENDAR OF MEETINGS

AUSTRALIA AND NEW ZEALAND

Date	Name of Meeting	Place	Secretariat
2010			
November			
10-12	Clinical Oncological Society of Australia Annual Scientific Meeting 2010	Melbourne, VIC	Clinical Oncological Society of Australia Level 1, 120 Chalmers Street Surry Hills NSW 2010 Tel : +61 2 8063 4100 Email: cosa@cancer.org.au Website: www.cosa.org.au
2011			
February			
10-12	23rd Lorne Cancer Conference	Lorne, Victoria	ASN Events PO Box 200, Balnarring VIC 3926 Phone: +61 3 9329 6600 Website: www.lornecancer.org
May			
3-6	Royal Australasian College of Surgeons Annual Scientific Congress 2011	Adelaide, SA	Royal Australasian College of Surgeons College of Surgeons' Gardens 250 – 290 Spring Street East Melbourne, Victoria, 3002 Australia Phone: +61 3 9249 1273 Email: conferences.events@surgeons.org Website: www.surgeons.org
November			
15-17	Clinical Oncological Society of Australia Annual Scientific Meeting 2011	Perth, WA	Clinical Oncological Society of Australia Level 1, 120 Chalmers Street Surry Hills NSW 2010 Tel : +61 2 8063 4100 Email: cosa@cancer.org.au Website: www.cosa.org.au

INTERNATIONAL

Date	Name of Meeting	Place	Secretariat
2010			
November			
6-10	National Cancer Research Institute Cancer Conference	Liverpool, United Kingdom	NCRI 61 Lincoln's Inn Fields PO Box 49709 United Kingdom London WC2A 3WZ Email: ncriconference@ncri.org.uk Phone: +44 207 438 5453 Website: http://www.ncri.org.uk
8-13	Chemotherapy Foundation Symposium Innovative Cancer Therapy for Tomorrow	New York City, NY, United States of America	Mount Sinai School of Medicine and Chemotherapy Foundation Box 11931 Gustave Levy Place New York City, NY, 10029 United States Phone: +1 212 866 2813 Email: jaclyn.silverman@mssm.edu Website: http://www.chemotherapy foundationsymposium.org
10-13	Neoplastic Hematopathology Update: New Insights into Old Questions	Hollywood, Florida, United States of America	University of Nebraska Medical Center, Center for Continuing Education, 986800 Ne Med Ctr Omaha NE 68198 United States of America Email: bram@unmc.edu Phone: +1 402 559 9250 Website: http://iaphomepage.org/2010_Hematopath_SavetheDate_westinpics.pdf
December			
8-12	33rd Annual San Antonio Breast Cancer Symposium	San Antonio, Texas, United States of America	Cancer Therapy & Research Center at UT Health Science Center San Antonio 7979 Wurzbach Road, MC 8224 San Antonio, TX 78229 USA Email: Rmarkow@ctrc.net Website:http://www.ctrc.net/ctrc_2_2.cfm?db_content=sabcs
2011			
January			
20-22	2011 Gastrointestinal Cancers Symposium	Alexandria, Virginia, United States of America	American Society of Clinical Oncology Phone: +1 571 483 1504 E: rachel.pensack-rinehart@asco.org Website: www.asco.org
February			
1-4	22nd International Congress On Anti-Cancer Treatment	Paris, France	International Medical Events 124, Boulevard Exelmans Paris France75016 Phone: + 33 1 47 43 50 84 Email: valerie.caillon@im-events.com Website: www.icact.com
3-5	Breast Cancer Coordinated Care – BC3 Conference	Washington DC, United States of America	International Conference Management (Georgetown University Hospital) 1018 Harding Street, Suite 207 Lafayette, LA 70503 United States of America Phone: 337-235-6606 Email: dvitrella@bc3conference.com Website: www.bc3conference.com

CALENDAR OF MEETINGS

Date	Name of Meeting	Place	Secretariat
March			
15-19	12th International Conference Primary Therapy of Early Breast Cancer	St Gallen, Switzerland	St. Gallen Oncology Conferences Phone: +41 71 243 0032 Email: info@oncoconferences.ch Website: www.oncoconferences.ch
24-26	EORTC EANO conference 2011: Trends in Central Nervous System Malignancies	Brussels, Belgium	European Cancer Organisation Phone: +32 2 775 0201 Email: info@ecco-org.eu Website: http://www.ecco-org.eu
April			
1-3	Women's Health 2011: The 19th Annual Congress	Washington DC, United States of America	VCU Institute for Women's Health Email:womenshealth2011@liebertpub.com Website:www.bioconferences.com/conferences WomensHealth/index.aspx
19-23	9th International Gastric Cancer Congress	Seoul, South Korea	Local Organizing Committee of 9 IGCC Phone: +82 2 837 0815 Email: office@9igcc.com Website: http://www.9igcc.com
May			
3-5	1st International Conference on UV and Skin Cancer Prevention	Copenhagen, Denmark	The Danish Cancer Society and TrygFonden; Cancer Council Victoria and Victorian Health Promotion Foundation Phone: +45 35257500 Email: info@cph-skincancer.com Website: http://www.cph-skincancer.com/
August			
14-19	2011 Pan Pacific Lymphoma Conference	Kaloa Kauai, Hawii, United States of America	University of Nebraska Medical Center Phone: +1 402 559 9250 Email: bram@unmc.edu Website:http://www.unmc.edu/cce
September			
22-27	ECCO 16 - 36th ESMO Multidisciplinary Congress	Brussels, Belgium	European Cancer Organisation Ph: +32 2 775 0201 info@ecco-org.eu http://www.ecco-org.eu
October			
06-07	IV InterAmerican Oncology Conference: 'Current Status and Future of Anti-Cancer Targeted Therapies'	Buenos Aires, Argentina	InterAmerican Oncology Conferences Email: secretariat@oncology conferences.com.ar Website:www.oncologyconferences.com.ar

CANCER COUNCIL AUSTRALIA

Cancer Council Australia is the nation's peak cancer control organisation.

Its members are the leading state and territory Cancer Councils, working together to undertake and fund cancer research, prevent and control cancer and provide information and support for people affected by cancer.

MEMBERS

Cancer Council ACT
Cancer Council New South Wales
Cancer Council Northern Territory
Cancer Council Queensland
Cancer Council South Australia
Cancer Council Tasmania
Cancer Council Victoria
Cancer Council Western Australia

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CLINICAL ONCOLOGICAL SOCIETY OF AUSTRALIA INC

The Clinical Oncological Society of Australia (COSA) is a multidisciplinary society for health professionals working in cancer research or the treatment, rehabilitation or palliation of cancer patients.

It conducts an annual scientific meeting, seminars and educational activities related to current cancer issues. COSA is affiliated with Cancer Council Australia.

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Further information about COSA and membership applications are available from:
www.cosa.org.au or cosa@cancer.org.au

Membership fees for 2010

Ordinary Members: $160
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Psycho-Oncology
Radiation Oncology
Regional and Rural Oncology
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Urologic Oncology

Information for contributors

Cancer Forum provides an avenue for communication between all those involved in the fight against cancer and especially seeks to promote contact across disciplinary barriers.

To this end articles need to be comprehensible to as wide a section of the readership as possible. Authors should provide sufficient introductory material to place their articles in context for those outside their field of specialisation.

Format

Cancer Forum welcomes original articles about medical, scientific, political, social, educational and administrative aspects of cancer control. All manuscripts should be submitted by email to info@cancerforum.org.au as MS Word documents.

Length: 2000-2500 words.

Font: Arial - 20pt for title, 12pt for headings and 10pt for text.

Following the title, include your full name, organisation and email address.

Include an introductory heading and sub-headings that describe the content.

Number pages in the footer.

Abstract

All manuscripts must include an abstract of approximately 200 words, providing a summary of the key findings or statements.

Illustrations

Photographs and line drawings can be submitted via email or on disk, preferably in tiff or jpeg format, or as transparencies or high quality prints.

If images are not owned by the author, written permission to reproduce the images should be provided with the submission.

Referencing

Reference numbers within the text should be superscripted and placed after punctuation.

The list of references at the end of the paper should be numbered consecutively in the order in which they are first mentioned and be consistent with the National Library of Medicine's International Committee of Medical Journal Editors' *Uniform Requirements for Manuscripts Submitted to Biomedical Journals.*

> eg. Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002 Jul 25;347(4):284-7.

A full guide is available at www.nlm.nih.gov/bsd/uniform_requirements.html

The Editorial Board will make the final decision on publication of articles and may request clarifications or additional information.

Manuscripts should be emailed to:

Executive Editor
Cancer Forum
GPO Box 4708
Sydney NSW 2001
info@cancerforum.org.au

GPO Box 4708, Sydney NSW 2001
Telephone: 02 8063 4100
Facsimile: 02 8063 4101
Website: www.cancer.org.au