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Contents

Skin Cancer

Australia's most common malignancy: skin cancer in focus

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The problem of skin cancer in Australia began over 200 years ago when the first fair-skinned Europeans settled on the shores of Sydney Harbour in 1788. Australians are more than five times as likely to develop a skin cancer as any other form of cancer, and two of every three will have developed some form of skin cancer by the time they reach 70 years of age.[1]

Non-melanoma skin cancer

Non-melanoma skin cancer (NMSC) is so common in Australia that reporting of this form of malignancy to state and national cancer registries is not a legal requirement, whereas reporting all other forms of cancer is mandatory. For NMSC, the amount of data would simply overwhelm existing systems, and the vast resources that would be required for its collection and processing would be extremely difficult to justify. As a result, accurate incidence data state by state and nationally are not available. Nevertheless, estimates that are likely to be reliable indicate that approximately 430,000 new cases of NMSC were diagnosed in 2008, 296,000 of them basal cell carcinomas (BCCs) and 138,000 of them squamous cell carcinomas (SCCs).[2] The enormous magnitude of the problem of NMSC in Australia is reflected by the huge sums in the national health expenditure budget that are spent on its diagnosis and treatment. Treatment of NMSC in Australia currently costs upwards of $340 million per year.[3]

For the majority of the Australian population the most common forms of NMSC, ie. SCC and BCC, are a cosmetic and economic burden and cause considerable inconvenience, but are not a threat to life. For some however, the risk is much greater. Transplant recipients for example, have a substantially increased likelihood of developing SCC, with a risk that is much higher still than that of the predominantly Caucasian general population in Australia. Comprehensive and highly accurate information is available from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), which has collected cancer incidence data for all renal transplant recipients and dialysis patients since 1963.[4] The data collected by the ANZDATA registry indicates that the risk of a renal transplant recipient developing an SCC is approximately 100 times the risk for the general population. Not only is the risk of developing SCC drastically higher in immunosuppressed transplant recipients, but the chance of metastasis to regional lymph nodes and systemic sites is much greater, and the risk of mortality much higher. Patients who are immunosuppressed for other reasons, eg. because they are receiving immunosuppressive drugs, or because they have an immunodeficiency state that is not drug-induced, (notably resulting from HIV infection but also in association with chronic haematological malignancies),[5] are likewise at high risk of developing SCC and dying as a result.

While the risk of metastasis and death from cutaneous SCC is much higher in immunosuppressed individuals, a small proportion of immune competent individuals also develop potentially life-threatening metastatic disease from SCC, BCC and other forms of NMSC, notably Merkel cell carcinoma (MCC). Overall, there were 448 reported deaths from NMSC in Australia in 2007.[2]

In this edition of *Cancer Forum*, several aspects of the investigation and management of patients with metastatic NMSC are addressed.

Emmett and Ho discuss the appropriateness of present-day imaging techniques for patients with NMSC and melanoma.[6] The more readily available access to sophisticated imaging technologies including CT scans, PET scans and MRI scans in recent years, has had an enormous impact on the staging and management of patients with all forms of skin cancer. However, it has also resulted in expensive tests sometimes being ordered inappropriately, subjecting patients not only to possible financial hardship, but also to unnecessary and potentially harmful radiation. It is important for all medical personnel who deal with patients with skin cancer to be aware of the current indications and contraindications for each of the modern imaging modalities. Emmett and Ho explore these matters in detail.

Guminski discusses the management of locally advanced and metastatic BCC that is not able to be dealt with by surgical excision or radiotherapy.[7] Although BCC is very

common, the great majority of patients are able to be cured using simple measures including surgery, radiotherapy, cryotherapy, topical imiquimod or photodynamic therapy. However, BCCs are occasionally more aggressive and recur locally, or metastasise to regional lymph nodes or distant sites, rendering successful treatment with surgery or radiotherapy difficult or impossible. Until recently no effective systemic treatments were available for metastatic BCC. But understanding of the "hedgehog" signalling pathway, which is active in both sporadic BCC and in the basal cell naevus (Gorlin's) syndrome, has led to the development of hedgehog signalling pathway inhibitors. These have provided a new treatment option both for patients with locally advanced or extensive BCCs, and for those with metastatic disease. Guminski discusses the role of these new agents in the treatment of patients with advanced BCC, and explains why the three hedgehog genes that have been identified in mammals were given the curious names desert hedgehog, Indian hedgehog and sonic hedgehog!

The role of radiation therapy in the management of skin cancers is discussed by Stevens.[8] Radiotherapy is widely used in the treatment of BCCs and SCCs, and in many patients is a better treatment option than surgical excision, as it provides a more satisfactory cosmetic outcome and avoids the risks inevitably associated with surgery. Stevens also discusses the role of radiotherapy for MCC, and its value as adjuvant and palliative treatment for patients with melanoma. He points out that radiotherapy plays an important role in the management of all the common skin cancers, but emphasises that the role of radiotherapy varies between the different cancers. He concludes by stressing the importance of individualising treatment and managing patients in a multidisciplinary setting whenever possible.

Gee and Hruby discuss present-day management of MCC, an aggressive but relatively uncommon form of NMSC that is frequently misdiagnosed and often managed inappropriately. It is only 40 years since this tumour type was first described,[9] and even today there is uncertainty about the origin and function of the cells from which they originate, first recognised by Friedrich Sigmund Merkel. He called them 'Tastzellen' or 'touch cells', and subsequent studies have confirmed that they appear to be involved in the process of touch, by which fine spatial details are appreciated. Although MCC is sometimes referred to as primary cutaneous neuroendocrine carcinoma, recent studies suggest an epidermal rather than a neural crest origin.

MCC is predominantly a disease of older people, with a median age at diagnosis of around 65 years. Exposure to solar ultraviolet radiation appears to be the major risk factor for developing MCC, but it has recently been shown that a polyoma virus can be identified in MCC in the majority of cases (although it is not clear whether it is causative). In their review, Gee and Hruby consider the epidemiology, diagnosis, staging and management of MCC and provide guidelines for patient management. Prompt referral to an experienced specialist centre for definitive management is recommended, because treatment delays are associated with a significantly worse outcome.

Melanoma

The other form of skin cancer that is of enormous significance in Australia is melanoma. Although the number of incident cases in the nation is much lower than the number of cases of NMSC, the proportion of patients who die from the disease is much higher. The most recent figures available from the Australian Institute of Health and Welfare indicate that 10,342 patients developed melanoma in 2007 (making it the fourth most common cancer), and 1279 patients died of the disease.[10]

Rational management of both primary and metastatic melanoma is entirely dependent on the accuracy of histopathological assessment. This is becoming even more important in the era of personalised therapy that we have now entered. In this edition of *Cancer Forum*, Scolyer and colleagues provide a comprehensive review of contemporary melanoma pathology, and explain how recent insights into the molecular pathogenesis of melanoma have allowed traditional histological assessment to be supplemented and enhanced by molecular pathology testing, providing more accurate classification and better estimates of prognosis, and allowing eligible patients to be selected for specifically targeted therapies.[11] Molecular testing has already found its way into everyday clinical use, for example by identifying patients who have a mutation in the BRAF oncogene. This is important, because if their melanoma is BRAF positive, they are likely to respond to therapy with a BRAF inhibitor. Scolyer and colleagues provide guidelines for molecular testing in patients with melanoma, and give practical advice on when and how to arrange testing, and which specimens to test, based on knowledge of the advantages and disadvantages of the various testing methodologies. They also explain that as well as the long-established melanoma prognostic indicators such as Breslow thickness and the presence or absence of ulceration, recent studies have demonstrated that other histopathological features also have prognostic significance. These include tumour mitotic rate, the extent of ulceration, tumour-infiltrating lymphocyte grade and the presence, extent and distribution of metastatic disease in sentinel lymph nodes.

Melanoma has a particularly adverse effect on years of productive life lost, because it is one of the most common cancers in young people.[12] Until recently, the treatment of systemic melanoma metastases with drugs was almost invariably unsuccessful. The most commonly used systemic agent was dacarbazine, but complete responses were rare and the partial response rate was less than 20%. The situation has now changed dramatically, and recent clinical trials have shown that signal pathway inhibitors (eg. the BRAF inhibitors vemurafenib and dabrafenib) and immunological modulators (such as the anti-CTLA-4, anti-PD-1 and anti-PD-L1 antibodies) can achieve much more impressive complete and partial response rates. Early results of clinical trials of these new agents are reported and discussed by Menzies,[13] and future prospects for effective combination therapies are outlined. Menzies summarises recent advances in the understanding of the molecular biology of melanoma that have led to the development of these new agents. He points out that although the signal pathway inhibitors

and new immunotherapeutic agents produce results that are vastly superior to previous chemotherapy regimens, they all have potentially serious side-effects, and durable long-term responses are rarely achieved. He explains that there are ongoing clinical trials of new agents and various combinations of existing agents, and also trials of some of these agents as adjuvant therapy in melanoma patients identified as being at high risk of recurrence. The results of these studies are keenly awaited.

Finally, the particular problem of management of locoregional melanoma recurrence, i.e. local, in transit and nodal metastasis, is considered by Geere and Barbour.[14] They explain that local and in transit recurrences are best treated by surgical excision whenever possible, but for patients with extensive disease other options exist. These range from topical therapy (such as the contact sensitiser diphencyprone),[15] to intratumoural injection therapy (such as with Rose Bengal).[16]

RT is sometimes useful for advanced localised disease, while for unresectable local and in transit recurrences confined to a limb, regional chemotherapy with vascular isolation (isolated limb perfusion or isolated limb infusion) is the current standard of care.[17]

Regional lymph node recurrence is best managed by surgical lymphadenectomy. Adjuvant post-operative radiotherapy has been shown in a recent Australian multicentre trial to significantly reduce the risk of regional recurrence in patients with surgically resected high risk stage III melanoma.[18]

Conclusion

The management of all forms of skin cancer is becoming increasingly complex and new therapeutic options are becoming available at an ever-increasing pace. As a result, patients with high risk, locally advanced or metastatic disease are best managed in specialist treatment centres, where treatment recommendations can be made on the basis of multidisciplinary team assessment. Such multidisciplinary teams now exist in most major population centres in Australia, and it is to be hoped that ready access to such facilities will improve the outcome for the large and ever-increasing number of Australians who are affected by skin cancer.

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IMAGING FOR MELANOMA AND NON-MELANOMA SKIN CANCERS

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Abstract

This review discusses the relevant imaging techniques for both melanoma and non-melanoma skin cancers, including basal cell carcinomas, cutaneous squamous cell carcinomas and Merkel cell carcinomas. The diagnostic value of sentinel lymph node mapping, CXR, CT, PET, PET/CT and MRI are discussed, and their role for each stage and type of cutaneous malignancies considered. There are currently no recommendations for the use of diagnostic CT or PET /CT for initial staging of low risk melanoma patients around the time of diagnosis. Both PET and PET/CT have been shown to change the management of many patients with advanced melanoma, and it is recommended that FDG-PET be performed prior to resection of regional or distant metastatic deposits. MRI plays an important adjunctive role in the assessment of brain metastases in melanoma, and for assessment of perineural invasion in non melanoma skin cancers. Cumulative doses of radiation to patients for staging and surveillance imaging, and the life expectancy of the individual patient, should be factored into any decisions regarding what scans are appropriate for them.

Recommendations for appropriate imaging in patients with melanoma rely heavily on the patient's disease status. In patients with stage II melanoma, there is a documented role for sentinel lymph node mapping using lymphoscintigraphy,[1] but no role for further imaging procedures in the absence of symptoms. However, the case is different in patients with higher risk tumours and those with recurrent disease, who may benefit from a range of imaging procedures.

Imaging of patients with early stage cutaneous melanoma (stages I and II)

Lymphatic mapping and sentinel lymph node biopsy are recommended for disease staging in patients with high risk stage I/II disease.[1-3] Lymphoscintigraphy involves the injection of a small volume of radiolabelled colloid around the tumour site, and then imaging to determine which regional node field contains the sentinel node or nodes (a sentinel node being defined as any node receiving direct drainage from a tumour site).[4,5] Imaging is important, as often more than one regional node field is involved,[4] and for accurate staging all sentinel lymph nodes should be pathologically examined. Lymphoscintigraphy identifies 94.5% of sentinel nodes.[6] The use of SPECT (Tomographic nuclear imaging)/CT, in addition to standard dynamic lymphoscintigraphy, further improves diagnostic accuracy.[7-9] Two studies have undertaken direct comparisons between lymphoscintigraphy and PET imaging, as a staging procedure in early stage melanoma. These found that lymphoscintigraphy was vastly diagnostically superior to PET imaging, with a sensitivity of 14% for PET imaging in both studies and a sensitivity of 86-100% for lymphoscintigrapy.[10, 11]

In early stage melanoma, sensitivities of just 17% have been found in a number of meta-analyses and pooled study results assessing the diagnostic value of PET and PET/CT in early stage melanoma.[6,12] This is not surprising, as sentinel lymph node involvement with metastatic melanoma is most commonly microscopic.[13] The sensitivity of PET/CT is limited by the volume of disease present, with the sensitivity for metastatic and lymph node disease dropping off significantly with tumour deposits of < 78mm3 in size (4mm diameter). PET has a sensitivity of < 50% for lesions < 4mm in size (80mm3).[14] Hence, there are currently no recommendations for the use of PET/CT or diagnostic CT for initial staging of low risk melanoma patients around the time of diagnosis.[15]

Imaging of patients with metastatic melanoma (stages III and IV)

PET and PET/CT

Metastatic melanoma deposits characteristically have high metabolic activity, showing up distinctly in 18F-FDG-PET/CT imaging. While FDG-PET/CT has not been shown to be diagnostically useful in early stage (stage I and II) melanoma where lymph node disease, if present, is usually of low volume and below the resolution limits for PET or CT technology, it has an important diagnostic role in patients with stage III and IV melanoma. This change in sensitivity, based on the stage of disease, was demonstrated elegantly by Wagner et al, who found a PET sensitivity of 0% in stage I disease, 24% in stage II disease, 81% in stage III disease and 100% in stage IV disease in patients with cutaneous melanoma.[16] Multi study reviews of PET have found similarly high diagnostic accuracy values for identifying metastatic melanoma in stage III and IV disease. A pooled analysis of 753 patients with stage III and IV melanoma showed that F18- FDG-PET had a pooled sensitivity of 88%, a specificity of 82% and an accuracy of 86%.[6]

The diagnostic accuracy of PET/CT is significantly higher, with fewer false positive and false negatives than FDG-PET alone.[17] It is now routine to undertake combined PET/CT imaging that is simultaneously or concurrently acquired on the same camera. The CT component can be either multislice contrast-enhanced, or a low radiation dose CT. A study of 50 patients with metastatic melanoma compared the diagnostic accuracy of contrast-enhanced diagnostic CT, PET and PET/CT (both contrast-enhanced and non-contrast low dose). The authors reported a sensitivity and specificity for diagnostic contrast-enhanced CT of 85% and 63%, for PET of 90% and 88%, for PET/non diagnostic CT of 97% and 93% and for PET/diagnostic-contrast-enhanced CT of 100% and 93% respectively.[18] It is interesting to note that while the addition of CT information to PET significantly improved sensitivity and specificity, there was little additional improvement in sensitivity and no improvement in specificity when comparing low-dose CT and contrast-enhanced CT.

Both PET and PET/CT have been shown to change the management of many patients with advanced melanoma, and it is recommended that FDG-PET be performed prior to resection of regional or distant metastatic deposits.[6] Etchebehere et al assessed the ability of PET/CT to change management in 78 patients with locoregional or distant recurrence of melanoma.[19] PET/CT changed management in 27% of the group studied.

There are a number of limitations to FDG-PET imaging that should be taken into account in evaluating scan results. High background activity in normal brain tissue reduces the sensitivity of PET for the detection of melanoma brain metastases. This mandates that either diagnostic CT of the brain or MRI be undertaken in patients at high risk of melanoma brain metastases. For technical reasons, the intensity of FDG uptake in small lung metastases may often be reduced, particularly at the lung bases. The combined technique PET/CT is particularly useful in the detection of small lung metastases, often missed on PET alone.[12] As FDG-PET measures glucose uptake, a low false positive rate due to scan findings related to inflammation, sarcoidosis and unrelated tumours, is inevitable.

Diagnostic CT

Although it is a widely used technique for staging and surveillance, there have been relatively few studies assessing the diagnostic value of contrast-enhanced CT in patients with melanoma.[6] The technique suffers the same limitations as FDG–PET in early stage melanoma as it requires anatomical distortion for detection. A meta-analysis of diagnostic imaging modalities in later stage melanoma found a significantly higher diagnostic accuracy for PET/CT in disease surveillance (86% sensitivity, 91% specificity) than for CT alone (sensitivity 63%, specificity 71%).[20] In fact, no study has found the diagnostic accuracy of contrast-enhanced CT to be higher than PET or PET/CT for cutaneous malignancies.

Magnetic Resonance Imaging

MRI plays an important adjunctive imaging role in the management of patients with cutaneous melanoma, particularly those with suspected or documented brain metastases. MRI is significantly more sensitive than CT for the detection of metastatic disease in the brain,[21,22] and also provides more detailed information about possible involvement of the spinal cord and leptomeninges. Contrast enhanced CT scanning is widely used because of its ready accessibility and relatively low cost. However, brain MRI for patients with primary cancers that frequently

Figure 1: *Contrasted enhanced axial MRI image demonstrates enhancement and thickening of the left trigeminal nerve (thick arrow) in the prepontine cistern extending into the left cavernous sinus. Right trigeminal nerve is of normal appearance (thin arrow).*

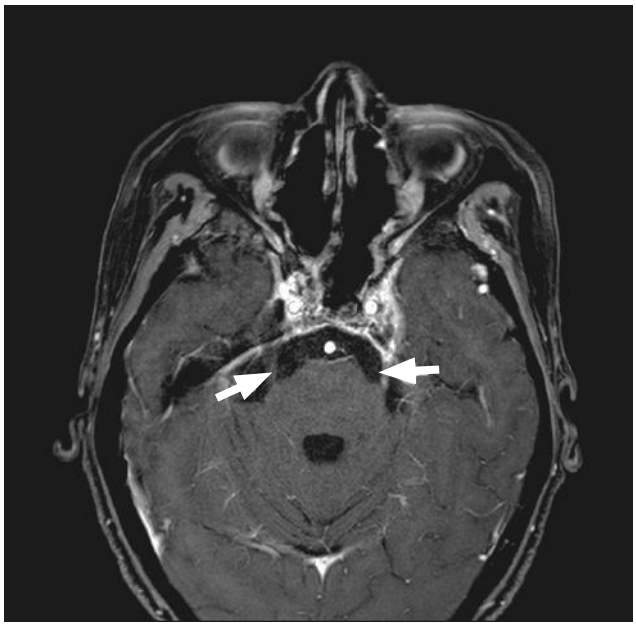
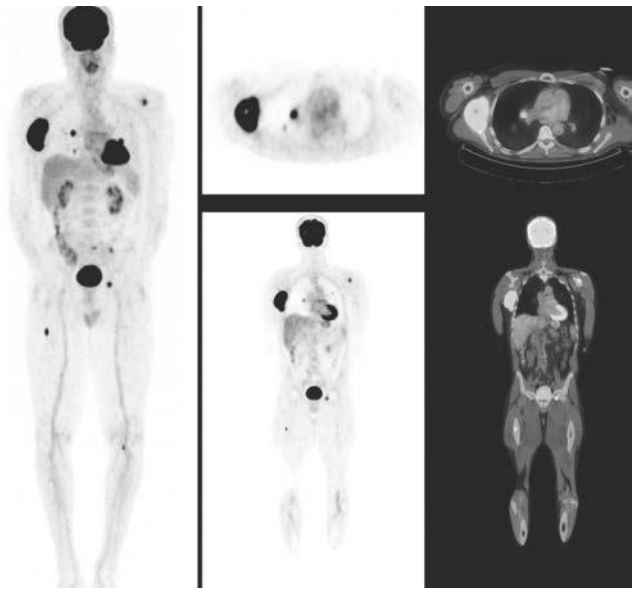


Figure 2: *PET/CT of a patient presenting with a right axillary mass. The PET images show the intense FDG uptake that is characteristic for metastatic melanoma. The organs involved, including lymph node, lung, bone and subcutaneous nodularity, show a classic pattern of metastatic dissemination commonly seen in patients with metastatic melanoma.*



metastasise to the brain (including melanoma) is probably cost effective. Numerous studies have shown that contrast-enhanced MRI detects two to three times as many lesions as contrast-enhanced CT, especially lesions less than 5mm in diameter. In addition, approximately 20% of patients with solitary metastatic lesions in the brain on CT show multiple lesions on MRI.[21-25]

Plain chest X-ray

Routine surveillance of patients at higher risk of melanoma recurrence with plain chest x-ray (CXR) has been recommended in treatment guidelines until recently. However, a review of 1235 patients with melanomas >1mm in Breslow thickness, followed for a median of 74 months, found that the sensitivity of surveillance CXR was 7.7% and the specificity 96.5%. Of those diagnosed with metastatic disease on CXR (0.9%), only 0.2% had isolated pulmonary metastases amenable to resection. Hence, CXR is no longer recommended for standard surveillance in melanoma patients.[26,27]

Imaging of non-melanoma skin cancers

Merkel cell carcinoma

Merkel cell carcinoma is a rare, aggressive skin malignancy with a high recurrence rate in regional node fields. Unlike in melanoma, the role of lymphoscintigraphy and sentinel lymph node biopsy is controversial in the management of Merkel cell carcinoma. Lymphoscintigraphy sensitivity in Merkel cell carcinoma varies in the literature from just 27% to 32%.[28, 29] However, a positive sentinel node has a high predictive value for relapse in the regional node field, and is an indication for adjuvant radiotherapy treatment.[28,30] Unfortunately, a negative sentinel node biopsy in Merkel cell cancer does not preclude early recurrence in the same lymph node field. The use of F18-FDG-PET in the staging of Merkel cell cancer is also yet to be established, with no large prospective studies to date. A retrospective study evaluating the use of diagnostic CT, PET/CT and MRI in the initial lymph node staging of 99 patients with Merkel cell carcinoma found a sensitivity of 85% and specificity of 95% with PET, 47% and 97% for CT, and 0% and 86% for MRI (histopathology of lymph nodes was used for determining sensitivity and specificity).[31] A further small study of 18 patients found that PET had a significant management impact in patients with Merkel cell cancer, altering staging in 33% and changing management in 43%.[32] While Merkel cell cancer is a form of neuroendocrine tumour, it tends to have a high mitotic rate, but imaging with radiolabelled Somatostatin analogues has not been shown to be more sensitive than 18F FDG-PET imaging.[33]

Basal and squamous cell carcinoma

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) constitute approximately 95% of non-melanoma skin cancers.[34,35] The majority of these cancers do not require diagnostic evaluation. However, high risk patients, particularly with recurrent or invasive tumours, tumours at risk for regional or distant metastasis or accompanied by clinical signs of perineural involvement, warrant imaging to assess morphology of the primary tumour site, as well as to identify distant metastatic disease.[36]

Given its superior soft tissue resolution, MRI is considered to be the imaging modality of choice for evaluation of the primary tumour site, with excellent depiction of the extent of locoregional disease. In certain locations it is particularly important in presurgical planning.[37] Given the tendency of some non-melanoma skin cancers to spread by perineural invasion, MRI is the modality of choice.[36,38] Nemzek and colleagues reported a 95% sensitivity for MRI detection of perineural invasion.[38] MRI is also superior in identifying intracranial metastases and intracranial extension, including meningeal involvement, as well as subtle marrow infiltration. Diffusion-weighted MRI has become a promising biomarker for assessing tumour response to therapy.[39]

For evaluation of nodal involvement and distant metastatic disease, molecular imaging with fusion PET-CT and diagnostic CT are the imaging modalities of choice.[34] The sensitivity and specificity of PET/CT in staging and follow up for aggressive non-melanoma skin cancers remain to be elucidated. Over the last decade, fusion PET/CT has become an established, powerful imaging modality in the field of oncology, providing functional and anatomical correlation. However, in non-melanoma skin cancers, few data are available regarding staging and follow-up evaluation. Boswell and colleagues reported cases with metastatic BCC to the lung that was detected on PET/CT.[40] In tumour of unknown origin, combined PET/CT has gained wide acceptance.[41] A recent meta-analysis with encouraging data showed that, overall, FDG-PET/CT is able to detect 37% of primary tumours in patients with cancers from an unknown primary, with both sensitivity and specificity of 84%.[42] Gourin and colleagues reported detection of distant metastatic disease in 15 of 64 patients, 13 of which were unsuspected prior to PET/CT.[43] In patients with head and neck cancers receiving radiotherapy, a negative PET/CT result within six months after radiotherapy correlated with statistically significantly improved two-year overall survival rates in a study by Kao and colleagues, who followed 80 patients over a median of 21 months.[44]

Given its ready availability and rapid acquisition times, diagnostic CT has been used widely for routine surveillance. One advantage of CT over MRI is the increased sensitivity in the detection of subtle cortical bony erosion,[34] but for small lesions or pathological changes in normal-sized tissues can be missed by CT.[41]

Radiation doses

Cumulative doses of radiation to patients for staging and surveillance imaging must be factored into any decisions regarding which scans are appropriate. Given that the diagnostic yield of either CT or PET/CT is low in melanoma patients with AJCC stage I or II disease, it is not recommended that diagnostic CT, PET/CT or CXR be used in the absence of symptoms requiring investigation. By contrast, lymphoscintigraphy has a high diagnostic accuracy and delivers a very low radiation dose to this group of patients with a better prognostic outcome. In patients with AJCC stage III or IV melanoma, life expectancy is considerably reduced, and the diagnostic value of regular imaging must be weighed up carefully against the relatively low lifetime risk of secondary cancers induced by frequent imaging procedures.

PET imaging now almost always incorporates a low dose CT for the purposes of attenuation correction and anatomical detailing. This low dose CT is weight dependent

in terms of radiation delivered and gives an average dose of 4mSv per patient in our institution (range 2.9-9.6 mSv). The 18F- FDG delivers 5-7 mSv per patient, giving an average radiation dose of 9 mSv per patient for a PET/low dose CT scan. A comparative study of radiation doses across institutions found similar results for low dose PET/CT images. They also found that, on average, a diagnostic CT scan added an extra 14-19 mSv to the procedure.[45] Putting this in perspective, the expected background radiation dose for a person living in Australia is 2mSv/year.

Conclusion

Rapidly evolving technology in imaging sometimes makes choosing the most appropriate imaging procedure for an individual patient difficult. MRI and lymphoscintigraphy have proven valuable in local disease characterisation and regional lymph node involvement, while PET/CT is proving the most diagnostically accurate procedure for assessment of distant metastatic disease. The clinician must take into account both the stage and type of cutaneous malignancy in deciding which imaging technique to employ, or indeed whether imaging is required at all.

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NEW SYSTEMIC TREATMENT OPTIONS FOR ADVANCED BASAL CELL CARCINOMA

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Abstract

Basal cell carcinoma is a very common skin malignancy that is usually able to be cured by simple local treatment (surgical excision, radiotherapy or cryotherapy). However, patients sometimes present with or develop locally advanced or metastatic basal cell carcinoma, requiring other therapeutic options to be considered. Aberrantly active hedgehog pathway signalling underlies both sporadic basal cell carcinoma and the basal cell naevus syndrome. Recently developed small molecule inhibitors of SMO, a transmembrane protein downstream of hedgehog and PTCH1 (which is mutated in basal cell naevus syndrome) have demonstrated remarkable clinical activity in locally advanced and metastatic basal cell carcinoma. Common side-effects of altered taste, hair loss and muscle cramps appear related to inhibition of physiological hedgehog pathway activity and necessitate discontinuation of systemic treatment in some patients. Inhibitors of hedgehog pathway signalling provide a new treatment option for patients with locally advanced or multiple basal cell carcinomas who otherwise require extensive or repeated surgery, and for patients with metastatic basal cell carcinoma for whom no active systemic treatments have previously been available.

Basal cell carcinoma (BCC) is probably the most commonly occurring malignancy in developed nations, however its true incidence can only be inferred from community surveys as it is not recorded by most cancer registries.[1] The predominant cause of BCC is ultraviolet radiation from sun exposure, although the pattern rather than the total cumulative amount of exposure appears to determine risk. Immune suppression increases the risk of developing BCC and associations have also been seen with exposure to arsenic and ionising radiation. The rare DNA repair deficiency disorder, xeroderma pigmentosum, is characterised by a high incidence of squamous cell carcinoma, however BCC is also increased in incidence, implicating a role for DNA repair integrity. The malignant cells resemble undifferentiated basal cells of the epidermis and its appendages. This stem cell-like nature is thought to be responsible for the multiple morphological types of BCC that are recognised (for review see Kasper et al 2012 and Rubin 2005).[2,3]

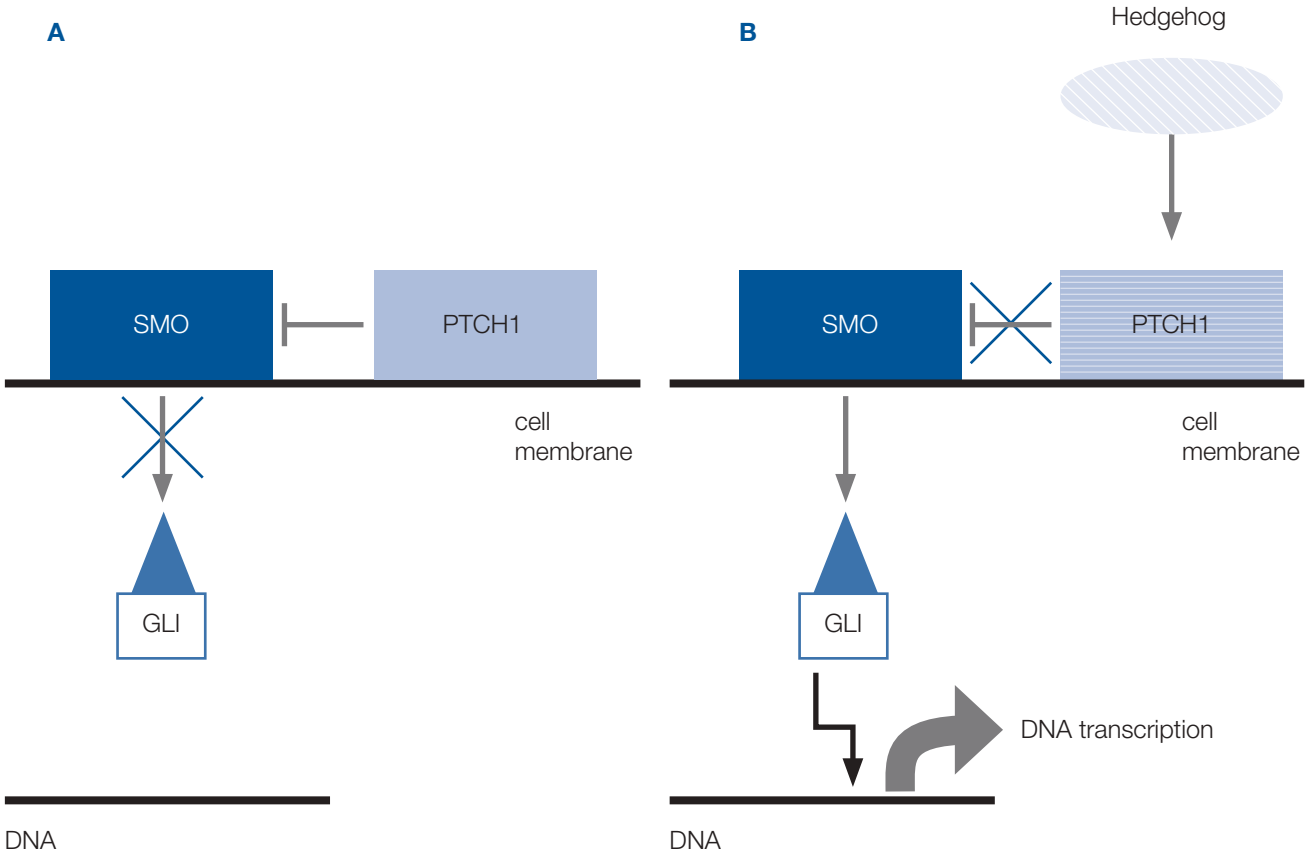
The overwhelming majority of BCCs are cured by local treatment such as surgical excision, radiotherapy or cryotherapy. A small proportion of BCCs are more aggressive and exhibit multiple recurrences to the extent that further local surgery or radiotherapy are not possible, or require substantial surgical procedures with sometimes complex reconstruction. Some patients have co-morbidities that preclude surgery with curative intent. Other patients with BCC present with neglected, locally-advanced lesions, again requiring quite substantial surgical procedures to effect cure. The metastatic potential of BCC is generally low, but occasional spread does occur, particularly to local lymph nodes and distantly to the lungs, liver and bone. Distant spread is currently incurable.

A number of pathological classifications for BCC have been proposed, reflecting an ongoing search for consensus in classification and prognosis. Certain histological variants are associated with a worse prognosis, including micronodular, morpheaform, infiltrative and basosquamous subtypes. Superficial and nodular subtypes generally have a less aggressive course.[4]

The molecular biology of BCC was substantially revealed by study of the rare entity of Gorlin's syndrome, also known as basal cell naevus syndrome.[5] This rare (incidence 1 in 19,000 to 1 in 57,000) autosomal dominant disease is characterised by jaw cysts, prominent jaw, wide set eyes, pitted depressions on the hands and feet and multiple, early onset BCCs, numbering many hundreds per patient over time. This can result in considerable scarring from repeated and extensive surgery. Affected individuals are also at increased risk of medulloblastoma, a tumour arising in the posterior cranial fossa in childhood and young adulthood, as well as rhabdomyosarcoma. Basal cell naevus syndrome patients inherit a germ-line mutation in one copy of the PTCH1 gene and BCCs occur when the remaining allele is inactivated.[6]

The molecular pathway is shown schematically in figure 1. Hedgehog family proteins are secreted glycoproteins. PTCH1 is a cytoplasmic protein that interacts with another cytoplasmic protein, SMO, a constitutive inhibitor of the transcription factor Gli, which controls expression of genes involved in cell survival, proliferation and apoptosis. Hedgehog signalling is a developmentally active transcriptional program regulating normal polarisation, among other functions. It is required to develop a normal midline zone of the foetal face and its absence leads to merging of the lateral facial structures resulting in a Cyclops appearance. Hedgehog signalling is also important for normal cell growth and differentiation. Abnormal hedgehog signalling is also prominent in medulloblastoma and rhabdomyosarcoma, and has been reported in tamoxifen-

Figure 1: *Panel A illustrates the quiescent state of the hedgehog pathway. PTCH1 inhibits SMO resulting in inhibition of Gli activation. In the presence of sonic hedgehog binding to PTCH1 inhibition of SMO is relieved and activation of Gli and DNA transcription occurs. In basal cell carcinoma, PTCH1 is inactivated by mutation and SMO is constitutively active.*



resistant breast cancer,[7] and oropharyngeal squamous cell carcinoma.[8] Abnormal activation of the hedgehog signalling pathway can arise due to overexpression of hedgehog proteins, or from mutation in the PTCH1 or SMO proteins, resulting in the loss of inhibition of Gli activation.[9,10]

Inhibitors of the hedgehog pathway also have an interesting historical background. Certain farms in Idaho in the 1950s reported the birth of lambs having a Cyclops appearance with a single midline eye and other cranial defects. The cause was found to be ingestion by pregnant ewes of a local plant the corn lily *(Veratrum californicum).* The mutagen isolated from the corn lily was termed cyclopamine and was subsequently found to be an inhibitor of hedgehog signaling.[11]

The hedgehog gene itself was first identified by Christiane Nusslin-Volhard and reported in 1980.[12] In studies in the fruit fly *Drosophila melanogasta,* embryos with a mutant phenotype displaying loss of hedgehog gene function were covered with denticles, resembling a hedgehog – hence the name. Three homologous hedgehog genes were subsequently shown to exist in mammals; desert hedgehog and Indian hedgehog were named after species of hedgehogs, while sonic hedgehog was named after the video game character Sonic the Hedgehog!

Recent clinical trials

Vismodegib (GDC-0449) is a low molecular weight inhibitor of the hedgehog signalling pathway, binding and inhibiting SMO, thus acting downstream of the mutated PTCH1 protein. Vismodegib has been one of the first agents tested in patients and a positive phase 1 study,[13] led to it being trialled in a group of patients with Gorlin's syndrome and also in a cohort of patients with locally advanced or metastatic BCC. These two important clinical trials have demonstrated the impressive activity of this SMO inhibitor; the results are summarised in table 1 and described below.

Sekulic et al (2012) conducted an international, multicentre phase II study with daily oral vismodegib 150mg given to 33 patients with metastatic BCC and 63 patients with locally advanced BCC.[14] The primary response was independently assessed. The trial design did not include a control arm on the basis that no effective systemic therapy existed, the historical observation that spontaneous remissions did not occur, and the relatively small potential patient population. A response rate of 30% was seen in the metastatic cases and 43% (with 21% having complete responses) in the locally advanced group. The median duration of response was 7.6 months in both cohorts. Serious adverse events were seen in 25% of patients, including seven deaths (one

Table 1: *A summary of the main results from two recently published trials of the SMO inhibitor Vismodegib in patients with metastatic and locally advanced BCC (Sekulic et al 2012) or Basal Cell Nevus Syndrome (Tang et al 2012). Note the negative biopsy rate includes patients assessed as either confirmed response, stable or progressive disease, and was performed at one site within the original lesion on 34 patients from the locally advanced cohort. Key: CR, complete response.*

Cohort	Number	Response rate	Reduction in new lesions	Median duration of response	Serious adverse event rate	Discontinuation rate due to patient choice, adverse event	Negative Biopsy rate
Metastatic BCC Sekulic et al 2012	33	30%	N/A	7.6 months	25%	6%, 12%	-
Locally Advanced BCC Sekulic et al 2012	63	43% overall 21% CR	N/A	7.6 months	25%	25%, 12%	54%
Basal Cell Nevus Syndrome Tang et al 2012	41 (26 on active drug, 15 on placebo)	Mean reduction of BCC 65% v 11%, no progressors seen on vismodegib	2 v 29	8 months	40%	N/A, 54%	54% at three months

each due to meningeal disease, myocardial infarction, ischaemic stroke, hypovolemic shock and three of unknown cause), however the relationship between these deaths on study and vismodegib is unknown. Across both cohorts, 12% of patients in total stopped the drug due to adverse events. Biopsy within the original area of tumour revealed absence of histological evidence of BCC in 56% of 34 locally advanced patients with clinical complete or partial responses, or apparent progressive disease.

In a concurrent study reported by Tang et al (2012), 41 patients with basal cell naevus syndrome were randomised in a double blind fashion to either vismodegib or placebo.[15] The primary endpoint was a reduction in the incidence of new surgically resectable BCCs (greater in diameter than 3mm on the nose or periorbital area, 5mm elsewhere on the face, or 9mm on the trunk or limbs) after three months of treatment. Reduction in the size of BCCs present at baseline was a secondary outcome. Patients were followed for a mean of eight months (range 1-15 months). A positive outcome in favour of vismodegib was seen, with the rate of new BCCs per patient per year being two versus 29 in the control group, this result being highly statistically significant. A significant decrease in existing lesions was also seen, with a mean reduction of 65% versus a reduction of 11% in the control group. Of note, some patients had complete resolution of all their BCCs and no patients had progression of BCC in the vismodegib arm.

Assessing response in locally advanced BCC is difficult and a composite method, including clinical annotation with photography as well as conventional CT, was used in the vismodegib trials. Independent review noted a lower rate of response than that assessed by investigators. Conversely, several patients with residual apparent lesions had histologically complete remission on biopsy. This highlights the issue of residual scarring or ulceration associated with healing, which are both seen clinically and which can confuse the assessed response. There is exploration of other modalities such as superficial soft tissue MRI in an attempt to distinguish residual BCC from treatment-related changes. Repeat biopsy with histological examination is likely to remain the definitive standard for assessing the response in residual lesions after treatment, although even this is subject to sampling error.

The side-effect profile included hair loss, loss of taste (dysguesia), muscle cramps and rhabdomyolysis, weight loss and fatigue. Some of these side-effects were predictable, as hedgehog signalling is required for normal maintenance of tongue papillae and hair follicles.[16,17] These side-effects appear to be class effects for a variety of inhibitors.

A number of systemic inhibitors of smoothened have been assessed in human clinical trials including GDC-0449 (Vismodegib), LDE-225, IPI-926, BMS-833923, TAK-441, and CUR61414. Vitamin D3 inhibits hedgehog signalling through smoothened and also has a pro-differentiation effect on keratinocytes independent of vitamin D receptor activation; a phase III clinical trial has been initiated. Another alternative pathway inhibitor currently being assessed in a clinical trial is tartrazine, which downregulates the RAR-β/RAR-γ pathway. Preclinical work has also focused on developing inhibitors of downstream targets such as Gli. This approach may overcome acquired resistance to SMO inhibitors, due to activating mutations in SMO occurring while on treatment with a SMO inhibitor (www.cancer.gov/clinicaltrials).

Perspective

Future issues include understanding the natural history of prolonged exposure to hedgehog inhibitors with regard to long-term side-effects and the duration of tumour control, as well as the nature and characterisation of tumour cells that develop resistance. An attractive approach will be to use an inhibitor prior to surgery to improve resectability and reduce the potential morbidity of surgery. An important uncertain issue in this setting will be whether all of the previously involved tissue needs to be resected, and careful biopsy mapping studies may assist in clarifying this. It is likely that tumour shrinkage by drug, then resection of residual disease followed by close surveillance and "cherry-picking" of any further recurrences, will be the least morbid approach. Direct injection or topical application of inhibitor may also be a technique to maintain efficacy, but reduce side-effects and avoid the need for long-term discontinuation. LDE225 has been administered topically in a small trial with evidence of BCC regression.[18] Whether there may be a role for hedgehog inhibitors as preventive agents in patients with Gorlin's syndrome also requires testing. The current advances show a remarkable ability to translate basic biological research into clinically meaningful treatments and provide a more acceptable therapeutic option for patients with locally advanced or multiple BCCs.

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Update: Radiation therapy for skin cancer

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Abstract

Effective management of skin cancer in Australia is important, due to its high incidence and enormous burden on the health system. Radiation therapy (RT) plays an important role in skin cancer management, both as definitive treatment and as a component of multimodal management. This article provides a brief review of the varied roles of radiation therapy in the common skin cancers (basal cell carcinoma, squamous cell carcinoma, Merkel cell carcinoma and melanoma) in both curative and palliative settings. Biopsy of all lesions is preferred to establish a histological diagnosis. Definitive radiation therapy is commonly delivered to small primary basal cell carcinomas and squamous cell carcinomas, particularly in the elderly with comorbidities and in sites where reconstruction would be difficult. Adjuvant postoperative radiation therapy to the primary site and/or regional lymph nodes has an important role in the management of Merkel cell tumours, larger squamous cell carcinomas and melanomas with adverse clinicopathological features. A major role of radiation therapy in melanoma is the palliation of metastases in stage IV disease.

Radiation therapy (RT or radiotherapy) is widely used in the management of skin cancers.[1-3] Due to the high incidence of skin cancer in Australia, which results in an enormous burden on the nation's health system, a consideration of the role and utility of RT is appropriate. This article provides a brief review of the use of RT in the management of the common skin cancers. It is important to appreciate the significant contributions of Australian researchers to the current understanding of this role. As with all cancers, multidisciplinary discussion is required for optimal outcomes.

Basal cell carcinoma

Basal cell carcinomas (BCCs) are extremely common in the elderly and typically occur on sun-damaged skin, especially in the head and neck region. Most small lesions are nodular, becoming ulcerated (forming 'rodent ulcers') as they grow. Although there is a very low rate of metastasis to regional lymph nodes or distant sites, neglected BCCs may cause major morbidity and extend across large areas, with destruction of adjacent and deeper structures including bone.

While surgical excision of small BCCs in favourable locations is generally preferred, their location often precludes simple excision and requires complex reconstruction.[4] For BCCs in surgically difficult sites in elderly patients, such as the tip of the nose and the inner canthus of the eye, RT is an attractive alternative. BCCs are generally radiosensitive cancers. Short treatment courses with superficial x-rays or electron beams, adding a 5-10mm margin around the tumour, result in high cure rates. Postoperative RT is generally recommended for positive margins, although only a proportion recur following surgery alone.[5]

Larger mobile BCCs remain curable with RT. With deeper infiltration and bone destruction, curative treatment generally involves excision with reconstruction. Postoperative RT is used for close or positive margins. If surgery is contraindicated due to the extent of the BCC or poor patient condition, RT with palliative intent is appropriate to achieve growth restraint and reduce bleeding.

Squamous carcinoma

Squamous cell carcinoma (SCCs) are also common on sun damaged skin. Small SCCs are often excised for convenience and for histological confirmation of the diagnosis. Features predicting local recurrence include: poor differentiation; infiltration of deeper tissues; close or positive margins; perineural spread; and previous recurrence. Re-excision to obtain wider margins, or postoperative RT is appropriate, depending on site.[6]

Following biopsy, definitive RT is commonly delivered to small primary SCCs, particularly in the elderly with comorbidities and in sites where reconstruction would be difficult.[2,4] As for BCCs, short RT courses using superficial X-rays or electron beams are used to treat the tumour with a 5-10mm margin, paying careful attention to the depth of the lesion to ensure adequate dose coverage at depth. Larger margins are needed when there is evidence of perineural spread.

While RT is a valid alternative to excision for many SCCs, there are situations for which surgery is preferred. These include: younger adults, who have many decades to express radiation-related complications; previous RT in that area; sites that will be subject to repeated injury (trauma or sun exposure); lesions with margins that cannot be defined; and tumours eroding into cartilage or bone.

The acute and late adverse effects of RT for small BCCs and SCCs are confined to the treatment volume. The main acute side-effects, either from definitive or postoperative RT, are hair loss within the treated area and a progressive skin reaction, similar to sunburn. This may lead to blistering and crusting, which resolves two to three weeks following the treatment course. As the size of the tumour increases, more protracted treatment schedules are needed to reduce the intensity of the skin reaction. Late effects include permanent hair loss and progressive atrophy, and depigmentation of the skin. Cartilage and bone necrosis are unlikely with careful patient and tumour selection.

Management of regional lymph nodes is variable.[7,8] Small, well differentiated and superficial SCCs have a low rate of lymph node involvement. In these situations clinical observation is appropriate. For tumours with adverse pathological features, sentinel lymph node biopsy can be used to assess the status of the regional nodes. Alternatively, the regional lymph nodes may be treated electively by surgical lymph node dissection or RT. Palpable or grossly involved regional nodes require a therapeutic node dissection, generally followed by adjuvant post-operative RT.

A feature of a small percentage of SCCs is perineural spread, in which the tumour can infiltrate the perineurium and extend for considerable distances along nerves.[9] In this manner, SCC can enter the cranial cavity, leading to cranial nerve palsies. Cranial nerves V and VII are most commonly involved. Although mostly incurable, high dose RT to the course of the involved nerves can reverse nerve palsies and improve quality of life.

Merkel cell carcinoma

Although much less common than BCCs or SCCs, and often regarded as a rare tumour, Merkel cell carcinoma is not a rare cancer in Australia. It also occurs on chronically sun exposed skin in the elderly, often as a rapidly growing nodule with a propensity for early spread, both locoregionally and to distant sites. Merkel cell carcinoma is a radiosensitive and chemosensitive skin cancer. A number of recent reviews have been published.[10-13]

The management of the primary tumour is wide excision if possible, though definitive RT results in a high local control rate if excision is not possible. Postoperative RT is commonly used following excision of Merkel cell carcinoma, although the benefits are uncertain if wide excision margins have been obtained.

The management of regional nodes remains uncertain. For clinically negative nodes, management options include: observation; sentinel lymph node biopsy and subsequent management depending on sentinel lymph node status; and elective dissection or elective RT. When regional lymph nodes are clinically involved, options include regional node

dissection, with postoperative RT for multiple involved nodes or extracapsular spread, or high dose RT alone. A dose response and volume relationship has been demonstrated and chemoradiation improves control rates in Merkel cell carcinoma considered to be at high risk due to size, recurrence or nodal involvement.[14,15] In the event of distant metastases, RT is useful for palliation in a number of sites, due to the radiosensitivity of Merkel cell carcinoma.

Overall there are many unanswered questions relating to the management of Merkel cell carcinoma, and clinical trials are hampered by its low incidence. Recent identification of a polyomavirus associated with Merkel cell carcinoma (but not necessarily causative) adds to the uncertainties in management.

Melanoma

There is limited use of RT in the management of primary melanoma, which is generally well managed with wide excision, with or without sentinel lymph node biopsy. Exceptions are adjuvant postoperative RT for the desmoplastic neurotropic subtype, which is being investigated currently, and definitive RT to treat large areas of lentigo maligna in the elderly.[3]

Melanoma has previously been considered to be poorly responsive to RT, despite good evidence for a wide spectrum of radiosensitivity.[1] The value of postoperative RT following therapeutic regional lymph node dissection has been a matter of controversy for several decades. A recent phase III clinical trial has helped to define this role, showing a statistically significant reduction in locoregional relapse with the addition of postoperative RT, compared with dissection alone in patients with stage III melanoma.[16] As anticipated, there was no survival advantage to the combination, with many patients progressing to systemic metastatic disease. Until the long-term complications of combined treatment (particularly lymphoedema) are reported, the net value of adjuvant RT remains unresolved.

The major role of RT in melanoma has been palliation of metastases in patients with stage IV disease.[3] Until the recent development of effective systemic therapies (BRAF inhibitors and immunomodulators), palliation of metastatic melanoma relied largely on surgery and RT. Although initial responses to targeted therapies (eg. BRAF inhibitors) are frequently spectacular, they are currently limited to tumours with the appropriate mutation (approximately 50% of metastatic melanomas) and response duration appears to be limited.

Recent technical developments are expanding both the role and effectiveness of RT in stage IV melanoma. Of particular interest is the management of cerebral metastases, due their high incidence and poor prognosis. The traditional treatment of cerebral metastases was dependent on the number of cerebral lesions, their locations and the patient's performance status. Single accessible metastases were resected surgically, postoperative whole brain RT was generally used, with phase III clinical trial evidence (not specific for melanoma) of a significant reduction in subsequent intracranial relapse.[17] Multiple brain metastases were treated with steroids alone or steroids plus whole brain RT.

Since the development and widespread use of stereotactic radiosurgery, the paradigm for the management of cerebral metastases has changed markedly.[18] Stereotactic radiosurgery involves a high single (ablative) dose of radiation, delivered with submillimetre precision to a defined intracranial target. Due to the steep dose gradient at the periphery of the treated metastasis, normal surrounding brain is spared potentially damaging effects of high dose radiation. By contrast with neurosurgery, stereotactic radiosurgery is a non-invasive outpatient procedure which can be used to treat multiple brain metastases in a single session, largely independent of their locations within the brain.[19] The response rates exceed 80% and seem comparable to the results following surgical excision, though no randomised trials have been undertaken. As for neurosurgical excision, the addition of whole brain RT to stereotactic radiosurgery reduces the risk of further intracranial recurrence.[20] Unlike whole brain RT, stereotactic radiosurgery may be repeated for new metastases.

The expansion of these stereotactic and image-guided techniques to the treatment of systemic metastases has been fruitful. Vertebral metastases, which are a common cause of pain and possible spinal cord compression, have a 90% durable response rate following treatment with single fractions of 24 Gray, with good pain control for the remainder of the patient's life.[21] Careful immobilisation and sculpting of dose, which are essential for these high single doses, protect the spinal cord from damage. Similarly, high response rates are achieved in liver and lung metastases using these techniques.[22] The recent development of effective systemic agents will undoubtedly modify the role of RT in patients with stage IV melanoma. Several drugs have intracranial activity, such that studies of combination therapy will be required.[23]

In conclusion, RT plays an important role in the management of all the common skin cancers, although the role varies between the different cancers. Despite the generalities outlined above, it is important to individualise treatment and to manage patients in a multidisciplinary setting wherever possible.

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Update on the management of Merkel cell carcinoma

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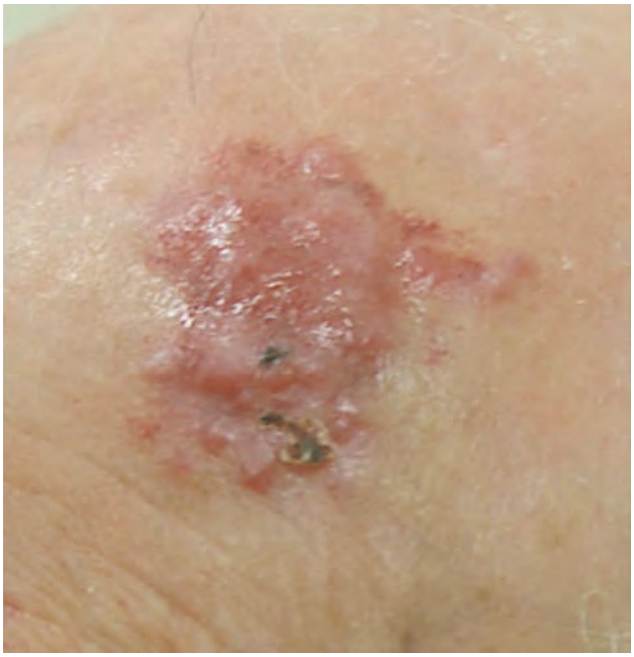
Abstract

Merkel cell carcinoma is a rare, aggressive, cutaneous neuroendocrine tumour which has a propensity for both loco-regional and distant spread. This review considers its epidemiology, diagnosis, staging and management, including the roles of surgery, radiation therapy and chemotherapy, and guidelines for patient management are presented. Patients should be referred promptly to an experienced specialist centre for definitive management, because treatment delays are associated with a worse outcome. Given the rarity of this tumour, patients should be enrolled on prospective databases and managed in a multidisciplinary setting, ideally in the context of a clinical trial.

Merkel cell carcinoma is an aggressive cutaneous tumour that tends to occur in the sun-exposed skin of the elderly. It was first described by Toker in 1972.[1] Merkel cell carcinoma is also called primary cutaneous neuroendocrine carcinoma, based on the ultrastructural finding of dense core granules within the tumour cells and immunohistochemical evidence of neuroendocrine differentiation.[2,3] Merkel cells were first described by Friedrich Sigmund Merkel as Tastzellen or 'touch cells', but details of their function and origin remained elusive. Merkel cells appear to be essential for the specialised coding by which afferent nerves resolve fine spatial details.[4] Skin graft experiments in birds initially implied that Merkel cells were neural crest derived, but more recent studies in mammals indicate an epidermal origin.[5]

Merkel cell carcinoma has a non-specific clinical appearance and is often diagnosed belatedly, or misdiagnosed. It may present as a painless, indurated, solitary dermal nodule with a slightly erythematous to deeply violaceous colour, and rarely, an ulcer (figure 1). Merkel cell carcinoma may infiltrate locally via dermal lymphatics, resulting in multiple satellite lesions.[6] Regional lymph nodes are involved at presentation in approximately one third of cases. In 10-20% of cases,

Figure 1: *Merkel cell carcinoma of the scalp.*



Merkel cell carcinoma presents solely as a lymph node metastasis, or the primary may have been cryo-ablated.[7] Investigators have used the acronym 'AEIOU' to summarise this tumour entity as possibly being Asymptomatic, Expanding rapidly, and more likely to occur in Immunosuppressed patients Older than 50 years in UV exposed skin.[8] To this previously described acronym we would add the letter 'R' for both Rare and Remember.

Ultraviolet irradiation is the major risk factor for developing Merkel cell carcinoma. Merkel cell carcinoma incidence increases progressively with age. The median age at diagnosis is around 65 years.[9] There is an increased incidence of this disease in immunosuppressed patients. Recently, it was discovered that a polyomavirus (termed Merkel cell virus, MCPyV) was clonally integrated into the genome of Merkel cell carcinoma in the majority of patients.[10] However, the role of the virus in the pathogenesis of Merkel cell carcinoma remains controversial, particularly since the prevalence of MCPyV appears to differ between Merkel cell carcinoma patients in the United States and Europe compared with Australia. Thus, there may be two independent pathways for the development of Merkel cell carcinoma – one driven by the presence of MCPyV, and the other driven primarily by sun damage.[11]

Merkel cell carcinoma consists of small round cells with hyperchromatic nuclei and scant cytoplasm. Typically, nuclei have evenly dispersed, peppered chromatin and inconspicuous nucleoli. Immunohistochemistry is useful to differentiate Merkel cell carcinoma from metastatic visceral neuroendocrine carcinomas, particularly from small cell lung carcinoma. CK-20, a low-molecular-weight intermediate filament, is a highly sensitive marker for Merkel cell carcinoma. Other helpful markers include CD117 neuron-specific enolase, chromogranin A, synaptophysin, and neurofilament protein. Conversely, Merkel cell carcinoma is typically negative for CK-7 and thyroid transcription factor-1 (both positive in small cell lung carcinoma), and for S-100 and leukocyte-common antigen, distinguishing it from melanoma and cutaneous lymphoma, respectively.[12]

Staging and investigation

Because loco-regional spread is common, newly diagnosed Merkel cell carcinoma patients require a thorough clinical examination for satellite lesions and regional node involvement. Imaging may include a computed tomography (CT) scan of the chest and abdomen to rule out primary small cell lung cancer, as well as distant and regional metastases. Fluorodeoxyglucose-positron emission tomography (PET-see Emmett and Ho, pp 134) results have been reported only in selected cases, but Merkel cell carcinomas generally show high avidity. PET can detect metastatic deposits in sub-centimetre lymph nodes that may not have been appreciated on initial CT assessment.[13] In a recent review of 18 patients with Merkel cell carcinoma, PET-CT contributed to altered staging in seven patients (33%) and a change in management in nine patients (43%).[14]

The American Joint Committee on Cancer (AJCC) staging system, modified in 2009, is based on the size of the primary lesion (<2cm or >2cm) and the presence or absence of lymph node involvement (table 1).

Table 1: *AJCC Staging system for Merkel cell carcinoma.*

Stage	Primary Tumour	Lymph Node	Metastasis
0	In situ primary tumour	No regional lymph node metastasis	No distant metastasis
IA	Less than or equal to 2cm maximum tumour dimension	Nodes negative by pathologic exam	No distant metastasis
IB	Less than or equal to 2cm maximum tumour dimension	Nodes negative by clinical exam* (no pathologic node exam performed)	No distant metastasis
IIA	Greater than 2cm tumour dimension	Nodes negative by pathologic exam	No distant metastasis
IIB	Greater than 2cm tumour dimension	Nodes negative by clinical exam* (no pathologic node exam performed)	No distant metastasis
IIC	Primary tumour invades bone, muscle, fascia, or cartilage	No regional lymph node metastasis	No distant metastasis
IIIA	Any size tumour (includes invading tumours)	Micrometastasis**	No distant metastasis
IIIB	Any size tumour (includes invading tumours)	Macrometastasis‡ -OR- In transit metastasis§	No distant metastasis
IV	Any size tumour (includes invading tumours)	Any lymph node metastasis	Metastasis beyond regional lymph nodes

* Clinical detection of nodal disease may be via inspection, palpation and/or imaging. ** Micrometastases are diagnosed after sentinel or elective lymphadenectomy. ‡ Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or needle biopsy. § In transit metastasis: a tumour distinct from the primary lesion and located either (1) between the primary lesion and the draining regional lymph nodes or (2) distal to the primary lesion. Adapted from *AJCC Cancer Staging Manual,* 7th Edition, 2009.[42]

The role of sentinel lymph node biopsy is not well elucidated. Some have suggested that sentinel lymph node biopsy may have a role in selecting patients with clinical stage I disease who may then avoid elective nodal treatment.[15] Others argue that sentinel lymph node biopsy is not an accurate predictor of loco-regional recurrence in Merkel cell carcinoma, with a higher false negative rate (range 5-33%) than is seen in melanoma or breast cancer.[16,17] For example, in a series from Melanoma Institute Australia, five of six patients with pathologically negative sentinel lymph node recurred within the node field.[17] In contrast, the failure rate for melanoma detection after a negative sentinel lymph node biopsy was only 2.7% in over 1000 patients treated at the same centre.[18] Despite this uncertainty, pre-operative lymphoscintigraphy to identify the location of sentinel lymph nodes and draining node fields may be of value in radiotherapy field planning in certain situations.[17]

The extent of disease at presentation provides the most useful estimate of prognosis. For stage I disease, a tumour diameter <2cm is associated with an improved outlook.[19] Other clinicopathological factors that influence prognosis remain poorly defined. It has been reported that p63 expression in primary Merkel cell carcinoma is strongly associated with clinical outcome.[20] However, a recent analysis of 95 patients with Merkel cell carcinoma found p63 expression was infrequent (9% of primary Merkel cell carcinoma) and showed no significant association with disease outcome. Tumour thickness was nevertheless significantly associated with disease-free survival in Merkel cell carcinoma.[21] The most relevant prognostic levels (akin to Breslow thickness in melanoma) remain to be elucidated, but it is strongly recommended that thickness be routinely measured in pathology reports.[22]

Early referral to a specialist centre experienced in managing Merkel cell carcinoma is important, as delays between diagnosis and treatment lead to poorer outcomes.[23] The exact integration of surgery, radiotherapy and possibly chemotherapy needs to be tailored to the patient, location of the tumour and stage of disease, from definitive treatment employing surgery or radiotherapy, through to the palliation of incurable disease.

Early stage Merkel cell carcinoma (localised disease)

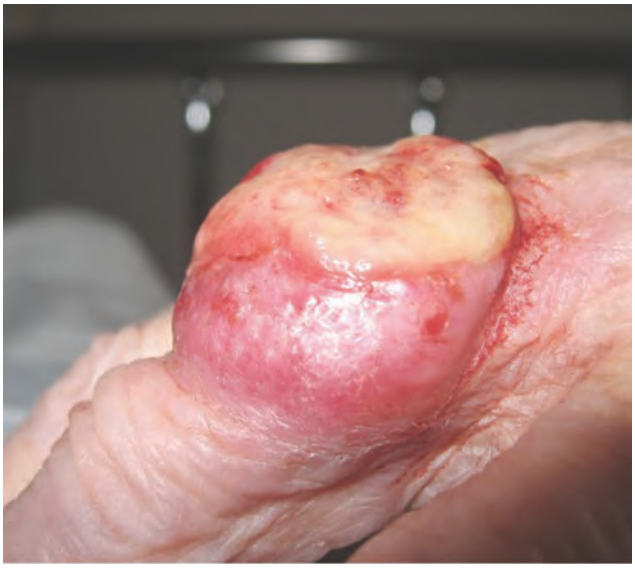
Primary lesion

Surgery is the initial treatment modality in most patients, even if only to establish the diagnosis. The extent of excision margins that are required remains a subject of controversy. Historically, wide local excision with a 2-3cm margin has been recommended, but no formal trial has ever been carried out to confirm this. Extensive surgery - given that Merkel cell carcinoma occurs predominantly in cosmetically challenging areas - becomes less critical if adjuvant radiation treatment is to be delivered to the primary site.

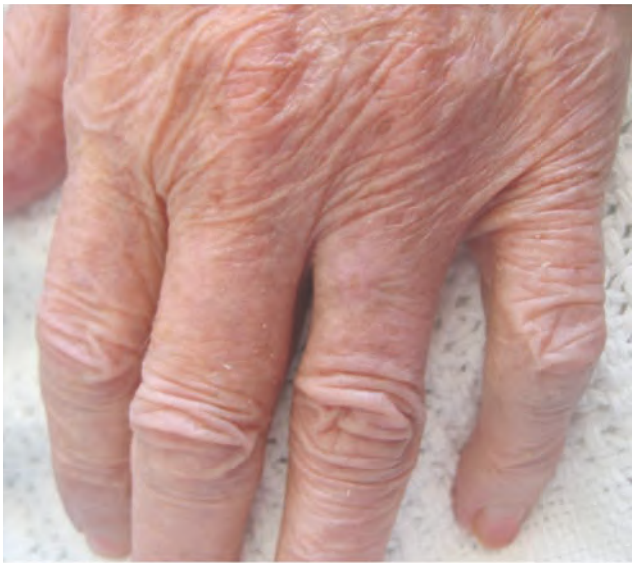
Occasionally, primary tumour excision is not possible, especially in elderly patients or in cosmetically sensitive areas. Several reported series document the use of radiation or chemoradiation alone to treat Merkel cell carcinoma, achieving durable local control (figure 2).

Figure 2: *(a) Locally advanced Merkel cell carcinoma and b) the same lesion two months after radiotherapy with 40Gy in 15#.*

(a)



(b)



Doses used in this setting have ranged from 45 to 60Gy in varying fractionation schedules.[24-28]

Elective irradiation of regional lymph nodes should be considered in patients with stage I Merkel cell carcinoma. It may be particularly valuable in the head and neck region where the draining node field is usually in close proximity to the primary tumour. Furthermore, elective radiotherapy obviates the need for sentinel lymph node biopsy. A recently published French randomised control trial (which has the distinction of being the only one in this disease),[29] demonstrated that regional irradiation reduced the probability of regional node recurrence (16.7% v 0%) but had no impact on progression-free or overall survival.

Adjuvant radiotherapy may follow surgery, either to the primary alone, or to both the primary and a directed

regional node field. Multiple series have demonstrated benefits from adjuvant radiotherapy in improving both loco-regional control and disease-free survival when compared to series managed with surgery alone.[6,30-34] An analysis of over 1600 patients in the US Surveillance, Epidemiology and End Results database demonstrated statistically significant improvements in survival with the use of postoperative (adjuvant) radiation treatment.[35] The use of adjuvant radiation was associated with improved survival in all age groups, and for all tumour sizes. Therefore, surgical and radiation oncologists should manage these patients together using a team approach.[36]

It appears important that radiation treatment be delivered promptly. A higher risk of progression (41%) was seen in patients who waited more than a median of 24 days for radiation treatment.[23]

High risk disease – the role of chemotherapy

Merkel cell carcinomas are generally sensitive to chemotherapy, with high initial response rates. However, relapse inevitably occurs. Chemotherapy may sensitise Merkel cell carcinoma to the effects of radiation treatment and thereby enhance the local cell kill from radiation treatment. It may also act further afield to eliminate subclinical micrometastatic disease. The most widely used chemotherapy agents for Merkel cell carcinoma are either cisplatin or carboplatin plus etoposide.

The Trans-Tasman Radiation Oncology Group (TROG) has investigated the use of adjuvant chemo-radiotherapy in patients with high-risk Merkel cell carcinoma. Trial 96.07 included 53 patients with high-risk Merkel cell carcinoma.[37] Patients had disease localised to the primary site and nodes, with at least one of the following high risk features: recurrence after initial therapy; involved nodes; primary tumour size > 1 cm; gross residual disease after surgery; or occult primary with nodes. Treatment consisted of radiation to the primary site and nodes and synchronous carboplatin and etoposide. This study demonstrated excellent overall survival and loco-regional control, with three-year overall and relapse-free survival rates of 76% and 65%, respectively, despite high-risk disease. However, grade 3 or more neutropenia occurred in 57% of the patients, with febrile neutropenia in 35%.

Given the advanced age of most patients with Merkel cell carcinoma, and in order to reduce the toxicity seen in trial 96.07, TROG investigators have piloted the use of weekly carboplatin synchronous with the radiation treatment, with three cycles of adjuvant carboplatin and etoposide.[38] This regimen forms the basis for a phase II efficacy study of chemo-radiotherapy in high risk Merkel cell carcinoma (primary greater than 2cm in diameter and/or involved regional lymph nodes), TROG trial 09.03.[39] Here, radiation treatment doses are tailored to disease burden and PET scans are performed to assess the proportion of patients in whom PET imaging results in a change in management, and also to assess metabolic response in those with macroscopic disease.

Advanced disease and palliation

The presence of distant disease carries a grave outlook, with the most commonly-affected organs being the liver, bone, lung, brain and skin. Responses to chemotherapy (either cisplatin, doxorubicin and vincristine, or etoposide and cisplatin) are generally short-lived and most patients die from the disease.[40,41] Furthermore, many patients are elderly and the chemotherapy regimens are especially toxic in this group.[12] Radiotherapy may also be employed for palliation of symptomatic disease, particularly bone or brain metastases.

Recommendations

Patients with Merkel cell carcinoma should be referred urgently to a multidisciplinary specialist centre with experience in the disease, and managed on a case by case basis. If a patient presents with positive margins after initial biopsy or resection, definitive radiation treatment or chemo-radiotherapy is an alternative to further surgery and, importantly, results in less delay to (adjuvant) radiation treatment. Such a patient may also undergo elective radiation treatment of the draining lymph node field, obviating the need for sentinel lymph node biopsy or full node dissection. Entering patients with Merkel cell carcinoma into prospective trials and recording information about them on national databases is essential if we are to better understand the behaviour of this rare disease and determine its optimal management.

Merkel cell carcinoma is a rare disease where treatment by definitive radiation treatment or chemo-radiotherapy has an expanding role in addition to surgery. It is important that recruitment to prospective trials (such as TROG 09.03) continues in order to validate and improve our approach to this enigmatic disease entity.

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RECENT ADVANCES AND IMPORTANT ISSUES IN MELANOMA PATHOLOGY: AN UPDATE FOR ONCOLOGISTS

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Abstract

The critical role of pathology in the multidisciplinary care of melanoma patients is becoming apparent in the rapidly changing modern era of personalised and precisely targeted medicine. Recent insights into the molecular pathogenesis of melanoma have allowed traditional pathological assessment to be supplemented and enhanced by molecular pathology testing to improve classification, prognostication and selection of patients for targeted therapies. The pathology report remains pivotal as it establishes the definitive diagnosis of melanoma in most instances, while the assessment and documentation of key pathological parameters allow the most accurate determination of prognosis to be made and are utilised to guide the next stages of patient management. Molecular tests (including fluorescent in situ hybridisation) are now routinely utilised to enhance the accuracy of classification and prognostication of selected melanocytic tumours in many institutions. Recent studies have also highlighted important melanoma prognosticators such as mitotic rate, the presence and extent of ulceration, tumour-infiltrating lymphocyte grade and sentinel lymph node biopsy. Pathologists also play a key role in the triage and selection of appropriate tumour tissue and tumour cells to test for various molecular markers which are used to select patients who may benefit from targeted therapies. It is important that clinicians understand important aspects of molecular testing in melanoma, such as when and how to arrange testing, which specimen to test, and the advantages and disadvantages of the various testing methodologies. These issues are addressed in this review.

Pathology is a key component of the multidisciplinary care of melanoma patients. While melanoma may be suspected clinically, the initial definitive diagnosis is usually established by pathological examination of a tissue biopsy. In clinically localised primary cutaneous melanoma, pathological assessment of various tumour parameters enables accurate estimation of prognosis and determines the most appropriate next step(s) in clinical management. Pathological evaluation of any potential or likely metastasis is also critical. Recent discoveries of the molecular pathogenesis of melanoma are now being harnessed clinically to improve patient management. Molecular pathology is now utilised to enhance melanoma diagnosis, classification, prognostication and to predict responsiveness to selective targeted therapies in melanoma, and will undoubtedly play an ever-increasing role in the management of melanoma patients. In this article we review selected important issues in melanocytic tumour pathology. We highlight some recent advances in the molecular pathology of melanocytic tumours and their current and potential clinical applications.

Biopsy of atypical or suspicious melanocytic tumours

Unless clinical circumstances dictate otherwise, excision biopsy with 1-2mm margins is recommended for pathological diagnosis of atypical or suspicious melanocytic tumours.[1] This enables accurate pathological assessment and allows planning of definitive treatment if a diagnosis of melanoma is confirmed. Incomplete biopsies may result in misdiagnosis because of non-representative sampling or because they do not include sufficient tumour tissue to allow assessment of the various pathological criteria necessary to establish a diagnosis.[2] Furthermore, in biopsies that do not include the thickest portion of the tumour or in superficial shave biopsies that transect the tumour, tumour thickness (an important staging and prognostic factor in melanoma) cannot be accurately determined,[2] which may lead to inappropriate management.

A pathological diagnosis of primary cutaneous melanoma usually rests on correlation of a range of histopathological features (including architectural and cytological features and features of the host response), with clinical data including patient age, clinical features and anatomical site of the lesion. The accuracy of the pathology report may depend on the amount of tissue provided and the availability of relevant clinical details. It is particularly important for the clinician to record on the pathology request form the occurrence of factors that may induce atypical pathological features in melanocytic naevi (such as a previous biopsy, trauma, surface irritation, topical treatment, pregnancy or recent prolonged intense sunlight exposure) that may lead to a misdiagnosis of melanoma.[3]

In most instances, a histopathological diagnosis of melanoma can be made rapidly, accurately, and reproducibly by an appropriately trained, experienced pathologist. Nevertheless, pathological diagnosis can be very challenging, particularly for some subsets of melanocytic tumours. If the clinical and pathological opinions are discordant, or if there is clinical concern about the nature of a lesion or the pathology report, it is often helpful for the clinician to discuss the case with the reporting pathologist. In some cases, it may also be appropriate to seek additional opinion from one or more pathologists experienced in the interpretation of diagnostically challenging melanocytic lesions.[4, 5]

Evolving concept of borderline melanocytic tumours

Most melanocytic tumours can be rapidly and accurately classified as either naevus or melanoma based on routine pathological assessment on haematoxylin/eosin-stained sections. However, there is a small subset of melanocytic tumours, the biological behaviour of which is not accurately predictable based on routine assessment of their pathological features, even by expert pathologists.[5] Examples of such tumours and the terminology used to describe them include atypical Spitz tumour,[6] atypical Spitz naevus,[7] melanocytic tumour of uncertain malignant potential,[8] melanocytoma,[9] and atypical blue naevus-like or deep penetrating naevus-like tumour of uncertain malignant potential.[10] There are also melanomas that

display many features of common acquired or dysplastic naevi, the so-called 'naevoid melanomas', that often cause diagnostic problems.[3,11] There is increasing recognition of the likely existence of a poorly defined intermediate grade of melanocytic neoplasms with low grade malignant potential which show frequent involvement of sentinel lymph nodes, with significantly less frequent extension of disease beyond the regional lymph nodes to distant metastastic sites; some of the aforementioned lesions probably fall into this class of tumours.[6,9,12,13] The assessment of risk and prognostics, (and as a consequence, management decisions) for such tumours remains problematic.[5]

Molecular pathology for the diagnosis of difficult melanocytic tumours

It has been known for more than a decade that melanomas are characterised by the presence of numerous chromosomal copy number alterations (CNA), including gains and losses, and that such aberrations are not seen in naevi,[14-16] an exception being the occurrence of losses of chromosome 11p or 7p in a minority of Spitz naevi.[17,18] Assessment for the presence of CNA may assist in the classification of difficult melanocytic tumours in which accurate characterisation of the tumour as benign or malignant is difficult based on routine histopathological assessment.

CNA may be detected in archival formalin-fixed, paraffin-embedded tissue by comparative genomic hybridisation (CGH).[14] While this technique has the advantage of being able to detect any aberrations occurring in the genome, it is generally not an appropriate adjunct to pathological diagnosis in routine clinical practice for a number of technical and practical reasons. These limitations include the requirement of a large amount of DNA (making it suitable only for thick bulky tumours), inability to visualise/verify that the findings reflect those of the melanocytic tumour cells themselves, the labour-intensive nature of DNA extraction and CGH testing, and the need for expensive, specialised equipment.

Fluorescence in situ hybridisation (FISH) is a technique that can identify specific CNA within individual tumour cells. While it has the limitation of only being able to test for a limited number of changes (compared to CGH which tests for CNA in the entire genome), FISH is more easily applied in routine clinical practice and can be performed on small tumour samples. Recent studies have shown that a combination of FISH probes targeting selected chromosomal loci can accurately classify naevi and melanomas,[17-19] and may also assist in the classification of histologically ambiguous melanocytic tumours.[20-22] Recent studies also suggest that the results of FISH testing may identify subsets of melanomas with poorer prognosis.[23] FISH is already used in many centres as a supplementary diagnostic aid in the assessment of problematic melanocytic tumours. Once the prognostic significance of FISH is validated in larger studies, this technique may also become commonly employed in estimation of prognosis in melanoma patients.

In many melanoma treatment centres with active translational research programs, tissue samples from fresh specimens may be utilised for tissue banking or other research purposes. The decision to provide tissue should only be made if it is certain that the diagnostic process and pathological evaluation will not be compromised. After close examination of the submitted specimen, the pathologist, in consultation with the clinician, is the most appropriate person to make this decision. As a safeguard, research use of the specimen should be deferred until the diagnostic process is complete. If there are any diagnostic problems, (eg. if it is difficult to readily determine whether a lesion is a naevus or a melanoma without examination of the entire lesion), the portion of the specimen that was stored for research can be retrieved and used for diagnostic purposes.

Melanoma prognosis

The provision of a reliable estimate of prognosis in melanoma patients is important to: better inform them and their treating physicians about likely outcomes; to determine the need for further investigations; to guide management (such as the width of further excision margins and the appropriateness of sentinel lymph node biopsy); and for assignment of risk status in patients entering clinical trials. The Melanoma Staging Committee of the American Joint Committee on Cancer (AJCC) has produced a free, web-based prognostic calculator derived from analysis of a large dataset of patients with long-term follow-up. Visit www.melanomaprognosis.org

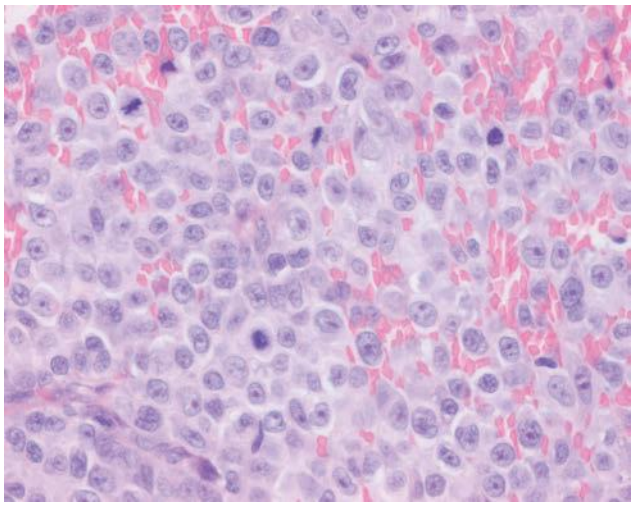
The histological examination of a primary melanoma provides important prognostic information, as pathological features constitute many of the key prognostic factors in melanoma.[24-26] The prognosis for a patient with clinically localised primary cutaneous melanoma is principally correlated with its vertical depth of tumour growth (Breslow thickness). Other important prognostic factors include the presence or absence of ulceration, the anatomical site of the tumour (melanomas on the extremities have a better prognosis), patient age and sex (young females fare better).[24,27] Recent studies have also highlighted a number of other important prognostic factors in primary cutaneous melanomas which are discussed in more detail below.

Tumour mitotic rate

Several recent studies, including an analysis of a very large number of patients performed by the Melanoma Staging Committee of the AJCC, have demonstrated that mitotic rate (figure 1) is an important prognostic factor for clinically localised primary melanomas.[28-37] In view of these findings, the 7th edition of the AJCC staging system recommends that mitotic rate should be assessed in all primary melanomas for prognostic purposes.[24] Furthermore, the presence or absence of mitoses in non-ulcerated thin (<1.0mm thick) melanomas is now used for staging (ie. for separating pT1a and pT1b tumours).[24]

The number of mitotic figures can vary greatly between different regions in a tumour. For consistency and reproducibility, a standardised method must be used to assess mitotic rate. It is recommended that the field diameter of the microscope used to assess mitotic rate be formally calibrated using a stage micrometer to determine the number of high-power fields that equates to a square millimetre. In the 7th edition of the AJCC melanoma staging system,[24] the recommended method to determine

Figure 1: *These melanoma cells have an epithelioid cytomorphology and show frequent mitoses. A high mitotic rate (such as in this case) is an adverse prognostic feature in primary melanoma.*



mitotic rate is to find an area in the dermis with obvious mitotic activity (the 'hot spot'), to begin counting in this area, and then to count mitoses in immediately adjacent non-overlapping high power fields adding up to a total area of one square millimetre. This method for determining the mitotic rate of melanoma has been shown to have excellent inter-observer reproducibility, even among pathologists with widely differing levels of experience in the assessment of melanocytic tumours.[28]

Extent of ulceration

Ulceration was first identified as an adverse prognostic factor for melanoma in the 1950s.[38,39] Subsequently, it was established that the prognostic value of ulceration was independent of primary tumour thickness,[40] and as a result, ulceration was incorporated into the AJCC melanoma staging system.[24,41] A recent study of 4661 patients diagnosed and managed at Melanoma Institute Australia (MIA),[26] showed that the extent of ulceration (measured either as diameter or percentage of tumour width) provides even more accurate prognostic information than the mere presence of ulceration. Both the presence and extent of ulceration were independent predictors of survival. The five-year melanoma-specific survival (MSS) for ulcerated and non-ulcerated melanomas was 77.6% and 91.3%, respectively. The five-year MSS was 82.7% in minimally/moderately ulcerated melanomas (ulceration measuring <5mm), compared to 59.3% in extensively ulcerated (>5mm) melanomas. The presence and extent of ulceration were independent predictors of poorer MSS after adjusting for other known prognostic factors.[26]

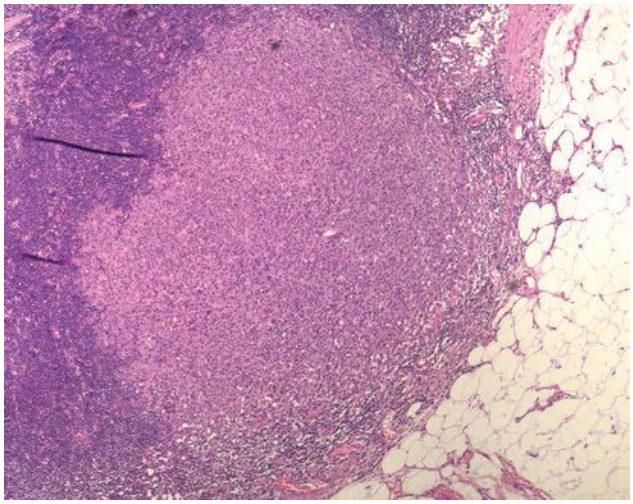
Tumour-infiltrating lymphocytes

The presence of tumour-infiltrating lymphocytes (TIL) in melanoma has been shown to be associated with a favourable prognosis in some studies,[42-49] and has been interpreted as indicating a more effective host immunological response to the tumour. A recent study of 1865 patients treated at MIA,[50] showed that TIL grade (graded 0 to 3, based on increasing extent and density of the TIL infiltrate) was an independent predictor of survival and sentinel lymph node status in melanoma patients. In this study, the majority of patients had either no (TIL grade 0, 35.4%) or few (TIL grade 1, 45.1%) TIL, with a minority showing moderate (TIL grade 2, 16.3%) or marked (TIL grade 3, 3.2%) TIL. Sentinel lymph node positivity rates for each TIL grade were: 0=27.8%, 1=20.1%, 2=18.3%, 3=5.6%; $p<0.0001$. Patients with a pronounced TIL infiltrate had an excellent prognosis.[50]

Sentinel lymph node biopsy

The sentinel lymph node biopsy procedure is a highly accurate and minimally invasive staging technique in melanoma patients. The tumour-harboring status of the sentinel lymph node (figure 2) provides the most accurate prognostic information currently available for clinically localised melanoma. As larger numbers of effective targeted therapies for melanoma are developed (see below), accurate identification of patients at high risk of disease progression (i.e. those with a positive sentinel lymph node) will become increasingly important. Careful identification, removal and pathological assessment of sentinel lymph node is critical to the accuracy of the technique,[51,52] and deficiencies in any of these steps may result in a falsely negative biopsy.[53] Pathologists should examine multiple sections from each sentinel lymph node, stained routinely with haematoxylin/eosin and immunohistochemically for melanoma-associated antigens.[51,52] In the third interim analysis of the results of a large, randomised, multi-centre clinical trial (the first Multicenter Selective Lymphadenectomy Trial, MSLT-I), there appeared to be a substantial survival benefit in sentinel lymph node-positive patients if they had an early complete lymph node dissection.[54,55] In MSLT-I, the five-year survival for patients who were sentinel lymph node-negative was 90.2%, whereas it was 72.3% for those who were sentinel lymph node-positive.[55] The ongoing second Multicenter Selective Lymphadenectomy Trial (MSLT-II) is designed to determine whether immediate complete lymph node dissection results in improved survival in melanoma patients who are sentinel lymph node-positive.[56]

Figure 2: *Sentinel lymph node containing metastatic melanoma.*



Structured/synoptic melanoma pathology reporting

It is important that all relevant histological features are described in the pathology report to allow accurate estimation of prognosis and formulation of an appropriate management plan. A structured or synoptic reporting format can facilitate this.[57-59] Recently in Australia, there has been widespread recognition of the need to improve the quality and completeness of cancer pathology reports. Efforts have been made to improve the quality of melanoma pathology reports by education of the pathology community. In 2010, as part of this endeavour, the Royal College of Pathologists of Australasia published a recommended structured pathology reporting protocol for melanoma.[12] Furthermore, the international pathology community (through the respective pathology colleges of the US, Canada, UK and Australasia) is also working to develop consensus melanoma pathology reporting guidelines for implementation in their respective jurisdictions.

Molecular and somatic mutation testing

Molecular genetic testing of melanocytic tumours has the potential to identify subgroups of tumours with specific genetic signatures that may accurately predict their likely clinical course and/or response to treatment.

An interesting finding of recently reported molecular studies is the confirmation that the well-established, traditional clinico-pathological classification of melanomas into lentigo maligna, superficial spreading and acral-lentiginous subtypes correlates with the genetic findings.[60] For example, tumours with prominent solar damage (lentigo maligna) commonly harbour NRAS and sometimes KIT mutations,[61] while superficial spreading melanomas from intermittently sun-exposed areas often have BRAF mutations.[60] BRAF mutation occur in about 50% of melanomas overall, but are more frequent in the melanomas of younger patients. Approximately 80% of BRAF mutations are $BRAF^{V600E}$, while the $BRAF^{V600K}$ mutation occurs in approximately 19%.[62,65+a] While much less common, activating KIT mutations or amplifications in melanomas have also been identified, usually in mucosal or acral lentiginous primary melanomas (about 10-12% of melanomas from such sites).[63-65] These findings have important clinical implications for targeted therapy, as the clinical efficacy of inhibitors of mutant BRAF and KIT (in melanomas carrying these respective mutations) has been recently demonstrated.[63, 66-70]

Important issues for clinicians to consider when ordering melanoma mutation testing:

1. When should melanoma mutation testing be ordered?

At the present time, mutation testing is most appropriate for planning treatment in melanoma patients with advanced stage (unresectable AJCC stage III or AJCC stage IV) disease.

2. Which specimen should be tested (primary or metastasis)?

At the current time, only limited data are available regarding the concordance of BRAF and NRAS mutation status between primary and metastatic melanomas from individual patients. In one recent study, the concordance rates ranged from 75% to 96% in metastases from different locations.[71] We therefore recommend testing of the most recent distant metastatic melanoma specimen. If this is not available, locoregional/in-transit metastases are preferred to the primary melanoma. Mutation testing of the primary tumour could potentially result in a falsely positive BRAF test if BRAF-mutant naevus cells are admixed with the melanoma in the analysed tissue (approximately 80% of melanocytic nevi harbour BRAF mutations[72]).

3. What type of tissue is required for mutation testing?

Mutation testing can be performed on routinely collected archival formalin-fixed, paraffin-embedded tissue. It can also be performed on fresh tissue, but this is not essential. Specimens containing a high percentage of tumour cells are the most suitable (sentinel lymph node containing micrometastases admixed with numerous lymphocytes are often unsatisfactory). Core biopsies and cell blocks made from fine-needle biopsy cytology specimens also often yield diagnostic results.

4. What information does the pathologist require from the clinician?

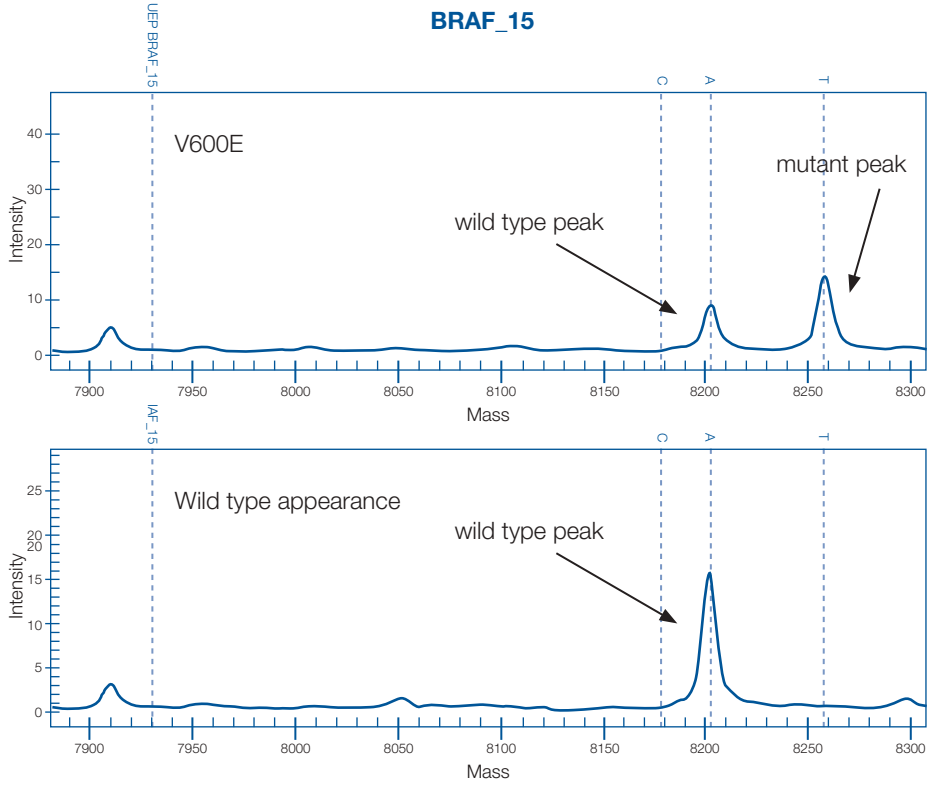
To enable the most efficient and timely testing, it is helpful if the pathology department is provided with the accession number of the specimen to be tested and the name and location of the laboratory in which the tissue is stored, along with a copy of the histopathology report of the specimen.

5. Which techniques for mutation testing?

There are various methods currently available for mutation testing. The ideal assay should be highly sensitive, simultaneously test all clinically relevant genes, cover all relevant mutations in each gene, be cost effective, allow high throughput, work well on small biopsies and formalin-fixed, paraffin-embedded tissue, and provide fast turnaround times/results. The sensitivity of the mutation test includes both its technical sensitivity (the minimum percentage of mutant tumour cells that can be detected as a positive test) and diagnostic sensitivity/comprehensiveness of the test (some assays will detect common targeted mutations only, while others will detect all mutations, including rare mutations of unknown significance).

Mutation testing assays include traditional Sanger sequencing, allele-specific reverse transcriptase-polymerase chain reaction (RT-PCR), pyrosequencing and mass spectroscopy/multiplex assays (eg. Sequenom) (Figure 3). Each of these techniques has some advantages and disadvantages, and as a consequence no one method is ideal. Sanger sequencing has traditionally been considered the gold standard (usually supplemented by pre-screening with high resolution melting curve analysis to select only abnormal specimens for sequencing). While it detects all known and new mutations (ie. it is comprehensive), it has only moderate technical sensitivity (about 25%) and is labour-intensive and slow. Allele-specific RT-PCR tests (eg. the Roche cobas 4800 BRAF V600 mutation test) offer high sensitivity but will only detect known targeted mutations. For example, the Roche cobas test was designed to detect $BRAF^{V600E}$ mutations

Figure 3: *Results from a Sequenom mass array analysis showing peaks identifying the presence of BRAF^{V600E} mutant melanoma (upper panel) contrasting with the presence of only BRAF wild-type cells in a different melanoma specimen (lower panel).*

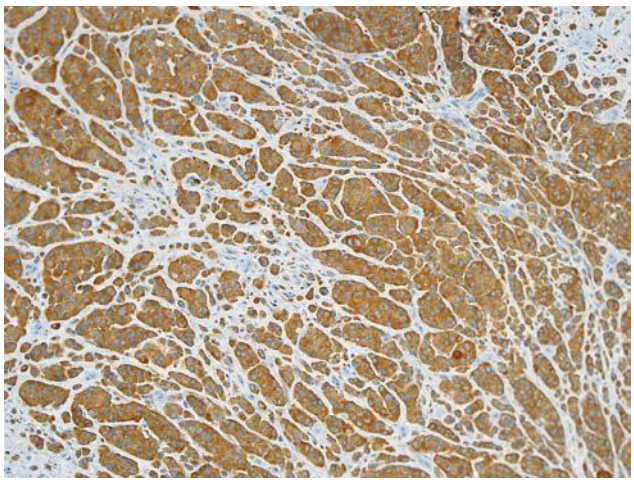


and does not detect all other BRAF mutations (including a significant proportion of BRAF^{V600K} mutations). This may have important clinical consequences, particularly in Australia, where BRAF^{V600K} mutations occur in 19-30% of BRAF mutant melanomas.[62,73] It is therefore important that oncologists understand the methodology and limitations of various mutation testing methods. Pyrosequencing and mass spectroscopy assays offer high sensivity and the ability to test for the presence of a range of mutations in a single test.

Immunohistochemistry (IHC) may also be used for molecular testing (figure 4). Recent studies showed correlation of IHC expression of the BRAF^{V600E}-specific antibody VE1 with the presence of the BRAF^{V600E} mutation in 97% of cases.[74] However, there was some intra-tumoural heterogeneity in VE1 expression,[74] implying that the diagnostic accuracy of IHC might be affected by the region(s) and size of the tumour sampled for testing. Variable results have been obtained in studies correlating IHC for KIT with KIT mutation status.[61,75] Additional studies are required to determine whether IHC (allied with morphological assessment) can be a useful technique for mutation testing, or for stratifying tumours into high and low likelihood groups (the former undergoing confirmatory mutation testing using other methods) for harbouring specific mutations.

There are a number of limitations to traditional mutation testing techniques. Most provide limited technical sensitivity (which can be a problem for specimens with a low percentage of tumour cells), and many do not cover all mutations of interest. There is also an increasing need for information about multiple genes and it would not be feasible to perform sequential mutation tests on small biopsies with limited DNA, which would also inevitably increase costs and turnaround times. Massively parallel (so-called 'next-generation') sequencing is a recently developed technique that combines the advantages of high technical sensitivity and comprehensiveness. It enables full sequencing of many genes in a single test.

Figure 4: *: Immunohistochemical stain with BRAF^{V600E}-specific antibody VE1. All melanoma cells are strongly positive. Recent studies have shown that this stain is highly sensitive and specific for the detection of BRAF^{V600E} melanoma.*



However, significant challenges remain to be overcome before its implementation into clinical practice, including infrastructure costs, interpretation of data, bioinfomatic support and overall cost.[76-78] Despite these issues, there is already great optimism that these challenges will be overcome and that next-generation sequencing will be routinely used in clinical practice in the very near future.

Conclusion

New genetic alterations in melanoma are being discovered at an increasing rate. Following functional validation some of these genes, their protein products and the cellular pathways in which they are involved could serve as potential targets for the development of novel therapies. The role of pathology in melanoma will continue to evolve as our knowledge of the molecular pathogenesis of melanoma evolves. Pathologists will play key roles not only in the histological assessment of primary and metastatic tumours (pre- and post-treatment), but also in the triage and selection of appropriate tumour tissue and tumour cells for clinical testing for various molecular markers, and in the correlation of clinical, pathological and molecular findings in research studies.

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NEW SYSTEMIC THERAPIES FOR METASTATIC MELANOMA – MAPK INHIBITORS AND IMMUNOTHERAPY

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Abstract

Metastatic melanoma has a poor prognosis and until recently systemic therapy was ineffective. Advances in the understanding of tumour biology and immune regulation have led to the development of targeted agents that have changed clinical practice. BRAF and MEK inhibitors target the constitutively active MAPK growth-signalling pathway in BRAF-mutant melanoma. They have a rapid mode of action, cause tumour regression in most patients, and offer improved survival compared with conventional chemotherapy. However, the near-universal and quite rapid development of acquired resistance is a major concern. Drugs targeting T cell regulation also show promise, with the anti-CTLA-4 antibody ipilimumab demonstrating a durable clinical benefit in a minority of patients but an overall survival advantage over conventional chemotherapy, while the emerging anti-PD-1 and anti-PD-L1 antibodies look likely to improve response rates with less toxicity. Trials of combinations of these therapies and new drugs targeting other molecular aberrations are under way, as are efforts to understand the mechanisms behind drug resistance.

Melanoma is increasing in incidence, and while it is curable in the majority of early stage cases, visceral metastatic disease carries an extremely poor prognosis. Until recently, systemic treatments were largely ineffective, with response rates of less than 10% and median overall survival times of only six to nine months.[1] The last few years have witnessed a revolution in systemic treatment, founded upon a rapidly evolving understanding of tumour biology and immune physiology, providing significant improvements in outcomes for patients with metastatic melanoma. Central to this process has been the discovery of specific driver oncogenes that exist in a large proportion of melanoma patients, as well as an improved understanding of the processes involved in immune regulation. Several targeted drugs have recently been shown to be more effective than previous systemic regimens, but while these have rapidly entered routine clinical practice, a large number of trials are under way, designed to build on the early success of these therapies.

Molecular pathways and therapeutic targets

Advances in the understanding of molecular biology have identified complex intracellular signalling pathways that control cell proliferation, survival, differentiation, motility and angiogenesis. One such pathway critical to most cancers is the mitogen-activated protein kinase (MAPK) pathway (figure 1). This pathway is dysregulated and overactive in melanoma as a result of molecular alterations in genes encoding key components of the pathway (eg. BRAF and NRAS mutations) or upstream alterations in cell-surface receptors (eg. KIT), resulting in uncontrolled tumour proliferation and survival.[2,3]

Mutations in BRAF occur in approximately 50% of melanomas.[4,5] Mutations generally occur at codon 600 in exon 15 of the BRAF gene, with 75% being V600E and 20% V600K.[5] Age is the best correlate of BRAF status, being inversely proportional to BRAF-mutant status.[5] While other clinical correlates exist such as tumour histological subtype, primary melanoma site and chronic sun damage,[6] BRAF-mutant melanoma is thought to carry a poor prognosis compared with BRAF wild-type disease once metastatic spread has occurred.[6]

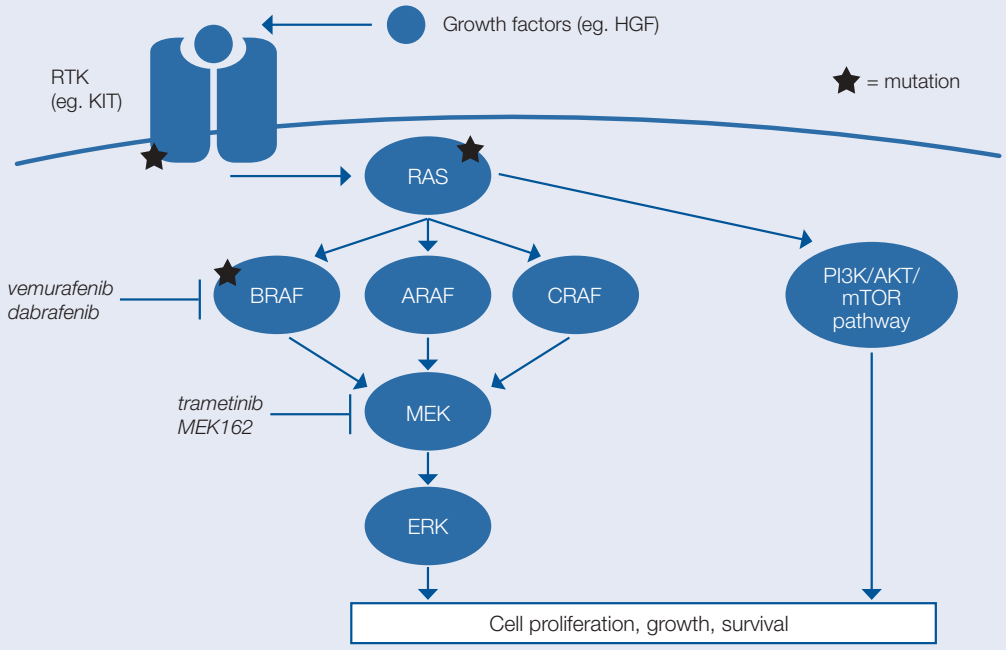
NRAS and KIT mutations are less common (20% and <5% respectively). No clinical correlates exist for NRAS-mutant melanoma, however KIT mutations occur more commonly in acral and mucosal melanomas, and NRAS-mutant melanoma may have a poorer survival after diagnosis of metastatic disease than BRAF-mutant or BRAF/NRAS wild-type disease.[4]

Several other pathways exist and are often abnormal in melanoma, such as the PI3K, Wnt and NF-κB pathways, however to date most interest has focused on the MAPK pathway.

BRAF inhibitors

Initial attempts to target mutant BRAF were unsuccessful. Sorafenib, a multi-kinase inhibitor, was trialled because of its known activity against RAF kinases. Phase 2 clinical trials failed to show significant efficacy, with pharmacodynamic analyses suggesting that only partial inhibition of BRAF signalling was achieved at maximum tolerated dose.[7,8] The selective BRAF inhibitors vemurafenib (PLX4032) and dabrafenib (GSK2118436) were designed to specifically inhibit mutant BRAF over other RAF kinases, enabling higher concentrations of drug to be administered without approaching the maximum tolerated dose, resulting in more complete inhibition of BRAF kinase activity.[9,10] The result of this has been an unprecedented improvement in clinical outcome for patients. However, specific toxicities have emerged, notably cutaneous squamous cell carcinoma.

Figure 1: *The MAPK pathway and BRAF and MEK inhibitors. In normal cells, growth factors bind to cell surface receptor tyrosine kinases (RTK), triggering signalling down various pathways, including the RAS-RAF-MEK-ERK (MAPK) and PI3K/AKT/mTOR pathways, resulting in cell proliferation, growth and survival. Specific aberrations in melanomas affecting the MAPK pathway include BRAF (50%), NRAS (20%) and KIT (<5%) mutations*



Vemurafenib, the first selective BRAF inhibitor, was developed with a companion PCR-based BRAF diagnostic test designed to detect the V600E BRAF mutation. Clinical trials in V600E BRAF-mutant patients demonstrated high activity, a rapid mode of action and a significant clinical benefit.[11,12] A small number of V600K patients were retrospectively identified and were also shown to have had benefit, and recent case reports suggest activity in all V600 BRAF-mutant melanomas. Initial results from a phase 3 trial were reported in 2011,[13] and recently more mature data have been presented.[14] When used as first line therapy in V600E BRAF-mutant metastatic melanoma, vemurafenib had a response rate of 53%, a median progression-free survival (PFS) of 6.9 months and a median overall survival of 13.6 months, much higher than conventional dacarbazine chemotherapy. Vemurafenib was approved by the Australian Therapeutic Goods Association in mid 2012. A phase 1 study in patients with brain metastases has shown intracranial activity,[15] and a phase 2 study in such patients is underway.

Dabrafenib, the second BRAF inhibitor to be developed, underwent phase 1 trials in V600E/K/D and K601E BRAF-mutant melanoma,[10] and phase 2 trials in V600E/K melanoma.[16] As with vemurafenib, initial results were impressive. Dabrafenib was shown to be highly active, but more so in V600E than V600K patients, and no activity was seen in patients with non-V600 tumours. Early analysis of the first line phase 3 study in V600E patients reported a response rate of 53%, and median PFS of 5.1 months.[17] Overall survival data are not mature. A phase 2 study in patients with V600E/K melanoma with brain metastases has recently been completed, demonstrating unprecedented activity and benefit in patients with untreated, and previously treated but relapsed, brain metastases, with response rates of 30-40%, a median PFS of 16 weeks and a median overall survival of 33 weeks in V600E patients.[18]

At this stage it appears that vemurafenib and dabrafenib share similar efficacy, but have different toxicity profiles. Class-like cutaneous toxicities, including rash, hyperkeratosis, cutaneous squamous cell carcinoma and keratoacanthoma occur with both drugs, but to a lesser degree with dabrafenib. Of note, cutaneous squamous cell carcinomas occurred in 19% of patients treated with vemurafenib,[13] and in only 5% of those treated with dabrafenib.[17] Other class toxicities such as arthralgia and fatigue also appear to occur at a higher rate and grade with vemurafenib. Drug-specific toxicities include photosensitivity and hepatitis (10% grade 3) with vemurafenib,[13] and pyrexia (3% grade 3) with dabrafenib.[17] Despite these toxicities, both drugs are generally well tolerated, with mild and manageable side-effects that rarely lead to drug discontinuation. A small number of patients on either drug have developed new primary melanomas, with studies ongoing as to whether this is an iatrogenic phenomenon.[19]

Most patients treated with BRAF inhibitors receive only brief benefit (a few months) due to the rapid development of acquired resistance. Much attention is currently focused on the specific mechanisms behind this. Based upon biopsies of progressing lesions from patients, it appears that 'MAPK reactivation' occurs in the majority. This is due to amplification and splice variation,[20,21] of BRAF, RAF isoform switching,[22,23] as well as new mutations in NRAS,[24] MEK,[25] and overexpression of COT (a partner kinase).[26] A minority of cases do not demonstrate MAPK reactivation,

but show increased signalling through other pathways (such as the PI3K pathway), apparently as a result of increased expression of growth factor receptors such as IGF-1R and PDGFRB.[22,24] To date, it appears that no single mechanism predominates, but that changes to the drug-binding site in the BRAF protein do not occur, as is the common mechanism of acquired resistance with other targeted therapies.[27,28]

MEK inhibitors

MEK inhibitors began development prior to BRAF inhibitors, the objective being to inhibit MAPK signalling at a downstream level. They were initially trialed in melanoma patients without knowledge of their BRAF (or NRAS) status with limited effect. Recently, trials have been conducted in BRAF-mutant and NRAS-mutant melanoma patients with impressive results.

Trametinib is the most studied MEK inhibitor in melanoma. A phase I trial in all BRAF-mutant and wild-type patients demonstrated significant activity in BRAF-mutant melanoma, with little activity in BRAF wild-type disease.[29] A phase 2 study in patients with or without prior BRAF inhibitor therapy demonstrated no response when given after BRAF inhibitor failure.[30] Initial reports from a recent phase 3 trial showed a response rate of 22% and a median PFS of 4.8 months. Overall survival data were immature, but currently the hazard ratio for progression or death is 0.54 when compared with chemotherapy (dacarbazine or paclitaxel).[31] Toxicity included MEK inhibitor class-like effects such as rash (including acneiform rash), hypertension, diarrhoea, oedema, transient mild cardiac dysfunction, as well as rare ocular toxicity (chorioretinopathy) and creatine kinase elevation. Most toxicities were mild and did not require drug discontinuation.

MEK162 has recently completed a phase 2 trial, examining activity in both BRAF-mutant and NRAS-mutant melanoma.[32] In BRAF-mutant melanoma patients (N=25), including 20% with prior BRAF inhibitor therapy, a response rate of 23% and median PFS of 3.5 months were seen. Among NRAS-mutant melanoma patients (N=28), a response rate of 21% and median PFS of 3.6 months were reported. Adverse events were similar to those associated with trametinib, but higher rates of grade 3 creatine kinase elevation and diarrhoea were seen, and less hypertension and cardiac dysfunction occurred.

Combination BRAF and MEK inhibitors

BRAF, and to a lesser extent MEK inhibitors, provide high initial efficacy, but the near-universal development of acquired resistance is often rapid. In order to further improve response rates and delay resistance, new approaches have been explored, such as combining therapies. The first attempt to do this was with the combination of dabrafenib and trametinib. The rationale behind this approach was based upon the individual activity and different toxicity profile of the two drugs. Furthermore, since both drugs target the MAPK pathway, and because BRAF inhibitor resistance generally results in reactivation of the pathway, it was postulated that combined blockade might suppress resistance. Finally, it was thought that combining the two drugs might reduce the toxicities of each drug when given individually (especially cutaneous toxicity from BRAF inhibitors).

Table 1: *Summary of BRAF and MEK Inhibitors.*

	vemurafenib[13,14] %	**vemurafenib[13,14] %**	**trametinib[31] %**	**dabrafenib + trametinib[35] %**
Outcome				
RR	57	53	22	63
DCR	97	95	78	100
PFS	6.9 mo	5.1 mo	4.8 mo	10.8 mo
OS	13.6 mo	-	-	-
Toxicity (G3/4)				
cutaneous squamous cell carcinoma	19	5	-	3
keratoacanthoma	10	2	-	-
hyperkeratosis	1	3	-	-
rash	9	-	9	2
other	hepatitis 10	fever 3	HTN 12 cardiac 7 ocular 1	fever 8

Outcome measures and grade 3/4 toxicities with BRAF and MEK inhibitors. RR, response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; HTN, hypertension.

NB. Only vemurafenib has mature outcome data at this stage.

An early analysis of data from the phase 1/2 trial of combination therapy was presented in 2011. A higher response rate was reported than that achieved with BRAF inhibitor monotherapy,[33] and an impressive 19% response rate was seen in those who had failed prior BRAF inhibitor therapy.[34] In BRAF inhibitor naïve patients a response rate of 63% and a median PFS of 10.8 months were recently reported.[35] Toxicities with this combination were mild. Notably, cutaneous toxicities such as hyperkeratosis, cutaneous squamous cell carcinoma, and keratoacanthoma seen with dabrafenib, and rash, hypertension, cardiac dysfunction seen with trametinib were greatly reduced (table 1). The most common toxicity was fever (8% grade 3), significantly more frequent than with dabrafenib monotherapy. The process behind this is incompletely understood, but it generally occurs early, is rarely repetitive, can be managed with brief dose interruption and corticosteroid prophylaxis (in recurrent cases), and does not necessitate dose reduction.[36] Furthermore, it does not appear to be related to disease burden or treatment response.[36] A phase 3 trial of the combination dabrafenib and trametinib versus dabrafenib monotherapy is underway (NCT01584648).

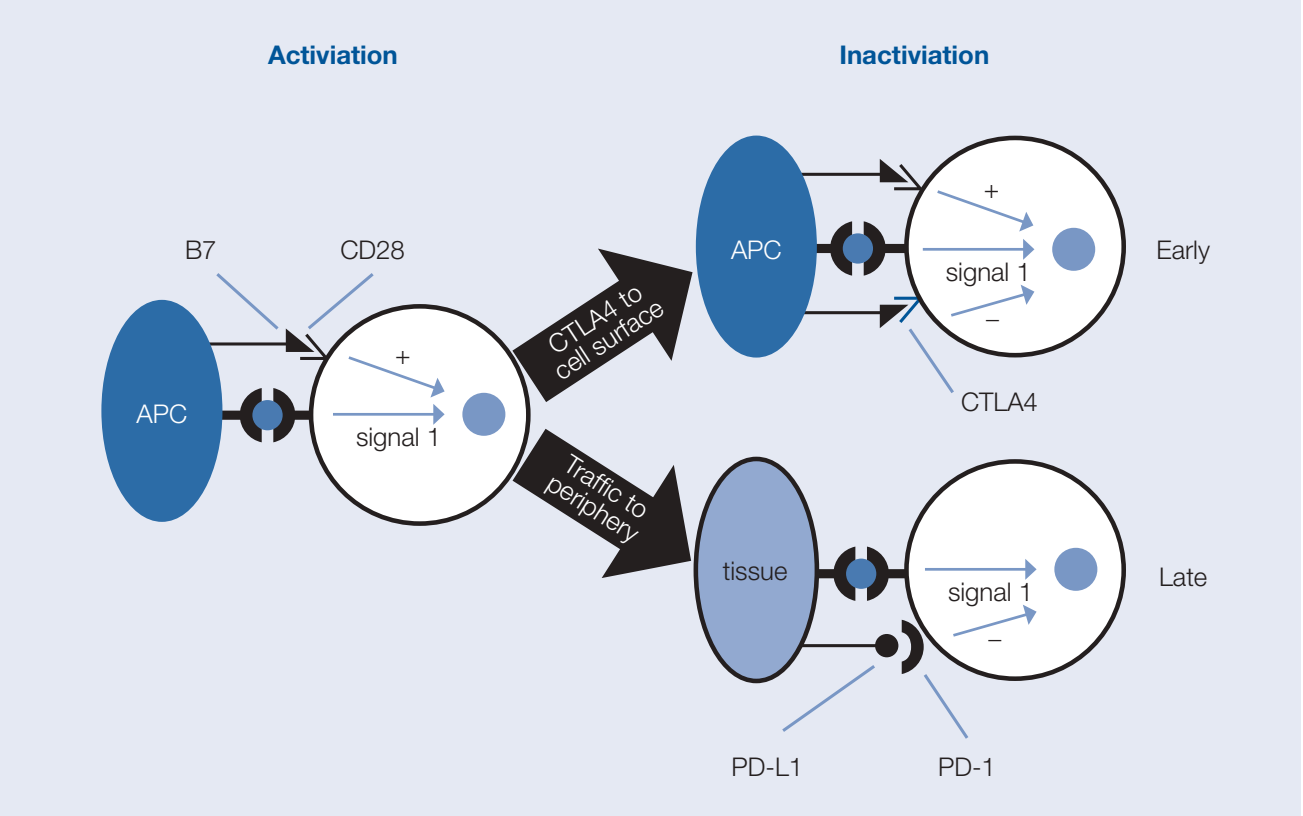
Immune regulation and drug targets

Immunotherapy has a long and generally disappointing history in melanoma, but no doubt remains a critical component of treatment. To date, immunotherapy for metastatic disease has been largely limited to a few centres worldwide. IL-2 and adoptive T cell therapy provide durable responses in a small subset of patients, but these therapies are highly toxic and not feasible for the wider melanoma population. Recent advances in the understanding of T cell regulation and the development of specific agents that target critical components of this have proven successful.

Regulation of the immune system is highly complex. T cells express numerous receptors on their surface that interact with antigen presenting cells (APCs), leading to T cell activation and inactivation. T cell activation occurs via two steps: 1) APCs present antigens (eg. tumour antigens) to the T cell receptor; 2) APCs express B7 which interacts with the T cell CD28 receptor. This co-stimulation is required for T cell activation (figure 2).[37]

Once activated, T cells are inactivated in a number of ways in order to prevent widespread autoimmunity. One process of inactivation that occurs early involves expression of the CTLA-4 receptor on the T cell surface, which binds to B7 on APCs and results in an inhibitory signal to the T cell. In peripheral tissues (such as tumours) at sites of inflammation, T cells express PD-1, which binds to PD-L1 expressed by tissue leading to inactivation and protection of tissues from collateral damage. CTLA-4 is therefore important early in the immune response and interacts with APCs, whereas PD-1 is more specific for peripheral tissues and can interact with tissue directly. Inhibition of CTLA-4 or PD-1 can therefore promote anti-tumour immunity.[37]

Figure 2: *T cell regulation. CTLA-4 modulates the early phase of T cell activation. PD-1 is expressed on T cells in the periphery, serving to limit the activity of T cells during an inflammatory response, thereby protecting normal tissues from collateral destruction. APC, antigen presenting cell. Adapted from Topalian Current Opin Immonol. 2012*



Ipilimumab

Ipilimumab is the first immune therapy shown to improve overall survival in a large group of metastatic melanoma patients. It is an anti CTLA-4 antibody that binds to and inhibits the CTLA-4 T cell receptor, resulting in sustained but non-specific T cell activation. Two phase 3 clinical trials have now been completed. The response rate in the first line combination trial (with dacarbazine v dacarbazine alone),[38] and the second line trial (Ipilimumab v Ipilimumab + gp100 vaccine v gp100 alone),[39] was approximately 11-15%, with median PFS 2.8 months, and median overall survival 10-11 months. One and two year survival was 47% and 26%, approximately a 10% increase over the control arms. Results from these trials suggest that ipilimumab has a slow onset but durable response and survival advantage in a subset of patients, but as yet a biomarker of response has not been identified. Activity has also been demonstrated in patients with small asymptomatic brain metastases.[40] Ipilimumab received TGA approval in Australia as second line treatment in mid-2011.

Toxicities from ipilimumab, as expected, are immune related and include cutaneous gastrointestinal, and endocrine toxicities. Early detection and intervention of toxicities is essential as some are potentially life threatening, and early intervention is necessary. Most, however, respond to corticosteroids and may not preclude further dosing.

Anti-PD-1 and anti-PD-L1 antibodies

This new class of immune agents aims to augment the anti-tumour T cell response at a more tumour-specific level, by blocking the interaction of PD-1 and PD-L1, preventing T cell inactivation at a tumoural level. Multiple anti-PD-1 antibodies are in development, and two phase I trials have reported activity in melanoma thus far. The first-in-class phase I trial of BMS-936558, including 94 melanoma patients, reported a 28% response rate, with 20 of 31 patients having an ongoing response for over one year.[41] The phase 1 trial of MK-3475 included two patients with melanoma, one of whom achieved a partial response.[42] In the BMS-396558 study, no responses were seen in those whose tumours did not express PD-L1, suggesting that this may be a predictive biomarker. Toxicity with both agents was immunological, affecting skin, gastrointestinal and endocrine systems, but appeared to be less frequent and severe than that with ipilimumab, possibly indicating the more tumour-specific nature of this therapy.

Anti-PD-L1 antibodies are also in development, again designed to block PD-1/PD-L1 interaction, thus preventing T cell inactivation. The first-in-class phase 1 trial of BMS-936559 including 52 patients with melanoma demonstrated a response rate of 17%, with 8 of 16 patients having an ongoing response for over one year.[43] Again, toxicity was generally mild and manageable.

Next steps

While MAPK inhibitors and new immunotherapies appear vastly superior to previous chemotherapy regimens, they all have limitations. BRAF and MEK inhibitors provide responses in the majority of patients, but their benefit is often brief. Immune therapies provide slower, more durable responses but in a largely unidentifiable minority of patients. Based on this fact alone, it appears logical to combine MAPK and immune therapies (such as vemurafenib and ipilimumab). Translational evidence for this approach is robust, with evidence that BRAF inhibition leads to increased expression of melanoma differentiation antigens, and an influx of tumour infiltrating lymphocytes.[44,45] Such trials (eg. of vemurafenib and ipilimumab) have commenced and results are eagerly anticipated. Trials of other combinations have also begun, shaped by research into BRAF inhibitor resistance mechanisms, targeting other cell signalling pathways (eg. BRAF and PI3K inhibitors).

Perhaps the greatest role for these new treatments will be in the adjuvant setting. Currently the risk of distant relapse and death in patients with high-risk early stage melanoma (IIC/III) is approximately 50%.[46] Adjuvant trials of vemurafenib (NCT01667419) and the combination dabrafenib and trametinib (NCT01682083) will commence shortly, while the results from an adjuvant ipilimumab trial (NCT00636168) are expected in 2013.

Conclusion

While results of recent clinical trials of MAPK and immunotherapy agents have been impressive, resulting in a seismic shift in the management of patients with metastatic melanoma, improvements are required to build upon the early success of these therapies. Adjuvant trials of many of these drugs are under way with the hope of improving cure rates for early melanoma, and as more molecular targets are identified and trials of combinations of targeted drugs commence, improvements in patient outcomes can be expected. The systemic management of metastatic melanoma has come a long way in a short time, but there is still a long way to go.

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MANAGEMENT OF LOCO-REGIONALLY RECURRENT MELANOMA

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Abstract

Loco-regionally recurrent melanoma encompasses local recurrence (usually defined as being within 2cm of the primary tumour site), in-transit recurrence and regional lymph node recurrence. Survival in patients with loco-regional recurrence is considerably reduced compared with survival in patients without recurrence. The most appropriate treatment of loco-recurrence varies according to presentation. Local recurrence is best treated by surgical excision. In-transit recurrence is also treated by excision when possible, but may involve other forms of treatment, such as topical therapy (with dyphencyprone cream) or intra-tumoural injection therapy (eg. with Rose Bengal). For unresectable local and in-transit recurrence, regional limb chemotherapy (isolated limb perfusion or isolated limb infusion) remains the standard of care. When regional limb chemotherapy is not possible or has failed, alternative treatment options that are sometimes effective include topical therapy, intra-tumoural injection therapy or external beam radiation therapy. Rarely, amputation may need to be considered for in-transit disease confined to a limb when all other options have been exhausted. Regional lymph node recurrence is managed primarily by surgical resection involving formal lymphadenectomy of the neck, axilla or groin. For metastatic melanoma in the axilla a complete level I-III dissection is standard treatment. However, the extent of groin and neck lymphadenectomy for metastatic disease in these sites may vary. Currently, sub-inguinal ('superficial') lymph node dissection is often recommended for patients with palpable groin recurrence, but there is evidence suggesting that an ilio-inguinal dissection may be a safer alternative. Iliac dissection is required for clinically involved pelvic lymph nodes. For metastatic disease in cervical nodes, a full level I to V neck dissection is standard, but selective neck dissection with adjuvant radiation therapy may be an alternative. Post-operative radiation therapy improves regional recurrence-free survival for patients with resected high-risk stage III melanoma. Systemic therapy for loco-regional recurrence is the subject of ongoing research. The only currently approved adjuvant therapy for stage III melanoma is interferon-alpha. Newer agents under investigation include vaccines, ipilumimab and inhibitors of the BRAF pathway.

Loco-regionally recurrent melanoma refers to melanoma that has recurred between the primary site and the regional lymph nodes, following previous excision of a primary tumour. Five-year survival from melanoma is as high as 96% if it is diagnosed early, when the disease is localised to the primary site.[1] However, all patients are at risk for the development of local and/or regional recurrence. If loco-regional recurrence does occur, survival is dramatically reduced.[2]

Recurrence may occur in up to 36% of patients with American Joint Committee for Cancer (AJCC) stage I or II melanomas, of which loco-regional recurrence represents 63% to 87%. Sixty-five percent of recurrences occur within the first three years of follow-up. Patients with local or regional recurrence have a better prognosis than patients who relapse at systemic sites: five-year survival is 55% following local recurrence; 51% following regional node recurrence; and at best 20% following systemic recurrence.[2,3] Loco-regional recurrence is influenced by known primary tumour prognostic factors including Breslow thickness, ulceration, mitotic rate and the presence of lymphovascular or perineural invasion.[4,5,6]

The need for adequate management of loco-regional recurrence is of great importance if loco-regional relapse-free survival and melanoma-specific survival are to be improved. Asymptomatic AJCC stage IV disease may be found in up to 20% of patients presenting with loco-regional recurrence. These patients should undergo complete staging with whole body CT and/or FDG-PET scans, and should ideally be managed by a multidisciplinary team of clinicians.[7]

Local recurrence

A local recurrence of melanoma is usually defined as a tumour appearing in the skin or subcutaneous tissue within 2cm of the wide local excision site (although many would regard any recurrence clearly separated from the wide excision scar as an in-transit recurrence). For invasive melanomas of any thickness, randomised clinical trials and large cohort studies of excision margins have demonstrated local recurrence rates of 1-3% when a wide excision margin of at least 1cm has been obtained.[6,8]

The standard treatment of local and in-transit metastases is surgical resection with histologically negative margins. There is no randomised clinical trials evidence that wide margins of excision result in better outcomes for patients with local or in-transit recurrence, however for true local recurrence a margin of at least 1cm is sometimes suggested, including the previous primary excision scar. Sentinel lymph node biopsy has been proposed at the time of resection of a local recurrence for staging, but efficacy data are lacking.[9,10]

For unresectable loco-regional recurrence, treatment options include regional chemotherapy, intra-lesional chemoablation, radiation therapy and topical immunotherapy (see below for in-transit recurrence).[9,11]

In-transit melanoma recurrence

In-transit metastases appear as the initial site of recurrence in 2-31% of patients after primary treatment of melanoma. This is dependent on the initial stage of the melanoma and is more common among patients with a lower extremity primary tumour.[12,13,14] In-transit melanoma is thought to represent lymphatic metastatic spread, which manifests as cutaneous or subcutaneous tumour nodules located between the primary site and the regional lymph node field.

Limited in-transit disease may be treated adequately by surgical excision. The goal is complete excision of all lesions with clear histological margins. Wide excision and deforming surgery are not recommended. Unfortunately, recurrence of in-transit disease is common and patients should undergo close surveillance.[9]

For unresectable in-transit disease a number of treatment options are available. These include chemoablation, topical agents, infusional therapy and radiation therapy. Direct therapies include diathermy, cryotherapy and CO2 laser ablation. Ablation by intra-lesional injection of several compounds, including Bacille Calmette-Guerin has been reported.[15,16] Analysis of 15 non-controlled trials of intralesional Bacille Calmette-Guerin injections in patients with metastatic melanoma revealed complete responses in 19% and partial responses in 26%.[15] Cutaneous metastases have a response rate >80% in several reports. Subcutaneous metastases, however, are more resistant, with <20% responding to therapy.[15]

Recently, the use of PV10TM (Rose Bengal; Provectus Pharmaceuticals), a water-soluble xanthine dye, has been explored as an agent for the local control of melanoma metastases by intralesional injection. The efficacy of PV10 was investigated in a phase II trial, and demonstrated a 25% complete response rate and a 25% partial response rate among treated patients.[16,17,18] For more extensive disease, intralesional PV10 followed by external beam radiotherapy has been reported to provide effective local control with acceptable toxicity.[19]

Diphencyprone (DPCP) is a potent topical contact sensitiser that has most frequently been used as immunotherapy for cutaneous warts and alopecia areata.[20] Previously, topical DPCP has been combined with oral cimetidine or dacarbazine and radiotherapy to treat cutaneous melanoma metastases.[21,22] DPCP therapy involves the deliberate elicitation of contact hypersensitivity dermatitis at areas of recurrence or in-transit metastasis; the mechanism of action is presumed to be promotion of lymphocyte-mediated tumour destruction.[23,24] DPCP has been shown to be active in cutaneous in-transit melanoma, with >50% of patients showing complete tumour clearance, and another third of patients having slowing or partial clearance of their disease.[25] It represents an effective treatment option for head, neck and trunk disease, as well as low volume dermal limb disease.

Radiation therapy has also been shown to be of benefit in the treatment of unresectable in-transit melanoma.[26] Approximately 25% of palliatively irradiated melanoma in-transit metastases respond completely to treatment, and another 33% respond substantially. Small-volume macroscopic tumours may be controlled by radiation therapy where other treatment options have failed.[26,27] However, radiation therapy should be administered below the knee with caution.

Isolated limb infusion and perfusion

Regional limb chemotherapy with vascular isolation is the standard of care for extensive unresectable local or in-transit melanoma confined to a limb. Isolated limb perfusion (ILP) has a long track record in the treatment of cutaneous melanoma and is still widely used.[9,28] ILP is performed by cannulation of the major extremity artery and vein, with hyperthermic (40-42°C degree) perfusion of the limb for 60-90 minutes using a pump oxygenator. It is an effective treatment delivering high-dose cytotoxic chemotherapy, usually melphalan, regionally to the affected limb, with minimal risk of serious systemic toxicity. Overall response rates are 80%, with complete response rates of 40-60%. However, responses may be of limited duration, with most patients experiencing recurrence within 12-18 months. Survival correlates with response: five-year survival for non-responders is <7% while for complete responders survival approaches 50%.[28] Repeat perfusion can be considered for patients who recur following an initial response, and is often effective.

Isolated limb infusion (ILI) was first reported by Thompson et al from the Sydney Melanoma Unit in 1994 as a less invasive alternative to ILP.[29] Catheters are inserted percutaneously, and melphalan, with or without actinomycin D, is circulated manually with a syringe via a three-way tap after vascular isolation of the extremity with a tourniquet (which determines the proximal extent of treatment). Outcomes for ILI have been shown to be similar to those for ILP, with the Sydney Melanoma Unit reporting a 38% complete response rate and a complication rate similar to that of ILP.[30]

Complications of both ILP or ILI can be significant, with localised effects including compartment syndrome, neuropathy, skin reaction, blistering and lymphoedema.[31] Some patients may require simple excision of in-transit disease proximal to the tourniquet after their ILI. In addition the patients must be fit for general anaesthesia.

Amputation for extensive in-transit recurrence may be a last resort for patients who have symptomatic localised disease and have failed other therapies.[32] At the Sydney Melanoma Unit, 6% of their total ILI-treated patients ultimately underwent amputation. Most of these patients suffered from deeply infiltrative lesions associated with severe pain or bleeding from ulcerated and necrotic lesions. Amputation of the affected limb resulted in effective symptom relief in all patients.[32] Five-year survival rates following amputation historically have been as high as 28%.[33]

Regional lymph node recurrence

Prior to the widespread implementation of sentinel lymph node biopsy, a minimally invasive procedure for identifying patients who harbour occult microscopic disease in regional lymph nodes,[34,35] regional lymph nodes were the most common initial site of recurrence. The risk of nodal recurrence for intermediate thickness melanomas (Breslow thickness 1-4mm) is 15-20% at five years.[36] With the introduction of sentinel lymph node biopsy regional recurrence rates are now <5%, however patients who have not undergone sentinel lymph node biopsy (and those with false-negative sentinel lymph node biopsy) may still present with lymph node recurrence.

Therapeutic lymph node dissection is the treatment of choice for both microscopic and macroscopic metastatic disease in regional lymph nodes, as complete resection offers the best chance of loco-regional control and survival for patients without metastatic disease at systemic sites. Nodal disease may present at an advanced stage with invasion/encasement of neurovascular structures or with ulceration through the skin. Care of these patients requires a team approach including general surgery, plastic surgery, vascular surgery and radiation oncology.

Axilla

Patients with metastatic lymph node disease in the axilla should undergo a complete (level I-III) axillary dissection. The goal is for removal of all lymph nodes, as surgical excision provides the best chance of cure. Surgical resection is curative in up to 50% of patients with palpable nodal disease.[37,38] Lymphoedema rates are <10% following a level I-III axillary dissection for melanoma. Recurrence within the surgical field may occur, the risk being determined by characteristics of the dissected lymph node field, such as the number of positive nodes and the presence of extracapsular spread. The prognosis following in-field recurrence is typically poor.[39]

Groin

A groin dissection is recommended for clinically palpable disease in the groin. Previously a 'radical' groin dissection (combined inguinal and pelvic lymph node dissection) including inguinal, iliac and obturator nodes, was often performed for metastatic melanoma in the groin. More recently, a trend has been seen towards a 'superficial' (inguinal only) node dissection in patients without evidence of disease above the level of the inguinal ligament on CT or PET/CT imaging.

However, these scans will not identify microscopic disease, and patients with metastases in sub-inguinal lymph nodes have a 20-30% chance of harbouring pelvic lymph node metastases. A positive Cloquet's node, four or more positive nodes on inguinal dissection, and palpable inguinal nodes are predictors of pelvic nodal status. Elective pelvic dissection may therefore be considered for selected patients when planning treatment.[40,41]

Inguinal lymph node dissection is associated with significant post-operative complications, including wound infection and seroma formation.[42] The addition of pelvic lymph node dissection is associated with somewhat higher rates of lymphoedema.[41]

Current decisions relating to the extent of lymph node dissection for AJCC stage III melanoma of the groin are largely institution based, with randomised trials required, but unlikely to be undertaken in the foreseeable future.

Neck

Although radical neck dissection has been the gold standard for metastatic melanoma in cervical nodes, modified radical neck dissection does not appear to compromise regional control in patients and allows preservation of the internal jugular vein, sterno-mastoid muscle and accessory nerve.[43] Radical neck dissection should routinely include levels II to V. Management of clinically apparent disease of the parotid gland should include a superficial parotidectomy, with neck dissection also indicated due to a 30% risk of occult neck node involvement.[44] Similarly, superficial parotidectomy should be considered with modified radical neck dissection where parotid nodes may be at risk, such as for primary lesions of the face and scalp. Most melanomas of the head and neck spread in a reasonably predictable manner based on the anatomical site of the primary melanoma. Knowledge of these patterns can be useful in limiting the extent of nodal dissection to those levels most at risk of metastatic disease (selective neck dissection). However, in the setting of clinically apparent nodal disease in the neck, selective node dissection may be associated with a higher recurrence rate than modified radical neck dissection.[45] Post-operative radiation therapy may help to reduce the risk of regional relapse after selective neck dissection.[45,46]

Radiation therapy

Following therapeutic lymph node dissection for regional lymph node recurrence, patients with extranodal spread of melanoma, an increased number of tumour-positive lymph nodes, and increasing size of involved nodes have a greater risk of recurrence in the operative field. Post-therapeutic lymph node dissection in-field recurrence can cause serious morbidity including pain, ulceration, malodour, lymphoedema and impaired function, as well as carrying a poor prognosis.

The results of a recent randomised controlled phase III intergroup trial conducted by the Australian and New Zealand Melanoma Trials Group and the Trans-Tasman Radiation Oncology Group demonstrated that adjuvant radiotherapy after nodal dissection for high risk patients substantially reduced the risk of further lymph-node field relapse (but with no significant effect on overall survival).[46] Adjuvant radiotherapy was associated with acceptable early toxicity. Lymph-node field relapse was predicted by extranodal spread of melanoma, increased number of tumour-positive lymph nodes, and increasing size of involved nodes.[46] Adjuvant radiation therapy should therefore be considered for patients with proven nodal metastases and a high risk of regional recurrence.[47,48,49]

For bulky, unresectable nodal disease, some studies have suggested a benefit with palliative radiation therapy. Quoted overall response rates are up to 84% for bulky disease,

with large fractions being beneficial. The median disease-free survival was seven months for those with inoperable disease, and the median overall survival 18 months.[50]

Adjuvant systemic therapy

Patients with AJCC stage III disease are at high risk of dying from melanoma, with <50% 10-year survival. These patients should be considered for adjuvant systemic therapy. The only drug with demonstrated efficacy as adjuvant therapy for high risk melanoma is interferon-α. Trials have shown that high-dose interferon improves progression-free survival by approximately 10% at five years. A recent meta-analysis of patients with high-risk cutaneous melanoma concluded that interferon-α2b adjuvant treatment resulted in small, but statistically significant improvements in both progression-free survival and overall survival.[51]

Patients with unresectable AJCC stage IIIc melanoma should be considered for systemic therapy. The current standard of care is dacarbazine, with response rates in the order of 10%. However, newer agents such as inhibitors of BRAF (for example vemurafinib) or the anti-CTLA4 antibody ipilumimab, have both shown significant improvements in survival compared with dacarbazine.[52,53] The utility of these newer agents as adjuvant therapy for resected stage III disease is the subject of ongoing clinical trials.

In summary, loco-regional recurrence of melanoma encompasses a wide clinical spectrum, ranging from easily resectable disease to the very difficult management problem of extensive in-transit and/or nodal disease. Treatment options vary for each individual, and are best addressed in a multi-disciplinary team setting where there can be discussion among relevant medical and surgical teams to develop an appropriate treatment plan for that patient.

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HORMONE REPLACEMENT THERAPY: THE NEED TO COMBINE CLINICAL AND EPIDEMIOLOGICAL DATA

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Abstract

In decision-making about the use of hormone replacement therapy, the risk/benefit analysis should encompass both clinical and epidemiological risk/benefit information. Many women benefit from the use of hormone replacement therapy to control the symptoms of menopause. However, there is evidence from observational studies and randomised trials of a temporal relationship between some hormone replacement therapy use and the risk of breast cancer. Both the Million Women Study and the Women's Health Initiative showed an increase in the risk of breast cancer, particularly with combined oestrogen and progestagen hormone replacement therapy, which increased with duration of use and was greater if the hormone replacement therapy commenced closer to menopause. They differ in the magnitude of risk and whether there is any increased risk of breast cancer with oestrogen-only hormone replacement therapy. The Million Women Study showed increased risks of endometrial and ovarian cancer with the use of unopposed oestrogens, while the Women's Health Initiative demonstrated an increased risk of lung cancer with combination hormone replacement therapy. Epidemiological studies show that the incidence of breast cancer falls in women over 50 years and older as hormone replacement therapy use reduces. The clinical translation of these results is that for women who require treatment for symptoms of menopause, the short-term use of unopposed oestreogens would be associated with the least risk of breast cancer (but non-hysterectomised women would have an increased risk of endometrial cancer).

It is important in practising evidence-based medicine that all of the evidence is considered and not selected evidence that may fit with a clinician's bias. However, varying types of evidence may need to be weighted differently to give an accurate picture when advising patients about the balance between potential risks and potential benefits of a proposed treatment. Such is the case with hormone replacement therapy (HRT), where clinical studies relate to the effect of treatments on individuals while epidemiological studies report risks and benefits to whole populations. Moreover, the data evolves over time. The aim of this paper is to present the risks and benefits of HRT when both of these data sources are considered. The focus will be the breast cancer risk as an example.

HRT is often prescribed for women whose quality of life is compromised by symptoms of menopause, and the introduction of hormonal therapy often results in significant symptom control. The clinical decision should however, be predicated on the benefits outweighing the risks. The 2004-2005 National Health Survey showed 11% of Australian women aged 45 years and over used HRT prescribed by a doctor, the majority (65%) for five years or more.[1] When population exposure is so widespread, safety is a paramount consideration.

HRT and breast cancer risk

There is now evidence from observational studies and randomised trials showing a temporal relationship between HRT use and breast cancer risk, which rises after initiation and declines after cessation of HRT. Risk increases with duration of use, with the effect consistent with our understanding of hormones in breast cancer biology. The effect was evident in the Million Women Study (MWS),[2] which analysed breast cancer risk factors and outcomes in 1,084,110 women in the UK between 1996 and 2001. It showed an increased breast cancer risk in women taking HRT, which was higher for those taking oestrogen and progestogen combinations than for women prescribed unopposed oestrogen therapy. The main reason for the use of unopposed oestrogen was to reduce the risk of endometrial cancer, which is greater with unopposed oestrogens as opposed to oestrogen/progestogen combinations. The breast cancer risk was higher in women with normal body weight and increased with duration of use.

The link between HRT and breast cancer was also demonstrated by the Women's Health Initiative (WHI),[3] a prospective control trial randomising 16,608 postmenopausal American women to HRT, comprising equine oestrogens and medroxyprogesterone acetate

or a placebo. The trial was stopped early (at 5.2 years of an intended 8.5 years) because of increased breast cancer incidence in the hormone arm, which also showed increased myocardial infarction and stroke, but decreased osteoporotic fractures and colorectal cancer (although they presented with more advanced disease). The WHI also randomised 10,739 postmenopausal women to oestrogen only or placebo, with the single hormone arm experiencing reduced rates of breast cancer, myocardial infarction (although these were not statistically significant) and osteoporosis, while the increase in thrombosis and stroke remained.

Further analyses of these studies show that some uncertainty remains. A re-examination of the WHI study suggests that if corrections are made for baseline differences in the groups and for multiple comparisons, since breast cancer is a secondary endpoint of the study, there is no increase in breast cancer, and it is suggested that the apparent increase in mortality may be due to a surveillance and detection bias. It is also suggested that the 11 year follow-up results show no increase in breast cancer in women who had not previously used HRT, which would be most in that study.[4] A more recent analysis of the MWS to explore the relationship between breast cancer risk and when the hormones were started in relationship to menopause, reaffirmed that in current users of hormonal therapy the incidence of breast cancer was greater if they started within five years of menopause, but returned to that of never users a few years after hormonal therapy ceased.[5] However, the relative risks of breast cancer were greater in current users if the use of HRT began at, or soon after menopause, compared to later for both oestrogen only and oestrogen-progestogen combinations. With oestrogen-only HRT there was no increased risk if use began five years or more after menopause.

The WHI parallels the finding that women who use oestrogen-progestogen therapy have a greater risk of breast cancer if they start within five years of menopause, however the magnitude was less than in the MWS.[6] In the WHI however, with oestrogen-only therapy, there was a similar timing effect, but there was no effect on breast cancer risk when oestrogen was started within five years of menopause. When started five years or more after menopause, the risk of breast cancer was reduced. There have been conflicting studies over the question of oestrogen-only HRT and the incidence of breast cancer. The European Prospective Investigation into Cancer and Nutrition and a study from Los Angeles County found that both oestrogen-only and combined menopausal hormone therapy users had an increased breast cancer risk, with continuous combined therapy being worse than sequential combined therapy.[7,8] Alternatively, studies from Washington State and Sweden found only the combined HRT was associated with an increased breast cancer risk, and not unopposed oestrogens.[9,10] The WHI, with a mean follow-up of just over seven years, shows no evidence of an increased risk of breast cancer in any group receiving unopposed oestrogens, although less evidence for deceased risk for those starting closer to menopause.[11]

Explaining divergent results

Although the design of the large MWS and the WHI are sufficiently different to make direct comparisons problematic, weight is added to the observations where the studies agree, but the explanation of divergent results is open for speculation. The authors of the MWS suggest that the difference in the risk of breast cancer with HRT between the studies stems from different risk factors. In the WHI, this means particularly obesity and the time of commencing HRT relative to the menopause.[5] Chlebowski et al, who wrote an editorial to accompany the update of the MWS, suggested that it was more likely that post menopausal breast cancer HRT recipients had more frequent mammographic screening than non-users and therefore had more breast cancers identified.[12,13] It has been previously reported that postmenopausal hormone therapy users have mammograms at more regular intervals than non-users and these identify more slow growing receptor-positive tumours that are diagnosed at an earlier stage.[14,15,16]

Chlebowski also cites prior mammography as a risk factor for subsequent breast cancer. In the WHI, the prior and subsequent mammographic screening in both arms was more tightly controlled than in the MWS.[17,18]

The MWS also reported that unopposed oestrogen use for more than five years increased ovarian and endometrial cancer risk,[19,20] while more recent studies attribute long-term HRT use to increased risk of cutaneous melanoma.[21] The WHI showed that women using combined oestrogen and progestogen had higher lung cancer mortality.[22] Also, an analysis of a group of 36,588 peri and postmenopausal women from the Vitamins and Lifestyle Study, found an increased risk of lung cancer associated with increasing duration of oestrogen plus progestin use.[23] The duration of use also correlated with advanced stage at diagnosis, with an approximate 50% increase with HRT use of 10 years or longer. The association with lung cancer was not seen with oestrogen-only HRT.

Breast cancer incidence

Population studies show associations but cannot demonstrate causal connections. There is however, further evidence from population studies that HRT usage does have an impact on breast cancer incidence. The link between HRT use and breast cancer has been reinforced by epidemiological data from Australia and elsewhere, showing that the reduced HRT use following the initial publication of the results from the MWS and WHI was paralleled by a fall in breast cancer incidence among women aged 50 years and older.[24,25] This decline has been to a different degree in different countries. In countries such as the US, Canada, Australia, Belgium and France – with a high peak prevalence of HRT usage – the decline is more marked than in low prevalence countries such as Italy, Spain, China or Japan.[26] Any change in mammography screening could confound the results and must be taken into account.

Weighing the risks for patients

Clinicians who treat the distressing symptoms of menopause with HRT have questioned the generalisation of these findings to individual women in an Australian

clinical setting. Wren in the *Medical Journal of Australia* in 2009 suggested the WHI study overestimated risk, because the women had other breast cancer risk factors – they were older than women typically commencing HRT and 69% were obese or overweight. HRT given earlier in menopause, he argued, improved the risk/benefit ratio, while the observation that decreased breast cancer incidence paralleled reduced HRT use was more consistent with HRT promoting, not initiating, cancer.[27] And the increase in breast cancer years after starting HRT might be due to the growth of carcinoma in situ or micro-invasive disease, however this is speculation and is not evidence based.

These considerations do not negate the evidence of risk. And some claims are inconsistent with the additional reports, such as the further WHI review that showed hazard ratios for breast cancer and total cancer were still significantly higher in women commencing combined oestrogen and progestogen use in early menopause.[28] Moreover, doubt can also go two ways – while there is no conclusive evidence of breast cancer risk increasing after HRT use for less than two years, the link cannot yet be dismissed. Post hoc sub-study analyses may never definitively resolve these doubts, irrespective of the result of a specific analysis. So applying large studies to decisions about individual patients will also depend on the clinical indication for HRT and the patients' specific needs and biological profile.

Two things are clear. The relationship between HRT use and cancer risk is important, and clinicians need more than claims and counter-claims in the literature to inform their practices.

Improved regulation of HRT use through listing, scheduling and reimbursement has a role to play in reducing harm. The Australian Drug Evaluation Committee guideline acknowledged the effectiveness of HRT for symptoms of menopause, subject to six monthly re-evaluation.[28] When clinicians feel constrained by or tempted to prescribe HRT outside the guideline, they and their patients should have recourse to clinical guidelines weighing up the evidence for alternative uses. Over time new information may help select individuals who may be at less risk from HRT. For example, there is a protective effect against breast cancer risk in women using HRT for 10 years or more when they have the CYP2C19*17 allele, because it increases the expression of a gene causing ultra-rapid metabolism of oestradiol and progesterone.[29]

Although there is still uncertainty about some aspects of the risks of HRT, it is not an uncertainty that can be resolved by selectively quoting data to explain away risks identified in large studies, but a risk which must be put into perspective to assist patients in making informed choices. Given competing risks such as heart disease, osteoporosis and cancer, all cause mortality results would be useful. So how would the epidemiological data be incorporated into clinical decision making?

There are general principles that apply to all therapies. Firstly, there should be sound medical indications for their use. Severe symptoms of menopause which interfere with quality of life would be such an example, as compared to more cosmetic pursuits. In addition to the cancers associated with HRT, other side-effects of HRT which would compromise quality of life, such as gall bladder disease or dementia, must be weighed into a treatment decision.[30] We can say with a high degree of certainty that the use of HRT for preventing chronic disease is unjustified. Secondly, a relative risk from an epidemiological study has to be expressed in terms that an individual can comprehend. For example, in the initial reports of the MWS it was suggested that HRT use was associated with five to six extra cancers per 1000 women with five years use and 15-19 cancers with 10 years use, and these were mainly breast cancers for combined oestrogen/progestogen preparations and endometrial cancer for oestrogen only use.[2]

There have been attempts at translating a woman's individual risk of breast cancer. In the Australian setting, Coombs et al used the attributable fraction method to assess the cumulative absolute risk of breast cancer from HRT in various ages up to 79 years.[31] There are risk calculators available where an individual's risk of breast cancer is calculated depending on the risk factors such as age, family history and use of HRT.[32,33]

Conclusion

In conclusion, to use the population data in clinical decision-making, unopposed oestrogens have a better risk profile than combined oestrogen-progestogen combinations. Even in women who have not had a hysterectomy and are at risk of endometrial cancer, their overall cancer risk has been shown as lower with unopposed oestrogens.[2] Secondly, the duration of use is important. There are no data, for example, which would preclude prescribing short-term unopposed oestrogen HRT for a woman with severe symptoms of menopause, considering the low risk of adverse effects such as breast cancer balanced against a great improvement in quality of life. The data on the timing in relation to menopause may be less helpful in clinical decision-making, since the timing of symptoms would dictate when the HRT was commenced. However, the information about the increased risk of breast cancer when initiating HRT close to the menopause should still be provided to patients.

A population health goal where the vast majority of HRT use is short-term unopposed oestrogens is highly desirable, and this would accommodate population data into individual patient care, rather than selectively arguing against the application of such data.

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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 2012, the topic was "Forty years after the war on cancer - How far have we come?" The essays are judged by members of Cancer Council Australia's Oncology Education Committee.

The winning essay in the 2012 Student Essay Competition was submitted by Jane Doan. Jane attended the summer school in Groningen, The Netherlands from 9-20 July. She received the WHO CCCE Award for best poster presentation at the summer school.

FORTY YEARS AFTER THE WAR ON CANCER - HOW FAR HAVE WE COME?

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Four decades ago, American President Richard Nixon signed the National Cancer Act, directing attention, and more importantly government funding, towards the need to research and find a treatment for cancer to make the "conquest of cancer a national crusade".[1,2] This act proved to be the impetus for significant advancements in cancer research and treatment, paving the way for numerous groundbreaking achievements in the field of oncology.[3]

More than 60% of people with cancer will now survive at least five years after diagnosis, and the mortality rate of cancer has decreased 16% in the past two decades alone.[4,5] New drugs are able to treat cancers and extend the lives and survival rates of its patients, and vaccines have been created that can prevent the development of certain forms of cancer.[6] The use of multimodal therapy has reduced the need for radical surgeries, and the development of personalised cancer treatment has allowed for more targeted and effective approaches to treatment.[7,8] However, cancer continues to be a leading cause of death and burden of disease, and locally, 1 in 2 Australians will be diagnosed with cancer by the age 85.[9]

This essay will discuss the progress that has been made in understanding the role of human genomics in cancer, the evolution of cancer care with regard to prevention, advancements in screening, detection and treatment, the evolving role of the health professional in cancer treatment, and the future direction of cancer therapy and research, with the ultimate goal of eliminating cancer as one of the biggest health challenges that faces us today.

Progress in the genetic understanding of cancer

The focus of cancer research has broadened considerably over the years. Scientists now have a greater appreciation of how a patient's individual genetic makeup can affect their chances of developing a variety of cancers, and its subsequent severity and response to treatment, reflecting the importance of understanding the entire spectrum of factors that contribute to the development of cancer.[9]

Research has led to the discovery that mutations that have occurred in our genes are the cause of most, if not all types of cancer. One of the most significant advances towards this was with the completion of the Human Genome Project, which allowed for the identification of more than 290 genes that relate to the causes of various cancers.[10]

The identification of these gene mutations has uncovered two key classes of cancer genes: oncogenes – genes that often drive the uncontrolled cell growth phase which is a hallmark of cancer; and tumour suppressor genes, which in normal states preserve the integrity and normality of the genome.[11] In cancerous states, these gene classes have mutated and are unable to function in an appropriate manner, and by Darwinian evolution, develop a survival

advantage with the potential to proliferate autonomously, invade tissues and metastasise to distant sites.[10]

Understanding that the changes in an individual's genes provides the catalyst for cancer initiation and development means that we are better equipped than ever before to design therapies that specifically target the molecular defects of the tumour. This principle can be extended to incorporate all domains of cancer management, from developing preventative measures, facilitating earlier detection and screening of disease of at-risk populations, to monitoring treatment responses and predicting patient outcome and prognosis based on their genotype.[12]

Advances in cancer prevention

An important shift in cancer research that occurred was to understand the causes of cancer and develop strategies to detect it and intervene early, or to prevent its onset completely.[10,13] Some of the most significant reductions in mortality rates have come from the application of preventative health measures and health promotion campaigns, based on the knowledge of common causes of cancer.[14]

Numerous studies have identified a link between lifestyle factors such as smoking, poor diet, physical activity, body weight or composition, and their role in both the development and recurrence of certain cancers, and the identification of the carcinogenic effects of certain environmental and occupational exposures. These have resulted in important changes in preventive interventions and public policy.[10]

Changing the incidence and mortality of cancer can be accomplished by investing funds into behaviour modification and health promotion and education campaigns.[10] Since the establishment of the causal relationship between tobacco use and lung cancer, measures to combat cigarette smoking, such as media campaigns, law changes and restrictions on public smoking areas, have all contributed to reducing rates of smoking and mortality from lung cancer, illustrating the success of public prevention strategies in cancer management.[15]

Infection-associated tumours comprise nearly 20% of all cases of cancer worldwide, and the development of vaccines in preventing bacterial or viral infection has played a significant role in reducing the morbidity and mortality of these diseases.[16] The hepatitis B vaccine was the world's first cancer prevention vaccine, preventing the progression of chronic infection to hepatocellular carcinoma.[15] And the development of a prophylactic vaccination against human papillomavirus 16 and 18 means that 70% of cervical cancer is now preventable.[17]

Advances in screening and early detection

The purpose of screening an asymptomatic individual to detect early evidence of an abnormality is to recommend preventative strategies or treatment that will provide the patient with a better health outcome than if the disease had been diagnosed at a later stage. Most cancers have a pre-invasive or precursor stage, and researchers have identified this 'window', during which it is possible to detect and treat the disease before it reaches an advanced, symptomatic stage, and this forms the basis for screening.[15]

Nationwide screening programs have been applied in Australia for the early detection of breast cancer, colon cancer and cervical cancer, among others, to great effect. Studies consistently demonstrate that the implementation of these programs is beneficial in reducing cancer mortality rates, and cost effective for society.[10] Routine mammographic screening in women aged 50-69 years has reduced the risk of dying from breast cancer by 25%, and screening for cervical cancer using the Pap test for detecting pre-cancerous cervical lesions has the potential to reduce the incidence of squamous cell carcinoma of the cervix by up to 90%.[18,19]

Currently, not all cancers are amenable to screening, and so the focus of future cancer research should be towards developing molecular biomarkers and tools that will allow us to identify markers of disease at an earlier stage of disease, and ultimately provide patients with a better chance of survival.[10]

Advancements in cancer treatment

The cornerstone of cancer treatment revolves around a triad of chemotherapy, surgery and radiation therapy, and the past four decades have been host to important advances in these treatment specialties, as well as the expansion of supportive or palliative care.[10]

Advances in chemotherapy

Despite the side-effects often associated with chemotherapy, these drugs have dramatically increased the survival rates of cancer patients, to the point that some cancers are now curable in the majority of patients.[10] Gleevec, a drug that targets a chromosomal defect found in most chronic myeloid leukaemia cases, has transformed this disease from a death sentence into a chronic, manageable condition with a five-year survival of 95%.[20]

Advances in surgery and radiotherapy

Continual refinement of surgical procedures over the past decades has culminated in fewer disfiguring surgeries for patients, with less damage to surrounding normal tissue and structure, faster healing times, improved post-surgical cosmetic results and improved recovery.[10] The use of adjuvant and neo-adjuvant chemotherapy or radiotherapy has similarly allowed for greater preservation of normal structures, best evidenced by clinical trials showing that a lumpectomy with radiation is as effective as a radical mastectomy in the treatment of breast cancer.[21] Radiotherapy, with its computer-guided precision, now allows for intensely focused doses of treatment to cancerous areas with less damage to surrounding tissue. It has also provided therapy for cancers in areas that were previously inaccessible to surgeons, becoming widely used in the domain of head and neck cancers.[22,23]

Advances in supportive care

The development of supportive care therapy has allowed treatment to become safer and has minimised the toxicities and side-effects associated with cancer

therapy. An increased understanding of pain management and mechanisms of pain in cancer patients has led to a wider use of multimodal analgesic use, drastically improving quality of life issues for patients at all stages of treatment.[24] Anti-emetic use has improved the tolerability of chemotherapy by reducing the incidence of nausea and vomiting. The administration of haematopoietic and colony-stimulating growth factors to replenish depleted red and white blood cell levels in the bone marrow has reduced the incidence of severe infections that were once a common side-effect of cancer treatment.[25]

Changes in the medical approach to patient management

The traditional concept of cancer management, with the malignant disease being managed by a single discipline, has largely been replaced by a multidisciplinary team approach.[26] There has also been a shift towards a more holistic approach to patient management.[27] Doctors must be aware of the different emotional and psychosocial aspects of malignant disease with which the patient must contend, as understanding the patient's thoughts regarding their diagnosis, is pertinent to achieving a successful doctor-patient relationship.[10,28]

Medical student education and knowledge

The importance of quality cancer education for medical students must not be overlooked. In Australia, cancer remains one of the leading causes of death in society, however improvements in survival rates of cancer patients means that there are now more people who have been affected by cancer than ever before. It is therefore incumbent upon students to be armed with current, relevant and comprehensive knowledge, as well as develop appropriate skills and attitudes to interact with cancer patients and survivors.[29]

Complete medical cancer education should incorporate aspects of cancer control (epidemiology, prevention, screening), clinical skills, patient communication skills and palliative care into the medical curriculum. Medical student learning has changed to predominantly problem-based and self-directed learning in response to a vast increase in the amount of medical knowledge of cancer and the shift in patient expectations of the medical profession.[26]

As oncology develops into a multidisciplinary specialty requiring the input of multiple medical and surgical units, medical students are coming across aspects of cancer management in an ever-increasing pattern throughout the curriculum. The development of the *Ideal Oncology Curriculum* by the Cancer Council Australia has identified five essential cancer clinical experiences for medical students, with the purpose of ensuring students have insight into a patient's perspective regarding the diagnosis of cancer and its management, while ensuring that oncology learning remains relevant in its clinical context.[28]

The future direction of the "cancer crusade"

Our current society has now reached a defining moment in our efforts to treat and cure cancer. The increasing number of cancer patients and survivors will test the capabilities and infrastructure of our healthcare system as physician shortages arise.[30] Despite this, the advances that have been made into the understanding of cancer place us at an exciting moment in the cancer development timeline, as we witness a shift towards personalised cancer treatment.

Increasing demand for care

An aging population, improved screening and detection rates, and more effective cancer treatment have culminated in a steadily increasing number of cancer patients and survivors.[31] New cancer therapies may prolong survivorship, however lead to treatment-related medical problems or require ongoing surveillance, ultimately leading to an overall greater utilisation of health resources per patient, per unit of time.[32]

In light of the increasing requirements of cancer patients, studies predict that the number of clinical oncologists will soon be insufficient to meet the needs of cancer patients in the community.[33,34] Appropriate care is imperative during the patient's transition from active treatment to follow-up and surveillance, and so new, innovative models of care may be required to alleviate the workforce deficiency in oncology specialists. Collaborative practice models, with the use of "physician extenders" – trained nurse practitioners or physician assistants, or general practitioners – may require these health professionals to assume a greater role in the ongoing care of the recovering cancer patient.[35,36]

Cost of cancer care in Australia

The economic expenditure involved in cancer research and care continues to grow as the burden of disease increases in developed countries. In Australia, cancer costs more than $3.8 billion in direct health system costs, with a markedly even greater cost to the economy once the losses due to premature death and disability are considered.[9,37] Greater emphasis is required in primary prevention and treatment strategies to ensure that the most effective approaches are being utilised in cancer care.

Continued collection of cancer data

Service providers, researchers, health administrators and government sectors require consolidated information on the burden of cancer in the community. It is important to ascertain how cancer and its risk factors affect different populations, how it is being managed, gaps that may exist in the availability and accessibility of services within communities, and the effect of government policy initiatives on cancer outcomes.[38]

The era of personalised medicine

The use of non-specific, non-targeted therapeutic agents against a broad variety of tumours has largely been overtaken by an approach in which cancer treatment and prevention strategies are based on both a person's genetic makeup, and the genetic determinants of the cancer itself.[31] This concept of personalised medicine has the potential to maximise the efficacy of cancer treatments, while simultaneously minimising its toxicity and side-effects, as we choose therapies specifically targeted towards the

molecular defect. Knowledge of certain defects in a cancer will also allow identification of populations at high-risk for a certain cancer type, strengthening our efforts in cancer prevention, screening and early detection.[10]

Conclusion

The advances that have taken place in the last 40 years into the understanding of cancer at the basic, molecular level have resulted in significant progress in the field of oncology. The use of personalised cancer medicine has replaced a one-size-fits-all treatment model, and our approach to the management of the cancer patient has also changed in this time. Emphasis has shifted towards the multidisciplinary approach with multimodal treatment and supportive therapy, with more directed efforts towards prevention, screening and early detection of these cancers.

However, with sustained population growth and Australia's aging community, the burden of cancer continues to grow, and this remains a major test for developed countries. The challenge that faces us is to sustain clinical research, support and funding in order to improve the entire spectrum of cancer care. The good news is that the significant advances that have already been made into the understanding of cancer position us to make even greater discoveries in the coming years.

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SARCOMA CLINICAL DATABASE: ENABLING COLLABORATIVE RESEARCH ACROSS AUSTRALIA

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The Australasian Sarcoma Study Group Limited (ASSG) is the peak body for sarcoma research in Australia and one of 13 national Cooperative Cancer Clinical Research Groups supported through Cancer Australia's Support for Cancer Clinical Research Program,[1] which is designed to build capacity to conduct cancer clinical research.

Sarcomas are a group of devastating cancers arising in the connective tissues including fat, muscle, cartilage and bone; two in five patients go on to die from their disease and the impact on the community in terms of disability-adjusted life years is significant.[2,3,4] The accurate measurement of clinical outcomes in practice facilitates research and is vital to mapping health service practice, nationally and internationally. Traditional mechanisms, such as cancer registries, that are used to collect accurate clinical data in patients with sarcoma have been challenging, mainly because of the discrepancies in sub-categorising what is essentially, a collection of more than 80 sarcoma subtypes, into their distinct entities. Accordingly, the collection of high-quality national clinical data and biospecimens was recognised as a key goal of both the ASSG and Cancer Australia. To effect this goal, the ASSG established a sarcoma clinical database and a virtual biospecimen bank. In addition, the ASSG provides the infrastructure for collaboration between multi-disciplinary teams and sarcoma resources for patients, families, carers, clinicians and research professionals who seek information about diagnosis, treatment and research.[5] The sarcoma clinical database is the focus of this report, which describes the status of the database, the data fields and current output and follows two earlier reports on the development of the ASSG and on the group capability achieved through centres of excellence.[6,7]

Getting connected: Establishing national infrastructure

BioGrid Australia Limited is a secure, internet accessible, research platform and infrastructure, which offers access to clinical, imaging and biospecimen data across jurisdictions, institutions and diseases, in an ethically approved and secure way that protects both privacy and intellectual property (each patient has a universal identification code and data custodians must firstly approve researchers' access to requested data).[8] One of the many source system available using the BioGrid platform is the Australian Comprehensive Cancer Outcomes and Research Database (ACCORD),[9] which is a cancer patient registry and outcomes database that provides real-time, accurate, pooled patient demographics and clinical information. Other source systems that are available, which use BioGrid Australia, include data on clinical and surgical cancer outcomes and on tumour biospecimens that have been donated for research purposes. BioGrid Australia is a virtual repository, which enables linkage across Australia between participating teaching hospitals, cancer research centres and integrated cancer centres to provide access to: multiple datasets; data on clinical outcomes; quality and audit data; genomic data; images; and analytical and reporting tools. The ASSG uses the BioGrid platform to combine and link data from: the Sarcoma (bone and soft tissue) Module of the ACCORD Database; other sarcoma databases; biospecimen data; outcome data; and other useful data sources (note, the Princess Alexandra site, under Queensland Health, operates Queensland Oncology On Line or QOOL,[10] which is compatible with the ACCORD Sarcoma Module dataset. However, privacy laws in Queensland prevent direct linkage to the federated system, therefore, de-identified data is extracted for inclusion in the ASSG dataset).

Pilot Study: Peter MacCallum Cancer Centre

In collaboration with BioGrid, a pilot for a sarcoma dataset was established at the Peter MacCallum Cancer Centre in early 2007, using a paper-based questionnaire. The objective was to estimate the feasibility of such a dataset, harmonise with parallel efforts in New South Wales and then support extension of a common dataset to ASSG sites. A minimum sarcoma dataset was agreed and in July 2008, BioGrid commenced building the electronic database. A number of hurdles had to be overcome at each site prior to establishing the national sarcoma clinical database, which included permission for the BioGrid Australia data linkage platform and authority from respective Human Research Ethics Committees to collect sarcoma data. In addition, as depicted in table 1, several key relationships associated with the success of this project required written agreement.

Table 1: ASSG clinical database relationships.

ASSG Clinical Database Relationships	
Parties	**Agreement**
Cancer Australia	Infrastructure funding for data collection
ASSG	Meet KPIs for data collection
BioGrid	Development, implementation and modification
ASSG	Funding modification, linkage and extraction
ASSG Sites	Collaboration, data contribution, matched funding and minimum data entry
ASSG	0.2 or 0.4 FTE funding for data manager support
BioGrid	Linking of data through the BioGrid Independent Research Repository
ASSG Sites	Adherence to BioGrid membership policies
Researchers	Appropriate use of the clinical data/biospecimens
ASSG Sites	Adherence to BioGrid data usage policies
Patients	Consent for clinical data/biospecimens to be collected, stored and used
ASSG Sites	Adherence to Human Research Ethics policies for data collection, storage, usage

Funding

Funding for the development, implementation and subsequent management and modification of the ASSG sarcoma clinical database had to be raised from different sources. Grants to BioGrid from the Victorian and Australian Governments contributed to the cost of developing the ACCORD Sarcoma Module and to establishing infrastructure at the seven ASSG sites, through obtaining ethics permission, setting up servers and delivering training.[11] Noteworthy, from 2010 BioGrid became self-funded and has been moving towards a user-pays system. For data-collection, management and modification, it was unlikely that such monies would have been available through philanthropic, industry or competitive funding sources, so a successful application was made to Cancer Australia (as part of the infrastructure grant made to the ASSG) to provide fractional FTE at 0.2 or 0.4, depending on the site patient population size, and a lap top computer to each site. To maximise efficiency and to ensure adequate resources for the data-collection posts, each site, complements the Cancer Australia-funded FTE with State-based FTE. Sites are also expected to meet all operational costs. The ASSG (through the Cancer Australia infrastructure grant) has funded: changes to some data fields; development of a proforma report; linkage between sites to the BioGrid network to enable a federated system (albeit modified to accommodate the Princess Alexandra site that uses QOOL); and will fund data extraction fees. In return, the obvious benefit is the co-ordinated, national reporting of a minimum dataset for sarcoma patient treatment, which until this point has not been possible. Indeed, previously, collection of robust data has been problematic.

Governance and quality control

Overall governance of the ASSG sarcoma clinical database rests ultimately with the ASSG Board and Executive. however, a steering committee comprising clinicians from across Australia, who represent the seven sarcoma clinical database sites, has been established to oversee strategic direction. At each site, a clinical supervisor oversees data-collection and management and takes responsibility for any decision making. A Database Users Group, comprising the seven data managers, has been formed to review standard operating procedures and collaborate, for example, on reporting, audit processes, research projects and for trouble-shooting. Table 2 displays the seven ASSG sites and their respective supervisors.

Table 2: ASSG Clinical Database Sites.

ASSG Clinical Database Sites			
	State	**Supervisor**	**Site**
1	ACT	Dr Christine Hemming	The Canberra Hospital
2	NSW	Dr Paul Stalley	Royal Prince Alfred Hospital
3	NSW	Dr Phil Crowe	Prince of Wales Hospital
4	SA	Dr Raghu Gowda	Royal Adelaide Hospital
5	QLD	Dr Warren Joubert	Princess Alexandra Hospital
6	VIC	Dr Jayesh Desai	Peter MacCallum Cancer Centre
7	WA	Dr Richard Carey-Smith	Sir Charles Gairdner Hospital

To promote consistency across the national data collection, data managers use a BioGrid procedure manual with data dictionary, that describes the processes for collecting and storing data, accessing data and troubleshooting; each data manager receives hands-on training from BioGrid for ACCORD, SAS Web Report Studio (reporting) and SAS Enterprise Guide (querying). Documentation is updated as required and training is renewed annually as part of an accreditation process. The ASSG is working with BioGrid to develop audit reports that will reveal any discrepancies in the data quality and quantity collected within the ACCORD Sarcoma Module. Consultation continues with Cancer Australia to compare epidemiological data and data about clinical care and standards against international benchmarks (to be progressed when national linkage is established and the data collection is more mature). The ASSG undertakes an audit every six months to monitor the number of entries against new sarcoma patients, types of tumours (using the World Health Organisation Bone and Soft Tissue Classification),[12] and to register any research activity that utilises the database.

ACCORD Sarcoma Module

The ACCORD Sarcoma Module is divided into eight sections as described in table 3. In terms of personal details, the patient's demographic information including postcode, Indigenous status, country of birth and main language spoken other than English is recorded under a universal ID (this number is used for the patient regardless of where treatment is received); whether patients are participating in particular clinical trials is also recorded.

ASSG clinical sarcoma database and virtual biospecimen bank

The outcomes expected from the ASSG sarcoma clinical database and virtual biospecimen bank include providing: high-quality annotated epidemiological data; help to ASSG sarcoma centres to audit data; assistance to ASSG multi-disciplinary teams to identify patient groups for clinical trials; data for outcomes based research including quality of life and economic studies; data for international comparison of care standards; and with the virtual sarcoma biospecimen bank, access to quality data to support tissue collection initiatives. Currently, data are collected on adolescent, young adult and adult patients, with a longer term goal to include paediatric data.

Sarcoma clinical database

Data managers at the seven sites undertake data entry and cleaning, resolve incomplete data and contribute to an audit of their respective site undertaken every six months. Over time, this audit has enabled the progress of the project to be documented. The following information offers a snap-shot of how sites (N=7) collect their data and the nature of the data that exists within the ACCORD Sarcoma Module.

Sites collect clinical data from a range of sources: patient notes (n=7); multidisciplinary team meetings (n=7); pathology or imaging results (n=7); hospital computer network admission system (n=6); a case record form that matches the database fields (n=2); and existing patient databases (n=3). Currently, six sites have access to the patient admission system and arrangements are underway to ensure that the remaining site gains access. Data managers attend multidisciplinary team meetings, weekly (n=3), fortnightly (n=3) or monthly (n=1) and over a six-month period, approximately 600 new sarcoma patients were reviewed (the annual sarcoma population in Australia is approximately 800 cases).[13] Regarding the Cancer Australia special population data collection, while all sites record postcode (to enable assessment of the percentage of patients by the Accessibility/Remoteness Index of Australia – metropolitan, rural, regional and remote),[14] no site was recording country of birth, ethnicity or language spoken. The demographic dataset was subsequently modified to include these Cancer Australia fields for specific groups.[15] Overall, data on 2782 patients has been collected, with 404 cases entered in the six months to June 30, 2011. Of these, based on the World Health Organisation Bone and Soft Tissue Classification, approximately two-thirds of the tumours were soft tissue.

Virtual biospecimen bank

Access to biological and clinical data increases opportunities for research, the development of repository protocols and contribution to the sarcoma knowledge pool. Accordingly, a virtual sarcoma biospecimen bank has been established on the ASSG members' sarcoma resource website, where a search can be undertaken for specific samples by location. Samples are catalogued using the World Health Organisation bone and soft tissue classification, which comprises 84 categories of tumour (46 soft tissue and 38 bone). The virtual bank is updated every six months. Currently, 11 biospecimen bank sites across Australia are participating and hold samples for 72 of the 84 categories. The ASSG acts as a liaison for collaboration between researcher and tissue holder and has already demonstrated both the need and utility of the virtual bank.

Output: reporting to research

Sarcoma reporting

Information gleaned from the six-monthly site audits highlighted that only three sites were running reports. These were to audit their respective collections by cross-checking with pathology specimens and searching for missing data fields. To facilitate the quantity and quality of data provided and to promote consistency of national reporting, a proforma was commissioned through BioGrid to enable the interrogation of practice standards, including referral sources, diagnostics services, treatment comparisons with tumour type and the measurement of co-morbidity and mortality (this proforma allows Queensland to contribute de-identified data). Sites are still encouraged to run independent data monitoring reports to gauge the accuracy and completeness of their respective datasets. Table 4 highlights the key elements of this report proforma, which is under pilot testing at the Peter MacCallum Cancer Centre. When it is complete, collective reporting will be commenced and collective datasets will be available. Meanwhile, several research projects that utilise the database are underway.

Table 3: *ACCORD Sarcoma Module.*

ACCORD Sarcoma Module†			
	Categories	**Field Headings**	**Sample of Data**
1	Patient Encounter With Sarcoma Service	1.1 First clinic consultation	• Referring clinician; Disease status and treatments received; History and Symptoms
		1.2 Pre-treatment imaging	• Procedure performed (CT – Chest/Local, MRI, PET, Thallium, X-Ray, Bone scan); Evidence of disease
		1.3 Diagnosis	• Date; World Health Organisation Bone and Soft Tissue classification; Method of diagnosis and for malignancies only – Basis of diagnosis; Stage at diagnosis
2	Diseases, Diagnostic Biopsies and Treatments	2.1 Diseases	• Disease type (Primary malignancy, Benign lesion, Metastasis, Local recurrence); Date of diagnosis; Disease site; Treated (If no, reasons)?
		2.2 Initial Diagnostic Biopsy	• Type of biopsy (Core, Fine needle, Excisional, Incisional); Surgeon; Earlier non-diagnostic biopsies
		2.3 Treatments	• Treatment type (Surgical, Chemotherapy, Radiotherapy); for Chemotherapy and Radiotherapy (neo-adjuvant to radiotherapy, adjuvant to radiotherapy and concurrent chemotherapy/radiotherapy)
3	Disease Details	3.1 Disease details	• Information source (Biospy, Resection, Imaging, Clinical Exam); Information timing (before Chemo/RT or after); Stage; Grade (1, 2, 3, N/A); Depth (Deep, Superficial); and for Resections only (Dimensions, Vascular invasion, Post-treatment necrosis, Tissue sent to)
4	Chemotherapy	4.1 Chemotherapy	• Start date; Treatment given by (Internal or External service); Type (Neo-adj., Adj., Definitive); Radiosensitising (N/A, No, Yes); Intent (Curative, Palliative); Agents; Stop date; Number of cycles completed; Reasons for stopping; Complications; Response (on imaging)
5	Radiotherapy	5.1 Radiotherapy	• Start date; Treatment given by (Internal or External service); Type (Neo-adj., Adj., Definitive); Intent (Curative, Palliative); Delivery (EBRT, Brachytherapy, Extracorporeal); Total dose (Gy); Total fractions; Stop date; Reasons for stopping
6	Surgery	6.1 Summary	• Date; Hospital; Surgeon
		6.2 Procedures	• Procedure; Margins involved; Margins assessed
		6.3 Post-operative complications	• Nerve palsy (Present, Expected, Sites); Blood loss (Present, Units); Other complications
		6.4 Reconstructions/ Prostheses	• Reconstruction/Prosthesis; For repair of procedures
7	Follow-Up	7.1 Reconstructions/ Prostheses	• Alive (Disease free, Local, Distant, Unknown disease status); Dead (Date, Cause, Cancers present at death); Status unknown
8	Codes: Bone and Soft Tissue	8.1 World Health Organisation Bone and Soft Tissue Classification	• Bone (38 categories). • Soft Tissue (46 categories)

† Copyright, ACCORD BONE & SOFT Tissue, October 2008

Table 4: *ACCORD Sarcoma Module: report Proforma.*

ACCORD Sarcoma Module Report			
	Categories	**Field Headings**	**Sample of Data**
1	Patients by Sex	Male, Female, Total	Percentage of males; females; total
2	Patients by Age	Age at diagnosis	0-25 years; 26-40; 41-65; >=66
3	Location of Patient Residence	Using the 2006 Australian Bureau of Statistics Local Area boundaries	Post Code for respective State/Territory
4	Duration of Symptoms	Mass, Pain, Pathological Fracture, Systemic Symptoms	Median; Mean; n; N
5	Pre- and Post-clinic Review Imaging by Tumour Type	Benign, Malignant, Not specified	CT (Chest/ Local); MRI; PET; Thallium scan; X-ray; Bone-scan
6	Time to Diagnosis confirmation greater than 21 days	Time of confirmation	Days
7	Diagnoses by World Health Organisation Category	Bone, Soft Tissue	Bone (38 categories) Soft Tissue (46 categories)
8	Stage at Diagnosis by Year	Year of Diagnosis	I A; I B; II B; II Not further specified; III; IV; IV A; IV B; IV Not further specified; Stage unknown
9	Time from Diagnosis to Treatment (Days)	Days	Minimum; Median; Mean; Maximum
10	Time from Diagnosis to Treatment Greater than 30 Days	Time to Treatment	Days
11	Surgeries by Year	Year and Hospital*	Year; PMCC/ SVHM
12	Post-operative Complications by Year	Year and Hospital*	Year; PMCC/ SVHM
13	Radiotherapy Treatments by Year - Internal	Radiotherapy Treatments	Year; Numbers of Treatments
14	Radiotherapy Treatments to Primary Malignancies and to Metastases by Year - Internal	Radiotherapy Treatments	Year; Numbers of Treatments; Numbers of Malignancies; Numbers of Metastases
15	Chemotherapy Treatments for Primary Malignancies and Metastases by Year - Internal	Chemotherapy Treatments	Year; Numbers of Treatments; Numbers of Malignancies; Numbers of Metastases
16	Complications by Year - Internal	Chemotherapy Treatments	Year; Numbers of Complications

* The Victorian site operates at the Peter MacCallum Cancer Centre (PMCC) and St Vincent's Hospital (SVHM)

Sarcoma research

The ASSG is sponsoring ASSG06-11 Sarcoma Lung Metastases,[16] which is a prospective study designed to collect data on adult patients with lung metastases from sarcoma, to describe quality of life, overall survival, relapse free survival and adverse events, in patients undergoing pulmonary metastasectomy for metastatic sarcoma. The aim of the project is to help guide management and inform future studies of this disease, through developing a pulmonary metastases register. ASSG06-11 Sarcoma Lung Metastases is a collaborative project between the ASSG, the Psycho-Oncology Co-operative Research Group and the Centre for Biostatistical and Clinical Trials. It utilises the ACCORD Sarcoma Module, PROMIS (Patient Reported Outcome Measurement Information System) and QOL-PRO (Quality of life and patient reported outcomes) instruments. Other projects arising directly from the database sites include: the Eilber Protocol for pre-operative chemoradiotherapy (Prince of Wales Hospital);[17] sarcoma tissue banking (Royal Prince Alfred Hospital); the CART-WHEEL project,[18] which is a registry for patients diagnosed with rare tumours (Peter MacCallum Cancer Centre); and a trial with limb salvage patients of recovery rates, quality of life and functional scores (Sir Charles Gairdner Hospital).

Summary

The anticipated outcome of this project – to add to the knowledge pool about sarcoma diagnosis, treatment, quality of life and survivorship – and thereby improve outcomes for sarcoma and related tumours in the Australian community, promises to out-weigh the significant cost in time, technology and funding that has been expended to establish seven clinical database sites across Australia. In particular, the contribution of Cancer Australia and BioGrid has been instrumental in establishing the ACCORD Sarcoma Module and in employing seven database managers. Overall, the collective effort of the ASSG, Cancer Australia and BioGrid has enabled this database to be effective in a short period of time. The project set-up will be complete when linkage between sites and BioGrid is connected and the report proforma is put into action. Then, high-quality, national, clinical imaging and biospecimen data collected across jurisdictions, institutions and diseases are expected and work will commence on comparing epidemiological data and data about clinical care and standards against international benchmarks. Despite early success and the ongoing commitment of support from BioGrid, developing a sustainable funding model will be a challenge. Finally, given the early signs of success from this national project, seeking interest from international collaborators seems a reasonable next step. To conclude, the sarcoma clinical database is an outstanding example of how a collaborative effort – in knowledge, time, technology and funding – can bring about such capacity for clinical, cancer research.

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AUSTRALIAN BEHAVIOURAL RESEARCH IN CANCER

Centre for Behavioural Research in Cancer (CBRC), Victoria

Did tobacco retailers comply with new legislation banning point-of-sale cigarette displays in Victoria, Australia?

A ban on point-of-sale (POS) displays of tobacco products came into effect in Victoria, Australia on January 1, 2011. In addition, new laws restricted the size of price boards and created the new requirement that a graphic health warning sign must be posted next to price boards. This study aimed to evaluate compliance with the new laws, and to assess prevalence of pro and anti-tobacco elements in stores pre and post-legislation. Three audits of 302 stores in Melbourne, Australia, by trained observers collected information on POS tobacco displays two to months before and three to four and 11-12 months after the enactment of the new restrictions. Between the first and second audits, nine stores stopped selling tobacco and three stores had either shut down or were closed for renovations. Of the remaining 290 stores, 94% observed the full ban on cigarette package visibility, while new restrictions on price board size and requirements for graphic health warnings were followed in 86% and 67% of stores, respectively. Between the second and third audits, another seven stores ended tobacco sales and two stores closed. In Audit 3, 90% of the remaining 281 stores complied with price board restrictions, and 82% of stores followed requirements for graphic health warnings. Overall, the prevalence of anti-tobacco signage increased and pro-tobacco features decreased between audits for every store type and neighbourhood socio-economic status. These findings indicate that POS display bans can be implemented successfully. This paper is in press in *Nicotine and Tobacco Research.*

Promoting cervical screening since the introduction of the human papillomavirus vaccine: the effect of repeated mass media campaigns

With the introduction of the human papillomavirus (HPV) vaccines in 2007, the context in which cervical screening takes place has become more complex from a public education perspective. In Australia, it is recommended women attend cervical screening every two years from the time they are aged 18 (or two years after sexual intercourse, whichever is later) until they reach age 69, even if they have been vaccinated. The current study tested the effectiveness of three targeted mass media campaigns, broadcast in 2007, 2009 and 2010, in promoting cervical screening. Seasonal time series was used to assess the effect of each campaign on the rate of weekly cervical screening tests in Victorian women from 2006-2010, with separate models developed for five screening interval groups. Results indicated the 2007 campaign significantly increased the number of cervical screening tests per week for lapsed screeners (>36 months since last test), overdue screeners (28-36 months since last test), and women never previously screened. For the 2009 campaign, there was a trend towards increased screening tests for overdue screeners. Lastly, the 2010 campaign was associated with a significant increase in weekly screening tests for lapsed screeners. Overall, this study highlights that well-researched and carefully pre-tested television advertising campaigns with accurate, actionable messages promoting cervical screening can elicit population-based behavioural change among appropriate subgroups against the backdrop of the HPV vaccine.

Newcastle Cancer Control Collaborative (New-3C) NSW

Do cancer helplines deliver benefits to people affected by cancer?

New-3C and Cancer Council NSW have conducted a critical review of evidence-based research to identify the benefits of cancer helplines to people affected by cancer. A broad, initial search in Medline, PsychINFO, EMBASE and CINAHL identified 830 potentially relevant publications, however only 30 publications met the criteria for the review. These 30 original research publications described samples from Australia, the United States, United Kingdom, Italy, the Netherlands, Canada, Sweden and Ireland. Twenty-two publications included all cancer types, while eight publications focused on specific cancer types (breast, colorectal or prostate, and brain). Twenty-seven of the studies were descriptive in nature, while only three used a randomised-controlled trial design. All three of these studies focused on the ability of helplines to reduce psychological distress in patients, and one study also looked at improvement in existential well-being. Overall the studies did not provide evidence that the helpline was effective in significantly reducing psychological distress in cancer patients. However, the helpline did achieve a higher reduction in psychological distress than mailed information alone. Further intervention-based studies are needed to assess the benefits of cancer helplines. These studies should not only focus on outcomes of psychological distress, but also other relevant outcomes including increased knowledge and information, greater involvement in decision-making, and improved problem-solving and self-efficacy. Studies should also focus on populations who are likely to have higher levels of distress, such as lung cancer patients and carers of cancer survivors.

Access to care and impacts of cancer on daily life: do they differ for metropolitan versus regional hematological cancer survivors?

Relatively little is known about access to care for hematological cancer patients, despite the challenging and long-term care often required. We conducted a study to compare metropolitan with non-metropolitan patients' experiences of barriers to care and financial and social impacts of the disease. A state-based Australian cancer registry identified adult survivors of

hematological cancers (including lymphoma, leukemia and myeloma) diagnosed in the previous three years. Survivors were mailed a self-report pen and paper survey. Of the 268 participants, 40% reported at least one locational barrier which limited access to care. Very few indicated that cancer-related expenses had restricted their treatment choices, while reports of financial or social impacts on daily life were common. Survivors living in a regional location were more likely to report barriers to care than those living in metropolitan areas. Providing more equitable access to care for hematological cancer patients in Australia requires addressing distances travelled to attend treatment and their associated financial and social impacts on regional and rural patients. Greater flexibility in service delivery is also needed for patients still in the workforce.

Behavioural Research and Evaluation (BREU), South Australia

Cancer Counselling Service evaluation

Cancer Council SA's Cancer Counselling Service offers free counselling to individuals affected by cancer. The service aims to reduce cancer-related distress and improve quality of life through the provision of therapeutic support, information and practical help. Data regarding levels of distress, quality of life and feedback about the service were collected through Cancer Council Helpline (n=168), a pre-counselling questionnaire (n=67), and a post-counselling questionnaire completed six weeks after the initial counselling session (n=40). Results indicated that levels of distress remained stable from first contact to pre-counselling assessment, and reduced significantly from pre to post-counselling. Emotional wellbeing significantly improved from pre to post-counselling. The majority of clients reported that the service was helpful in adjusting to the issues that were distressing them (72%) and they would recommend the service to others (96%). These results suggest that the Cancer Counselling Service has a positive impact on psychosocial functioning, and that clients perceived the service favourably.

Mindfulness-based cancer stress management program

A pilot study previously conducted by Sharplin and colleagues (2010) published in the *Medical Journal of Australia* assessed the impact of an eight-week Mindfulness-based Cognitive Therapy program offered to individuals experiencing cancer-related distress. Participants (n=21) completed measures of anxiety and depression at pre-intervention, post-intervention and three-month follow-up. Results showed significant and sustained improvements in anxiety and depression following the intervention. The Mindfulness-based Cognitive Therapy program was modified to address distress by incorporating elements of mindfulness-based stress reduction and a follow-up evaluation was recently conducted. Data concerning psychological distress, quality of life and spiritual wellbeing were collected across four eight-week mindfulness-based cancer stress management programs from 2010-2011, at pre-intervention (n=47), post-intervention (n=31), and three-month follow-up (n=26). Analyses for this study are currently underway, however: preliminary analysis indicates improvements across several domains of psychosocial functioning, suggesting that the program is likely to be effective in improving psychosocial functioning.

Evaluation of the 'Give up smokes for good' social marketing campaign

As part of the Tackling Smoking initiative to reduce the prevalence of smoking among the South Australian Indigenous population, SA Health is implementing an Indigenous-specific social marketing campaign, 'Give up smokes for good'. The campaign was piloted in Port Lincoln, Port Augusta and northern metropolitan Adelaide in 2011. To determine the impact of the campaign, Tobacco Control Research and Evaluation conducted quantitative surveys in Port Lincoln (n=94) and metro-north Adelaide (n=96) and 12 focus groups were also held across Port Lincoln, northern metropolitan Adelaide and Port Augusta. Findings suggest that the campaign was well received, with high recall of the campaign and large proportions of participants reporting smoke-free homes and cars, a key message for the pilot. The campaign is in the second phase expanding across metropolitan and regional areas. The evaluation is employing the same mixed methods approach, with the quantitative component including two additional sites, Port Augusta and Murray Bridge. Focus groups will be conducted in the upcoming months in northern metropolitan Adelaide, Port Augusta and Murray Bridge.

CANCER COUNCIL AUSTRALIA

New research shows 75% surge in global cancer burden by 2030

A combination of lifestyle and demographic changes are set to increase the global cancer burden by more than 75 per cent by 2030, according to new research published in June.

Cancer Council Australia CEO, Professor Ian Olver, said the new international research, published in *The Lancet,* coincided with Australia's annual focus on increasing awareness of bowel cancer. Professor Olver said a predicted 22.2 million cancers would be diagnosed globally in 2030, compared to 12.7 million in 2008, with bowel cancer a key reason for the increase, internationally and in Australia.

"The Government took a commendable step when Health Minister Tanya Plibersek announced $50 million in the budget to expand the National Bowel Cancer Screening Program," he said.

"The key now is to get a lot more eligible people screening, so we can boost the program's participation rate well above the current figure of around 40 per cent."

New online directory puts translated cancer resources within click of a mouse

Cancer Council launched a new online initiative in June to assist Australians from culturally and linguistically diverse communities access cancer information in their own language.

The CALD Cancer Resource Directory, a searchable online library of 600 publications, videos and websites, provides a wide range of translated cancer information including prevention, treatment and support.

Professor Olver said the directory was designed to provide a single point of access to cancer resources in Australia published in languages other than English. The free service would make it easier for health professionals and the public to locate evidence-based cancer resources in their preferred language.

CALD Patient Support Coordinator, Anna Epifanio, said the site itself was in English, but provided information in a range of languages including Arabic, Chinese, Greek, Italian, Macedonian and Vietnamese.

Search the CALD Cancer Resource Directory at cancer.org.au/CALD

Free course helps indoor workers balance vitamin D with skin cancer risk

Cancer Council launched a free online education resource in July to address recent confusion around how much sun you need to produce sufficient vitamin D and how much will increase your risk of skin cancer.

The course is primarily aimed at indoor workers, whose typical pattern of minimal sun exposure during the working week and high recreational sun exposure on sunny weekends or summer holidays can put them at risk of vitamin D deficiency, while also increasing their risk of skin cancer.

'Working indoors – a SunSmart balance for vitamin D and skin cancer protection' is the first course available on Cancer Council's eLearning platform.

Professor Olver said it was in all employers' interests to strive for a healthy and productive workplace.

Sign up for the course at elearning.cancer.org.au

Bowel cancer screening saving lives

Research released in July confirmed that the National Bowel Cancer Screening Program is making a major impact on patient survival, further emphasising the importance of eligible Australians participating in the program.

Using data made available through BioGrid Australia, Victorian researchers have shown that patients diagnosed as a result of a positive screening test have a much higher survival rate than patients presenting with symptoms.

Analysis from six Victorian hospitals showed an increased number of early stage cancers diagnosed via bowel screening. Dr Peter Gibbs and colleagues analysed diagnosis and survival information for 103 patients, none of whom displayed symptoms of bowel cancer, diagnosed as a result of the National Bowel Cancer Screening Program between May 2006 and 2012. They compared these to 703 patients of the same age presenting with symptoms over the same timeframe.

Those picked up by screening had a projected five year survival of 95% compared to 73% for patients of the same age who were diagnosed with symptoms.

"Fully implemented, the National Bowel Cancer Screening Program could save 30 lives a week," Professor Olver said. "This analysis adds to the current weight of evidence that early detection is key to higher survival rates. It also strengthens the case for encouraging maximum numbers of eligible people to participate in the screening program."

Australian food buyers face risk of deception if labelling unchecked

Cancer Council and the National Heart Foundation are concerned about an announcement from the intergovernmental forum on food regulation, which supports "self-substantiation" of health claims on foods – in effect, enabling food companies to claim a health benefit without any independent verification.

The key concerns are that food companies may be able to put new products making health claims on the market before any independent verification – a recipe for misleading advertising at a time when diet-related health problems are on the rise.

CEO of the National Heart Foundation of Australia, Dr Lyn Roberts, said diet choices were becoming increasingly important as Australians sought to take responsibility for their own health.

"If food companies are permitted to use health claims as a marketing tool with no verification, Australians will end up having no confidence in the nation's food labelling system," Dr Roberts said.

Professor Olver and Dr Roberts urged the government to add greater rigour to the system to protect Australians from unsubstantiated health claims.

New clinical guidelines for endometrial cancer

Cancer Australia, in partnership with Cancer Council Australia have published new clinical guidelines, *Clinical Practice Guidelines for the Treatment and Management of Endometrial Cancer,* to assist doctors and their patients to make informed treatment choices.

The guidelines focus on the management of apparent early stage low and high risk endometrial cancer – the most common invasive gynaecological cancer in Australia – affecting 1 in 69 Australian women before the age of 75.

Dr Alison Brand, from the Gynaecological Oncology Unit at Westmead Hospital Sydney and Chair of the Endometrial Cancer Guidelines working party, said that when apparent early stage endometrial cancer is more advanced than initially thought, treatment is a complex area with conflicting evidence.

"These guidelines document the evidence currently available to assist those involved in treating women with endometrial cancer to make informed choices based on individual patient circumstances," she said.

The guidelines are available online on Cancer Council Australia's Cancer Guidelines Wiki: wiki.cancer.org.au

High Court ruling on tobacco packs a win for Australia's health

The long-term health of young Australians is the real winner from the High Court ruling in August in favour of the Federal Government's tobacco plain packaging laws, according to Cancer Council Australia.

Professor Olver said the court's rejection of the tobacco industry's challenge against plain packaging was a landmark ruling that put public health before vested commercial interests.

"When the laws on plain packaging come into effect from December, young Australians will no longer be lured into smoking by the flashy look of a slick, branded pack."

Professor Olver said one in five Australian cancer deaths was caused by smoking. "We hope other nations follow Australia's lead and eliminate the use of tobacco packaging as a marketing tool, to help reduce the global tobacco death toll – which is on track to reach half a billion people this century," he said.

Professor Olver acknowledged Australia's federal parliament for its broad support of plain packaging and, in particular, the former Health Minister and current Attorney-General, Nicola Roxon, for her determination in developing the legislation and defending it against the tobacco industry challenges.

Cancer Council welcomes new government plans for asbestos-free future

In August Cancer Council welcomed a new government-supported plan to remove asbestos from all commercial and government buildings by 2030 and take other vital steps to reduce the risks of asbestos-caused disease.

Professor Olver said the new Asbestos Management Review, developed by an independent expert group and released by the Department of Education, Employment and Workplace Relations, provides a blueprint for managing the deadly building material.

"The new Asbestos Management Review provide clear recommendations for minimising the risks posed by the abundance of asbestos in Australian buildings," he said. "The key now is to get on with implementing the recommendations in the review."

Recommendations include developing a plan for the safe removal of asbestos from government and commercial buildings by 2030, the development of new laws to underpin compliance with safety procedures and establishing a national agency to coordinate the plan's overall implementation.

Cancer Council seeks participants in world-first study on spiritual wellbeing

Cancer Council launched a world-first study in August to further understanding of how spiritual wellbeing affects quality of life for those affected by cancer.

The study seeks to measure the importance of feelings such as hope, love, peace and forgiveness and their impact on patients' emotional and physical wellbeing – such as energy levels and pain – at different stages of the cancer journey.

Cancer Council Australia researcher Dr Hayley Whitford, based at The University of Adelaide, will analyse the information provided to determine which aspects of spiritual wellbeing, including the less acknowledged aspects such as appreciation and connectedness, are the most important in improving cancer patients' resilience and quality of life.

Professor Olver said it was an important area of research for anyone coping with, or treating, cancer. "This study builds on a decade of research on hope and spiritual wellbeing and is the first of its kind to attempt to psychometrically assess the underlying aspects of spiritual wellbeing such as love, peace, meaning and faith, and how they each affect people's resilience against depression, anxiety and stress," he said.

Find out more at cancer.org.au/2020vision

Draft National Food Plan seriously undercooked: 'recipe for ongoing obesity' say health groups

The Government's draft National Food Plan, released in September, puts business before health while millions of Australians risk eating themselves to an earlier death than past generations, according to leading public health organisations.

Professor Olver said Australia's unprecedented obesity rates were noted throughout the draft, yet there were no robust recommendations for addressing a problem that could cause life expectancy for millions of Australians to drop compared with their parents.

"Business and health should coexist as shared priorities in a genuine national food plan, but the draft suggests the Government is more interested in the commercial side of food. This won't provide a net benefit to Australia if the community costs of obesity keep rising."

CLINICAL GUIDELINES NETWORK

Cancer Council Australia's Clinical Guidelines Network is steadily increasing its portfolio of clinical practice guidelines that can be accessed on the Cancer Guidelines Wiki platform at wiki.cancer.org.au/australia

As well as new guidelines, published clinical guidelines that are still current are being transitioned online in readiness for their revision phase. In the meantime, these guidelines are available on the Cancer Council Australia website at cancer.org.au/clinicalguidelines

For more information contact Clinical Guidelines Network Manager, Christine Vuletich, on 02 8063 4100 or christine.vuletich@cancer.org.au

Guidelines currently under revision

Clinical practice guidelines for the Prevention, Diagnosis and Management of lung cancer

The revision of the treatment section of the guidelines, comprising management of non-small cell lung cancer and small cell lung cancer topic sections is being finalised. Following Cancer Australia approval, the guidelines will be available on the Cancer Guidelines Wiki at wiki.cancer.org.au/australia/Guidelines:Lung_cancer

Planning is also underway to revise the prevention and diagnosis sections of the guidelines. A multidisciplinary working party is being established and will meet in November to develop clinical questions and literature search strategies.

New guidelines in development

Clinical practice guidelines for the management of sarcoma

Literature searches have been completed and the search results sent to working party authors to assess the literature and develop their topic content and evidence-based recommendations. The draft guidelines are planned to be released for public consultation later this year. Relevant organisations, experts and interested parties will be consulted during the public commenting phase.

Clinical practice guidelines for the diagnosis and management of Barrett's oesophagus and mucosal neoplasia

The working party has met to discuss the scope of the guidelines, develop topic groups, key clinical questions and search strategies for each question. The literature search will be completed in November 2012 and the results will be sent to the working party for their assessment.

Launched guidelines

Clinical practice guidelines for surveillance colonoscopy in adenoma follow-up, following curative resection of colorectal cancer, and for cancer surveillance in inflammatory bowel disease.

These guidelines, approved by National Health and Medical Research Council in December 2011, are an update and expansion of several chapters of the 2005 *Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer.* They focus on the appropriate use of colonoscopy in colorectal cancer prevention and address: (i) when to repeat colonoscopy after adenomatous polypectomy; (ii) when to repeat colonoscopy after curative resection for colorectal cancer; and (iii) when to perform colonoscopy in those patients with inflammatory bowel disease, who have an increased risk of developing colorectal cancer. The guidelines are available on the Cancer Guidelines Wiki at wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer/Colonoscopy_surveillance

Clinical practice guidelines for the treatment and management of endometrial cancer

These guidelines focus on the management and treatment of apparent early stage low risk and high risk endometrial cancer and were developed with funding received from Cancer Australia. The guidelines are available on the Cancer Guidelines Wiki at wiki.cancer.org.au/australia/Guidelines:Endometrial_cancer/Treatment/Early_stage

CLINICAL ONCOLOGICAL SOCIETY OF AUSTRALIA (COSA)

Annual Scientific Meeting

By the time you read this you will have already attended the COSA ASM in Brisbane. I hope you enjoyed the opportunity for COSA to expand the psycho-oncology program this year through our partnership with the International Psycho-Oncology Society (IPOS) and their Australian collaborators Cancer Council Queensland, PoCoG and OZPOS.

The melanoma and skin cancer theme really complemented the sunny Brisbane location. I must thank the COSA Program Committee, diligently led by our convenor Christine Carrington, for their extraordinary efforts in pulling together such an exciting program.

In 2013, the COSA ASM will be held in Adelaide, 12-14 November 2013. The theme will include gastrointestinal cancers – encompassing gastric, oesophagus and hepatobiliary tumours – as well as geriatric oncology. COSA welcomes Dr Nimit Singhal as convenor in 2013. A staff specialist in medical oncology at Royal Adelaide Hospital, Dr Singhal's main areas of interest include clinical trials and cancer in the elderly.

Regional and rural cancer services

Over 60 people attended the 'More than bricks and mortar' workshop in Canberra in August 2012, to discuss cancer service development in regional and rural Australia. Participants included doctors, nurses, allied

health professionals and administrators working in cancer service delivery around Australia as well as consumer representatives and research professionals. Central to discussions throughout the day was the need to focus on the experience of patients living outside our major cities. Participants agreed that the outcomes by which the success of a regional cancer centre is measured must be determined by the local community and incorporate quality of life endpoints in addition to clinical end points. The need to take advantage of existing resources in a fiscally tight environment, in particular the importance of improving access to educational activities and up-skilling current staff, was also highlighted. The identification of areas of expertise that health professionals could call upon through functional networks would improve the efficiency of cancer services. Underlying these suggestions was the need for communication, the sharing of information and co-operation between services based on clinical needs, not jurisdictional boundaries.

Of the many recommendations resulting from the workshop, the following five were ranked most highly:

1. Encourage funding bodies to provide support for research studies and clinical trials at regional centres by requiring projects to include a regional site.
2. Establish processes for data linkage between cancer registry, Medicare and hospital registry data sets to facilitate health services and outcomes research.
3. Transfer administrative tasks from clinicians to the non-clinical workforce to ensure optimum use of everyone's time and skills.
4. Encourage regional cancer centres to assess their capability against agreed service criteria.
5. Set standards for follow-up care and involve the community in survivorship issues.

Many of the recommendations made during the workshop are relevant to cancer service provision in Australia, not just regional and rural areas. It was agreed that the development of regional and rural cancer services presented an opportunity to lead the way in many initiatives that could improve cancer services throughout Australia. The full report will be available shortly.

Leadership in improving cancer research

The Consumer Engagement in Clinical Cancer Research project will be completed and delivered to the project funders Cancer Australia by the time of publication. COSA delivered an extensive (but possibly not exhaustive) set of high quality online educational resources and tools for consumers working in the Cancer Cooperative Trials Groups. We have worked with a broad range of stakeholders – including the trial group consumers, executive officers, chairs, researchers and other health professionals – to identify the requirements for, develop and deliver this valuable resource. We look forward to Cancer Australia's final acceptance and implementation of the resources and thank everyone involved in the process.

The McKeon Review of Health and Medical Research in Australia recently released a consultation paper outlining issues and proposed recommendations from the review. This consultation paper has been released as a draft document to canvass the Panel's current views of the various issues and seek feedback on proposed recommendations. Many of the recommendations included in our joint submission with Cancer Council Australia have been adopted by the review panel and we are in the process of preparing a response.

Australian Psycho-Oncology Awards

Australia has a proud history of excellence in psycho-oncology care and research. In collaboration with the Australian Psycho-Oncology Group and the Psycho-Oncology Cooperative Research Group, COSA has fostered this field of oncologic care and ensured its place as part of multi-disciplinary care. In recognition of the efforts of individuals whose contributions ensure ongoing quality psycho-social care for people living with cancer, COSA has introduced two inaugural awards in psycho-oncology in 2012. Nominations were reviewed by an independent committee.

The Australia Psycho-Oncology Award recognises the highest level of contribution to psycho-oncology from among COSA members. We are proud to announce the 2012 Australia Psycho-Oncology Award recipient is Professor Afaf Girgis. The New Investigator in Psycho-Oncology Award is an opportunity to recognise an investigator, early in their career, for outstanding research contributions in the field of psycho-oncology. COSA is delighted to announce the recipient of the New Investigator in Psycho-Oncology Award in 2012 is Dr Haryana Dhillon.

Both recipients will be formally recognised at the COSA-IPOS conference dinner on Wednesday 14 November.

Senate Inquiry into Palliative Care in Australia

In October, the Senate committee released its report of the inquiry into palliative care in Australia. In collaboration with Cancer Voices Australia, COSA made a joint submission to the inquiry. It was very pleasing to see our submission acknowledged in the report which can be accessed via the Parliament of Australia website.

Asia Pacific Mentoring Program fellowships

Following a successful pilot in 2011, COSA has again funded a visiting fellow under our Asia Pacific Mentoring Program for a 12 week observation. In October we welcomed our third fellow funded under the program, Dr Sanjay Dhiraaj, from the Sanjay Gandhi Post Graduate Institution of Medical Sciences in Lucknow, India. Dr Dhiraaj is being hosted by Dr Odette Spruyt, Director of Pain and Palliative Care at the Peter MacCallum Cancer Centre. While this is a costly program, COSA is dedicated to continuing its support for health professionals working in the Asia Pacific region. We are also investigating other grant opportunities as a means of funding additional fellows.

Marie Malica, Executive Officer

FACULTY OF RADIATION ONCOLOGY, RANZCR

Access to quality radiation oncology services

Access to radiation oncology services remains a problem for many Australian patients, despite improvements in radiation oncology infrastructure over the last decade.

The Faculty of Radiation Oncology and the Tripartite Committee in Radiation Oncology, together with consumer representatives, are working to highlight this key issue and its repercussions for cancer patients across Australia.

Australia needs a consistent strategy for investment in and consideration of access to radiation oncology, in particular:

- National access targets for radiation oncology are needed to measure the quality of services. These include an evidence-based target of 52.3% of new cancer patients accessing radiotherapy and a measure of patient waiting times to commence treatment.
- Fragmentation in planning and a disjunction between investment in facilities, and a corresponding action on workforce, make radiation oncology vulnerable. National coordination and planning across jurisdictions are critically needed.
- Currently, there are significant delays in the introduction of technological innovations, irrespective of whether they are more cost-effective. This creates a barrier for patient access to the most appropriate and best-available treatment techniques.

The faculty is working with stakeholders across the sector to highlight these issues.

Further information is available as part of '*Planning for the Best: Tripartite National Strategic Plan for Radiation Oncology in Australia 2012-2022'* and also online at www.radiationoncology.com.au

Faculty of Radiation Oncology Annual Scientific Meeting

The Faculty of Radiation Oncology held its Annual Scientific Meeting in Cairns in July.

Over 250 delegates representing radiation oncology professions, governments and industry attended the meeting.

The theme of the meeting – 'Implementing New Technologies in Radiation Oncology' – is well aligned with the Faculty's strategic priorities, as well as the trends in the worldwide radiation oncology sector.

Distinguished guest speakers from the US and Europe shared their experience and perspectives with their Australian counterparts. It is a shared view that timely patient access to appropriate modern radiotherapy treatment techniques is of paramount importance.

All sessions of the conference (FRO 2012) can be viewed online at http://webcast.ranzcr.edu.au.

The 2013 Annual Scientific Meeting of RANZCR will be held at SkyCity Convention Centre, Auckland, New Zealand from 17-20 October 2013.

The theme of the meeting is 'Clinical collaboration' and further information is available online http://ranzcr2013.com/.

Radiation oncology workforce

The Allen Consulting Group was commissioned to develop the workforce modelling for radiation oncology for the next decade.

The projections were based on the increasing incidence of cancer and were done for the three professional groups on the radiotherapy team: radiation oncologists; radiation therapists; and radiation oncology medical physicists (ROMPs).

A key problem highlighted by the projections is the disjunction between infrastructure funding by governments and workforce planning. A prospectively planned and nationally coordinated radiation oncology service is needed in Australia, with closer consultative collaboration between governments, policy-makers, service providers, patients and the professions, to ensure the most effective use of resources.

Assuming the achievement of target radiotherapy utilisation rate of 52.3 per cent of all new cancer patients by 2022, significant workforce shortfalls of all three professions would occur by 2022.

The ROMP workforce is facing a serious shortage even at the current under-utilisation rate of 38.2 per cent. The ROMP workforce crisis requires an urgent and multi-faceted response. The Radiation Oncology Tripartite Committee recommended that a national workforce summit must be held by June 2013 to get consensus on the implementation of workforce solutions across the sector.

The workforce projections were developed as part of the Tripartite National Strategic Plan, to provide a factual basis for policy decisions. The full report on the projections is available online at www.radiationoncology.com.au/supporting-documents/

A/Prof Chris Milross, Dean, Faculty of Radiation Oncology

MEDICAL ONCOLOGY GROUP OF AUSTRALIA (MOGA)

The Medical Oncology Group of Australia's (MOGA) 2012 Annual Scientific Meeting was held in Brisbane in August.

The theme for the 2012 ASM 'Targeting Cancer from Diagnosis to Cure', reflected the opportunities and challenges that targeted therapies and approaches are generating, almost daily, in all areas of medical oncology, related disciplines and cancer management.

The scientific program focused on targeted therapies and new advances in melanoma, lung, breast, prostate and colorectal cancers. A line-up of distinguished local and international guest speakers was organised.

The program included sessions devoted to: addressing the specialised education and communications skills needs of Australian trainees in medical oncology; trial developments in targeted oncology; access and approval of new oncology drugs and treatments in the Australian market place; and the role of advanced health directives in Australia. Two Industry symposia examined high interest subjects, the first on 'Surrogate End-Points in Oncology Drugs and the Australian Marketplace' and, the second on 'Introducing Angiogenesis into Clinical Practice in 2012 and Beyond'.

The Australia and Asia Pacific Clinical Oncology Research (ACORD) 2012 Workshop, presented in September on the Sunshine Coast, attracted 60 participants across all oncology disciplines from the region and was supported by 21 international faculty members. This educational program has successfully been presented every two years since 2004 and plays an important role in building regional expertise, networks and a body of skilled professionals in clinical oncology trials design and practice.

For 2012, a new Faculty Fellows Program was put in place that identified and brought to the workshop young clinicians to be developed as future ACORD Faculty Members, with the aim of supporting their career development and deploying their expertise to provide additional support for the workshop participants and faculty. The Association thanks our many program partners and supporters for assisting with this year's Workshop.

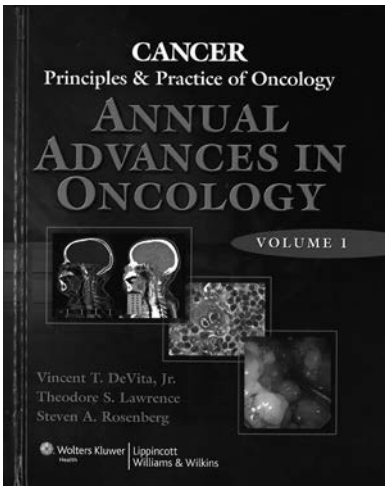
MOGA's advocacy and lobbying activities for access to various oncology drugs and treatments for Australian patients and clinicians continues to be core business for the association and has again seen positive developments. The Pharmaceutical Benefit Advisory Committee recently recommended that restrictions around trastuzumab (Herceptin) be extended to include: initial treatment for HER2 positive locally advanced breast cancer, commencing concurrently with neoadjuvant chemotherapy and; the duration of PBS-subsidised treatment authorised for 52 weeks.

MOGA is pleased with this outcome for patients with locally advanced HER2-positive breast cancer and their clinicians, for whom equity of access to trastuzumab has long been an issue and the subject of an extensive campaign waged by the association.



Cancer Principles and Practice of Oncology

Annual Advances in Oncology Vol 1
DeVita Jr VT, Lawrence TS, Rosenberg SA
Wolters Kluwer, Lippincott Williams Wilkins 2010
ISBN 978-1-4511-0314-4
Price $US 153.50
427 pages



With the 8th edition of *Cancer Principles and Practice of Oncology,* updates were published in *The Cancer Journal: Principles and Practice of Oncology.* These updates have been collected into a monograph. As a result the subjects are diverse, with the common thread being that they are cutting edge subjects.

The book commences with a major issue in survivorship, that of sexuality after cancer. Twelve chapters cover broad topics focusing on fertility, body image and rehabilitation, to more specific discussion of sexuality in BRCA carriers, after breast cancer, prostate cancer, pelvic radiation and haematopoietic stem cell transplantation. The subject is comprehensively addressed and the chapters are well referenced.

The next chapters address a completely different issue – controversies in the management of Hodgkin lymphoma. It is perhaps ironic that this is still a hot topic almost 50 years after the first use of MOPP chemotherapy, which followed the demonstration of cures with extended field radiation. However, the major issue is the use of combined modality therapy, with less radiation to reduce the toxicity. Will this result in the same durable responses? The roles of each treatment modality are discussed and the late effects of the disease and its treatment are presented.

Moving on to the management of peritoneal carcinomatosis, we have the best illustrated section of the monograph. The subject is presented in terms of the surgical challenges, as well as intraperitoneal chemohyperthermia and the pharmacology of intraperitoneal chemotherapy. These topics are highly specialised, however it is useful that all of the latest literature is collected together in this series.

Another highly specialised topic is that of charged particle therapy. The issue here is the expense of proton beam accelerators and the question of whether they are still justified given trials of intensity modulated radiation therapy, such as in prostate cancer where it appears to be as good as proton beams. However, for other indications, collecting the evidence requires an investment into the technology, which is problematic.

A more general, but most important subject, is that of measuring therapeutic response to treatment. Several pivotal questions to be addressed include the significance of stable disease, particularly with the new targeted therapies, the significance of progression free survival and whether it really is a surrogate end-point for survival, what biomarkers can be used in trials and how meta-analysis can be used to validate markers.

The final subject explores the use of new agents in myeloma and how to integrate them into standard therapies, including with haematopoietic transplants, and their use in refractory disease and maintenance therapies. The next generation immunotherapies are introduced.

This is an important update supplement to the well-known oncology textbook and deserves to sit next to it on the bookshelf for the wealth of information it contains.

Ian Olver, Cancer Council Australia, NSW.

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Reviews are published in the online and printed editions of *Cancer Forum*

If you are interested in completing book reviews in the future, please email info@cancerforum.org.au to recieve our survey form.



CALENDAR OF MEETINGS

AUSTRALIA AND NEW ZEALAND

Date	Name of Meeting	Place	Secretariat
November			
9-10	12th Queensland Palliative Care Conference 2012	Sunshine Coast, Queensland	Palliative Care Queensland Website: www.palliativecareqld.org.au/qld-conference-2012 Email: enquiries@palliativecareqld.org.au Phone: +61 7 3211 2299
11-15	14th World Congress of Psycho-Oncology	Brisbane, Queensland	International Psycho-Oncology Society (IPOS) and Clinical Oncological Society of Australia (COSA) Website: www.ipos-society.org/ipos2012 Email: cosa@cancer.org.au Phone: + 61 2 8063 4100
12	COSA Cancer Parmacist Group CPD	Brisbane, Queensland	Clinical Oncological Society of Australia (COSA) Website: www.cosa.org.au Email: cosa@cancer.org.au Phone: +61 2 8063 4100
13-15	Clinical Oncological Society of Australia (COSA) 39th Annual Scientific Meeting	Brisbane, Queensland	Clinical Oncological Society of Australia (COSA) Website: www.cosa.org.au Email: cosa@cancer.org.au Phone: +61 2 8063 4100
13-16	Australasian Leukaemia & Lymphoma Group (ALLG) Scientific Meeting	Melbourne, Victoria	Australasian Leukaemia and Lymphoma Group (ALLG) Website: www.allg.org.au Email: Dilupa.Uduwela@petermac.org Phone: +61 3 9656 2764
December			
3-6	2nd Biomarker Discovery Conference	Shoal Bay, New South Wales	Biomarker Discovery Conference Website: www.bdc.mtci.com.au Email: bdc@mtci.com.au Phone: +61 2 9524 1799
10-11	Palliative Care Nurse Australia Conference	Melbourne, Victoria	Palliative Care Nurses Australia Website: www.pcna.org.au/conference Email: pcna@palliativecare.org.au Phone: +61 2 6232 4433
2013			
February			
1-3	2013 Survivorship Conference	Glenelg, South Australia	Australasian Society for Breast Disease Website: www.asbd.org.au Email: info@asbd.org.au Phone: +61 7 3847 1946
March			
7-8	International Meeting on Psychosocial Aspects of Hereditary Cancer	Sydney, New South Wales	International Meeting on Psychosocial Aspects of Hereditary Cancer (IMPAHC) 2013 Website: www.impahc2013.com.au Email: info@impahc2013.com.au Phone: +61 2 9382 3440
May			
8-10	11th Behavioural Research in Cancer Control Conference	Adelaide, South Australia	Cancer Council South Australia Website: www.brcc2013.com.au Email: brcconference2013@cancersa.org.au Phone: +61 8 8177 2215
15-17	Second Lowy Cancer Symposium 'Discovering Cancer Therapeutics'	Sydney, New South Wales	Lowy Cancer Website: www.lowycancersymposium.org Email: KT@asnevents.net.au Phone: +61 3 9329 6600

Date	Name of Meeting	Place	Secretariat
August			
25-31	InSiGHT 2013 Conference	Cairns, Queensland	Meeting Makers Website: www.wired.ivvy.com/event/cairns Email: info@meeting-makers.com Phone: +61 3 8344 1831
November			
12-14	Clinical Oncological Society of Australia's (COSA's) 40th Annual Scientific Meeting	Adelaide, South Australia	Clinical Oncological Society of Australia (COSA) Website: www.cosa.org.au Email: cosa@cancer.org.au Phone: +61 2 8063 4100

INTERNATIONAL

Date	Name of Meeting	Place	Secretariat
November			
1-2	2012 American Institute for Cancer Research Annual Research Conference on Food, Nutrition, Physical Activity and Cancer	Washington, United States of America	American Institute for Cancer Research (AICR) Website: www.aicr.org/cancer-research/conference Email: aicrweb@aicr.org Phone: +1 202 328 7744
2-3	4th Annual meeting on Translational Research in Ovarian Cancer	Liverpool, United Kingdom	European Network for Translational Research in Ovarian Cancer Website: www.eutroc.org Email: eutroc@trmoncology.com Phone: +3 170 306 7200
2-4	3rd Kosovo International Congress of Oncology	Pristina, Kosovo	Kosovo Association of Oncology-SHOK Website: www.kao-congress.org/ Email: skerliu@hotmail.com Phone +3 774 415 3400
4-7	National Cancer Research Institute Cancer Conference	Liverpool, England	National Cancer Research Institute (NCRI) Website: www.ncri.org.uk/ncriconference Email: ncriconference@ncri.org.uk Phone: +44 020 3469 5453
8-10	BCY1 – Breast Cancer in Young Women	Dublin, Ireland	European School of Oncology (ESO) Website: www.eso.net/events-2.html Email: eso@eso.net Phone: +3 902 854 6451
9-10	2nd International Conference on Cancer and the Heart	Houston, United States of America	MD Anderson Cancer Center Website: www.mdanderson.org Email: register@mdanderson.org Phone: +1 713 792 2223
13-15	Russian National Cancer Congress (Joint Symposium)	Moscow, Russia	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300
13-17	2012 International Tumor Microenvironment Conference	Suzhou, China	Cold Spring Harbor Asia (CSH Asia) and International Cancer Microenvironment Society (ICMS) Website: www.cancermicroenvironment.tau.ac.il/suzhou-china.html Email: tumic@post.tau.ac.il Phone: +97 254 661 5108

CALENDAR OF MEETINGS

Date	Name of Meeting	Place	Secretariat
22-25	2nd International Multidisciplinary Forum on Palliative Care	Florence, Italy	International Multidisciplinary Forum on Palliative Care Website: www.imfpc.org Email: secretariat@imfpc.org Phone: +41 022 533 0948
24-30	4th European School of Oncology (ESO) –Society for Industrial and Organisational Psychology (SIOP) Europe Masterclass in Paediatric Oncology	Rome, Italy	European School of Oncology Website: www.eso.net/events-2.html Email: dknupfer@eso.net Phone: +4 191 811 8450
December			
4-8	35th Annual San Antonio Breast Cancer Symposium	San Antonio, United States	UT Health Science Center San Antonio Website: http://www.sabcs.org/ Email: sabcs@uthscsa.edu Phone: +1 210 450 1550
30-1	American Society of Clinical Oncology's Quality Care Symposium	San Diego, United States of America	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300
2013			
January			
24-26	2013 Gastrointestinal Cancers Symposium	San Francisco, United States of America	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300
31-2	The 15th International Symposium on Anti-Angiogenic Therapy: Recent Advances and Future Directions in Basic and Clinical Cancer Research	San Diego, United States of America	MD Anderson Cancer Centre Website: www.mdanderson.org Email: dschultz@mdanderson.org Phone: +1 713 745 9208
February			
5-7	International Congress on Anti-Cancer Treatment	France, Paris	International Medical Events Website: www.icact.fr/ Email: infos@im-events.com Phone: +33 1 4743 5000
6-9	2nd World Congress of Cutaneous Lymphomas (WCCL)/ 6th International Symposium on the Biology and Immunology of Cutaneous Lymphoma (ISBICL)	Berlin. Germany	MCI Deutschland GmbH Website: www.cutaneouslymphomas2013.com E-mail: lymphomas2013@mci-group.com Phone: +49 0 3020 4590
7-8	3rd International Congress of Breast Disease Centers 2013	Paris, France	CFEE Executive Organization Email: congres@eska.fr Phone: +33 (1) 42 86 55 69
7-9	4th International Conference on Innovative Approaches in Head and Neck Oncology	Barcelona, Spain	European Society for Radiotherapy and Oncology (ESTRO) Website: www.estro.org Email: events@estro.org Phone: +32 2 775 9340
10-13	ASCO-MECC Palliative Care Workshop	Muscat, Oman	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300
14-16	Symposium on Palliative Care (Advanced Cancer Course)	Mexico City, Mexico	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300

CALENDAR OF MEETINGS

Date	Name of Meeting	Place	Secretariat
14-16	2013 Genitourinary Cancers Symposium	Florida, United States of America	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300
22-23	2013 Multidisciplinary Head and Neck Cancer Update	Weston, Florida, United States	Cleveland Clinic Website: http://www.clevelandclinicmeded.com/live/courses/headneck/overview.asp
March			
6-7	Inaugural Prostate Cancer Research and Translation Symposium	Winston, Salem, United States	North West AHEC Website: northwestahec.wfubmc.edu/mura/www/?utm_campaign=none&utm_source=redirectlink&utm_medium=none/#/event/37579
7-8	International Meeting on Psychosocial Aspects of Hereditary Cancer	Sydney, Australia	International Meeting on Psychosocial Aspects of Hereditary Cancer (IMPAHC) 2013 Website: www.impahc2013.com.au Email: info@impahc2013.com.au Phone: +61 2 9382 3440
12-16	13th International Conference of Primary Therapy of Early Breast Cancer	St Gallen, Switzerland	St Gallen Oncology Website: www.oncoconferences.ch Email: info@oncoconferences.ch Phone: +41 0 71 243 0032
19-22	Reach to Recovery International Breast Cancer Support Conference	Cape Town, South Africa	African Agenda Website: www.reachtorecovery2013.org/ Email: info@reachtorecoveryinternational.org Phone: +27 21 683 2934
April			
3-4	Updates in Hepatobiliary Cancer and Pancreatic Cancer	Riyadh, Saudi Arabia	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300
18-20	3rd ITLT Essen 2013 - Interdisciplinary Treatment of Liver Tumors	Essen, Germany	INTERPLAN Congress, Meeting & Event Management AG E-mail: itlt2013@interplan.de Web: www.interplan.de
May			
9-11	European Multidisciplinary Conference in Thoracic Oncology (EMCTO)	Lugano, Switzerland	European Society for Medical Oncology (ESMO), Website: www.esmo.org/events/lung-2013-EMCTO.html Tel. +41 (0)91 973 19 25
23-25	BIT's 6th Annual World Cancer Congress	Xi'an, China	Organizing Committee of the World Cancer Congress East Wing, 11F, Dalian Ascendas IT Website: http://www.bitlifesciences.com/cancer2013 Email: sherry-wcc@wcc-congress.com Phone: 0086-411-84575669-857
26-30	18th International Congress of Cytology	France, Paris	18th International Congress of Cytology Website: www.cytologyparis2013.com Email: info@cytologyparis2013.com Phone: +33 0 1 53 85 82 75
30-2 June	13th World Congress of the European Association for Palliative Care	Prague, Czech Republic	European Association for Palliative Care Website: www.eapc-2013.org Email: eapc2013@interplan.de Phone: +49 0 89 5482 3473
31-4 June	2013 American Society Clinical Oncology Annual Meeting	Chicago, United States of America	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300

CALENDAR OF MEETINGS

Date	Name of Meeting	Place	Secretariat
June			
19-22	12th International Conference on Malignant Lymphoma	Lugano, Switzerland	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300
19-22	12th International Conference on Malignant Lymphoma	Lugano, Switzerland	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300
20-22	The 6th International Nasopharyngeal Carcinoma Symposium 2013	Istanbul, Turkey	Ea Organizasyon Website: www.npc2013.org Email: npc2013@eaorganizasyon.com.tr Phone: +90 216 465 3540
27-29	Multinational Association of Supportive Care in Cancer (MASCC) International Symposium on Supportive Care in Cancer	Berlin, Germany	Congress Organizer: Kenes International Website: www.mascc.org/2013-symposium---berlin Email: mascc@kenes.com Phone: +41 22 908 0488
July			
19-22	12th International Conference on Malignant Lymphoma	Lugano, Switzerland	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300
26-28	Multidisciplinary Cancer Management Course (MCMC)	La Paz, Bolivia	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300
August			
9-10	Best of ASCO Chicago	Chicago, United States	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300
16-17	Best of ASCO Los Angeles	Los Angeles, United States	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300
23-24	Best of ASCO Boston	Boston, United States	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300
29-31	11th Annual Meeting of Japanese Society of Medical Oncology (JSMO2013)	Sendai, Japan	Congress Corporation Website: www.congre.co.jp/jsmo2013/english/index.html Email: jsmo2013@congre.co.jp Phone: +81 22 723 3211
September			
7-9	2013 Breast Cancer Symposium	San Francisco, United States	2013 Breast Cancer Symposium Website: http://breastcasym.org/
22-24	5th International Symposium – Primary Systemic Treatment in the Management of Operable Breast Cancer	Cremona, Italy	American Society of Clinical Oncology (ASCO) Website: www.asco.org.au Email: membermail@asco.org Phone: +1 571 483 1300

Date	Name of Meeting	Place	Secretariat
26-1 Oct	17th European Cancer Organisation (ECCO) - 38th European Society of Medical Oncology (ESMO) - 32nd European Society for Therapeutic Radiology and Oncology (ESTRO) European Cancer Congress	Amsterdam, The Netherlands	European Cancer Organisation (ECCO) Website: www.ecco-org.eu Email: info@ecco-org.eu Phone: +32 2 775 0201
27-28	Cancer Survivorship Conference	Houston, United States	MD Anderson Cancer Centre Website: www.mdanderson.org Email: dschultz@mdanderson.org Phone: +1 713 745 9208
October			
4-5	Symposia on Cancer Research, Genomic Medicine	Houston, United States	MD Anderson Cancer Centre Website: www.mdanderson.org Email: register@mdanderson.org Phone: +1 713 792 2223
10-11	V InterAmerican Oncology Conference: 'Current Status and Future of Anti-Cancer Targeted Therapies'	Buenos Aires, Argentina	InterAmerican Oncology Conferences Website: www.oncologyconferences.com.ar/index.html
10-12	Global Breast Cancer Conference	Seoul, Korea	INTERCOM Convention Services Inc. Website: www.gbcc.kr Email: gbcc@intercom.co.kr Phone: +82 2 501 7065
17-18	International Clinical Trials Workshop	Santiago, Chile	MD Anderson Cancer Centre Website: www.mdanderson.org Email: register@mdanderson.org Phone: +1 713 792 2223
31-1 Nov	Advances in Cancer Survivorship Practice: A Conference for Health Care Professionals	Houston, United States	MD Anderson Cancer Centre Website: www.mdanderson.org Email: register@mdanderson.org Phone: +1 713 792 2223

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.

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Cancer Council Tasmania
Cancer Council Victoria
Cancer Council Western Australia

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CLINICAL ONCOLOGICAL SOCIETY OF AUSTRALIA

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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MEMBERSHIP

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

Membership fees for 2012

Medical Members: $160
Non Medical Members: $100 (includes GST)

PROFESSIONAL GROUPS

Breast
Cancer Nurses Society of Australia
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Cancer Biology
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Social Work
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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.

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> 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

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