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Melanoma and melanoma management

Introduction

This edition of Cancer Forum reports a series of papers prepared for a Festschrift held in honour of Emeritus Professor William McCarthy AM at the Royal Prince Alfred Hospital on 29 July 2005. Professor McCarthy is a former President of COSA and has been a notable contributor to developments in medical education and melanoma management in Australia. He retired from clinical practice at the Sydney Melanoma Unit on 29 July 2005. We are delighted to have Professor McCarthy as our Guest Editor for this issue of Cancer Forum.

Editorial

Alan Coates

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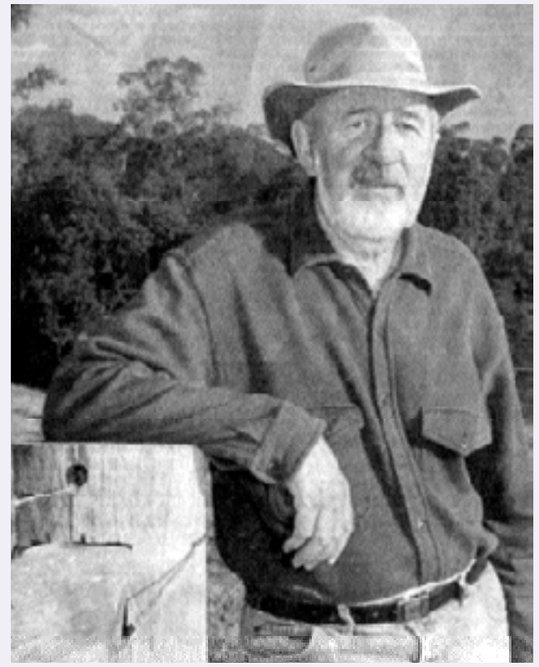
It's hard to imagine Bill McCarthy retiring. That's never been part of his character. Whether it was a rocket to an inadequate surgeon at St Elsewhere's, a campaign to save Sydney Hospital or a demonstration against the iniquity of a third runway dumping kerosene on his beloved Glebe, you never had any difficulty knowing where Bill McCarthy stood. I'm sure that side of Bill's nature will never change.

I first met Bill in the mid 1970s in the correspondence columns of the National Times, when the editor thought to forward to me for comment a diatribe Bill had penned in response to something – fairly innocuous I'd thought – that I had written on the subject of melanoma immunotherapy. I think it was the temerity of a Mexican (well Melburnian) venturing an opinion on anything to do with melanoma that had raised Bill's ire. I felt obliged to respond, but offered the editor the option of publishing neither letter. Luckily he agreed. When I later came to work in Sydney (in mid 1978), it took all of 30 milliseconds to decide whether to work with the Sydney Melanoma Unit or set up in competition with it. I have enjoyed my membership of SMU and a warm (OK – occasionally heated) friendship with Bill McCarthy for over a quarter century.

Bill's tenure as Director of SMU built on the tremendous foundation established by Gerry Milton. Bill set about establishing a sound financial basis for the expanding activity of the unit by establishing the Melanoma Foundation, with activities as diverse as celebrity balls and rustic cricket matches. Internationally, he was active in the WHO Melanoma Group and successfully organised the Fourth World Melanoma Conference in Sydney in June 1997. He was passionate about recruitment and collaboration, establishing both the Melanoma and Skin Cancer Research Institute and a national network of melanoma clinicians. Within the Clinical Oncological Society of Australia Bill chaired the Melanoma and Skin Group, then served as President. Since passing the baton of SMU leadership to John Thompson, Bill has continued to provide a valuable clinical service both at Royal Prince Alfred Hospital and the clinic he established at Nowra.

Bill was an expert in medical education, as described by Ann Sefton elsewhere in this issue. His enormous contributions in so many fields stand as a legacy as he completes the professional phase of his distinguished career. Those of us who have also been fortunate to know Bill in gumboots chasing cattle around his farm know that he will not be idle in retirement.



Swapping carcinomas for cattle: Professor Bill McCarthy AM on his southern NSW farm.

Overview

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Melanoma is known as the Australian cancer. The papers in this edition of Cancer Forum cover many aspects of melanoma from prevention to the management of advanced disease. Leading Australian clinicians and researchers have contributed to this series of articles.

The situation for those unfortunate enough to develop melanoma has changed for the better over the last 30 years. From almost epidemic rises in incidence rates, these rates have now almost stabilised and the death rate, while not yet stable, has fallen dramatically. At the present time survival for melanoma exceeds 90%.

Melanoma screening is not recommended by authorities in Australia, yet routine skin examination is widely practised. Mark Elwood's paper looks at the evidence and issues surrounding this controversial subject.

Susceptibility to melanoma is an important new area of genetic research in Australia. The melanoma genetics laboratory under the direction of Graham Mann has become a leader in this area. Mann's paper reviews the current understanding of the role of genetic factors in causation of melanoma.

Early diagnosis of melanoma has been substantially improved by dermoscopy, a topic discussed in detail by Scott Menzies, while a new direction to identify the presence of malignant cells in lymph nodes and possibly in the skin by magnetic resonance spectroscopy is outlined by Jonathon Stretch.

The management of melanoma involves surgery, medical and radiation oncology. Surgery for melanoma, reviewed by John Thompson, has gone from radical and disfiguring wide excisions down to narrow excisions based on new understandings of genetic susceptibility, melanoma biology and behaviour. Thompson looks at sentinel node biopsy, the advent of which has seen elective radical nodal surgery all but disappear.

Richard Kefford and Graham Stevens discuss the management of advanced melanoma, which remains less than satisfactory despite many clinical trials involving chemotherapy, biochemotherapy and immunotherapy. Currently most patients who develop advanced melanoma are entered into controlled clinical trials seeking a better outcome than can be achieved at the present time.

Immunotherapy, reviewed by Peter Hersey, has evolved as a promising new approach to the prevention of recurrence and perhaps the treatment of advanced melanoma. Adjuvant immunotherapy is under intensive investigation but to date results have not justified the introduction of this technique as standard therapy. Many vaccine trials are currently in the accrual phase.

During my career as a surgical academic at the University of Sydney and in the Sydney Melanoma Unit I have been privileged to take part in major developments in melanoma management and medical education. My paper, in this edition of Cancer Forum, outlines my views of those developments in melanoma management, and my academic colleague Ann Sefton outlines the developments in medical education at the University of Sydney, which has undergone dramatic change over the last 30 years. From a traditional six-year preclinical to clinical program, the curriculum has gone firstly to a five-year program and then to the current four-year program. From a didactically presented teaching methodology, the four-year program concentrates on small-group learning and problem solving tutorials allowing the student to gain knowledge and skill by interacting with other students and with computer-based interactive learning programs

I hope this edition of Cancer Forum will be interesting and informative for our readers.

Is screening for melanoma in average risk subjects beneficial?

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Abstract

Routine skin examination, either conducted by a doctor or by self-screening, is widely practised in Australia, although authoritative groups and clinical guidelines do not recommend screening. This inconsistency is due to the very limited information from studies with the ability to assess the value of screening. There are no randomised trials of the effects of screening for melanoma on end points like mortality. As a consequence, we have no rigorous evidence to show or disprove the value of routine skin cancer screening. Partial body self-screening is particularly prevalent, and whole-body screening and screening by a doctor are also commonly done. This high level of screening activity results in greater intervention. This may be beneficial; but there are also concerns that substantial numbers of non-progressive lesions are being detected and removed. These and other issues are explored.

One of the most contentious issues in regard to skin cancer is whether we should be encouraging or discouraging routine screening of average risk people for early melanoma, in addition to surveillance or case-finding in high risk individuals. This is perhaps the most difficult issue in the prevention and early diagnosis of melanoma. Bill McCarthy has given a valuable summary of Australian experience in these areas.[1]

It seems obvious that regular skin examination should lead to earlier diagnosis of melanoma, thinner tumours at diagnosis and therefore fewer deaths. However, in public health and policy terms, cancer screening requires evidence of overall benefit. The often stated requirement is to have evidence of a reduction in mortality, or at least in morbidity, produced by offering screening to a general population and supported by the results of one or more randomised trials. Thus, randomised trials showing benefits have been the rationale for the publicly funded programs of population screening for breast cancer by mammography and the current pilot programs of colorectal cancer screening. The other established cancer screening program, Pap smears for cervical cancer, was introduced before large scale clinical trials became established as an evaluation method, so the justification of that screening program is based on the results of cohort and case control studies. However, there is no evidence from randomised trials that skin screening can reduce deaths or morbidity from melanoma.

Recommendations on screening policy

Australian practice on melanoma screening is very mixed. There is no organised screening program. On the other hand, screening is widely practised and much of the screening is paid for through the Medicare system. Screening in the private sector is a considerable growth industry. Many expert groups who base their findings on 'evidence-based' reviews of scientific literature do not recommend screening. The NHMRC-approved clinical guidelines developed by the Australian Cancer Network in 1997 (a revision is in progress) do not recommend screening on a population basis:[2] "There is no evidence that population screening for melanoma is a cost effective way of controlling melanoma mortality". The US Preventive Services Task Force[3], The Cancer Council Australia,[4] and the Royal Australian College of General Practitioners do not recommend screening of average-risk subjects. These groups do recommend surveillance of high-risk subjects and advocate awareness and good clinical management of skin lesions, but even for high-risk subjects there is no level one or two (randomised trial) evidence. The RACGP (the 'red book') recommends screening for skin cancer in high-risk individuals, giving it grade III – C evidence ('poor evidence').[5] In contrast, the American Cancer Society,[6] the American Academy of Dermatology[7] and a National Institutes of Health Consensus Conference[8] support regular screening, on its own or linked to a general health check.

Skin screening in Australia

Despite this lack of consensus, screening for melanoma is widely practised in Australia. A telephone survey of a random sample of 3100 adults aged 30 or more in Queensland, conducted in 1998 with a response rate of 67%, showed that 79% of subjects said that they or another non-medical person had deliberately checked the skin on all or parts of their body for early signs of skin cancer in the past year, not including checks of particular moles or spots. This is the highest prevalence of self-screening yet reported.[9] Using the stricter criterion of 'whole-body' checks, 26% reported practising whole body self-examination at least once in the last 12 months and 34% in the last three years. Whole-body self-examination was increased in those under age 50, those with more education and those with more concern about skin cancer. Self-examination in the last three years was increased to over 60% if their doctor had suggested it, had instructed them in how to do it or if the doctor has done a skin examination. Men and women showed similar rates of skin self-examination.

Of the same group, 11% had had a whole body skin cancer check by a doctor within the last year and 31% reported a partial body check.[10] The frequency was only slightly higher in women and in younger adults. Those who had had skin examinations were at higher risk of melanoma as judged by skin type, numbers of moles and history of non-melanoma skin cancer (NMSC).

Screening for skin cancer is a substantial business in Australia. As well as general practitioners and dermatologists offering screening to higher risk patients or more generally, there is a growing number of walk-in skin clinics in which screening examinations are carried out either using clinical examination alone, or using dermoscopy or computerised imaging systems. Skin screening is also offered to employee groups using various methods. None of these services has provided any valid information on their clinical results.

Evidence about screening: survival and trends in melanoma

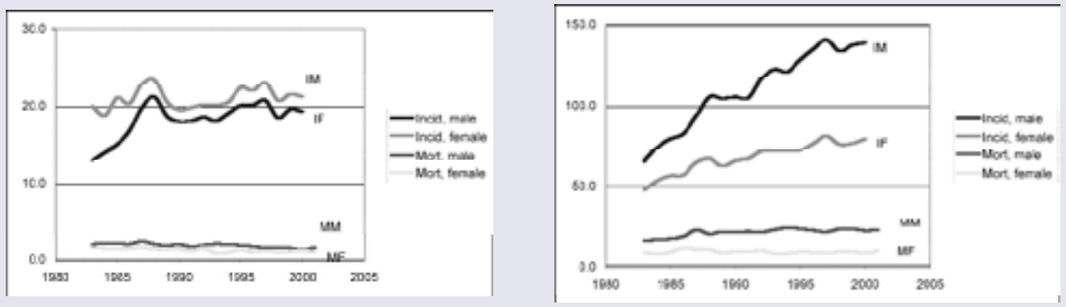
What then is the evidence for, or against, the benefits of screening? In Australia survival rates for melanoma are 90% in men and 95% in women (five-year relative survival, patients diagnosed 1992-97).[11] This shows effective early diagnosis as well as good treatment. This has been used as an argument for screening; in that, if this good situation is due to high awareness and early clinical diagnosis, doing more screening should improve it further; but it also means that any further benefits from the introduction of a systematic screening program would be limited by the already excellent survival of patients under current care. The overall mortality rates, all ages, for melanoma have been stable in men since about 1987-88. In women there has been a modest decrease since about the same time. The trends vary by age. At ages under age 50, there has been a small but clear decrease in mortality in both men and women. At these ages, after rises in the late 1980s, the incidence rates have shown variations, but around a stable long term trend (see Figure 1: data from Australian Institute of Health and Welfare).

Above age 50, the mortality rate for women has been stable since the 1980s and the men's rate has been stable since about 1995 (see Figure 1). But the incidence of melanoma is still rising sharply in the over 50 age group. Over the last 20 years the incidence in women over 50 has increased by more than 50% and the incidence is men has more than doubled. In Queensland from 1979-80 to 1999, age-adjusted incidence rates increased in all depth categories, with the greatest proportional increase for lesions less than 1.5mm thick.[12] In 1979-80, 64% of incident invasive melanomas in men and 79% in women were less than 1.5mm thick. By 1997, this had increased to 79% in men and 83% in women. However, this change in the proportional distribution was due to an increase in the incidence of thin lesions rather than a decrease in the incidence of thicker lesions. The population-based incidence rate of melanomas more than 3mm deep increased from 2.5 to 4.7 per 100,000 population per year in men over the 20 years and from 1.6 to 1.9 per 100,000 in women. So while the proportion of thick melanomas has decreased, the population incidence of deeply invasive melanoma, which will be the main driver of melanoma mortality, has been increasing over time.

The incidence trends by thickness also vary by age. In NSW from 1989 to 1996, at ages 15-34 the incidence rates of all melanoma, thin (<1mm) and thick (>1mm), decreased, while at ages over 65 the incidence of all types increased. In the intermediate age group of 50-64, the incidence of thin melanoma increased while that of thick melanoma decreased.[13] These trends suggest a real reduction in incidence in adults under age 50.

The short-term objective of screening and early diagnosis programs, which are designed to ultimately reduce deaths from melanoma, should be the reduction on a population basis of the incidence rate of deeply invasive melanoma. It would

Figure 1:



Incidence and mortality rates, per 100,000 population, by year, 1983 to 2000, Australia, for ages up to 49 years (left graph), and for ages over 50 (right graph); age-standardised within each age range. The two graphs have different vertical scales. Data from Australian Institute of Health and Welfare.

be helpful to study trends and clinical and epidemiological characteristics of deeply invasive melanoma as a specific target.

Some 20% of incident melanomas in Queensland in 1997 were thicker than 1.5mm. Deeply invasive melanomas are over-represented in men over the age of 50.[14] The presenting features of thin and thick melanoma differ, with the classical textbook definition of ABCD (asymmetry, border, colour, diameter) characteristics applying mainly to the diagnosis of thin melanomas. Thick melanomas present differently, with more red or uncoloured lesions, more frequent itch and bleeding, and other atypical presentations. Nodular melanoma, which forms a high proportion of thick melanoma, often has atypical characteristics and the diagnosis may be delayed.[15,16] So although most doctors and the general public have been made aware of the classical ABCD features of melanoma, these apply best to thin, probably slow growing and radial growth phase melanoma, rather than to the deeply invasive, nodular or vertical growth phase melanomas which result in a sizable proportion of deaths.

The question of non-progressive lesions

Early intervention for a lesion which is not progressive will not be beneficial. There is substantial evidence that a proportion of thin melanomas may not progress or progress only very slowly.[17-20] There was a very rapid rise in the incidence of melanomas in Australia in the 1980s, due mainly to a great increase in thin (less than 0.75mm depth) lesions. In-situ lesions also increased. At this time the total number of people having skin lesions removed was increasing by 14% per year and a careful analysis of this situation suggested that increased diagnosis of a non-metastasising form of melanoma could be a major part of the explanation.[17]

The issue is whether we are detecting and removing substantial numbers of lesions which are classified pathologically as early invasive or in-situ melanoma, but are not progressive, and therefore represent unnecessary intervention. This concept is not unexpected or unusual in cancer screening situations. Indeed, any cancer screening test, whether it be a high technology method such as mammography or spiral CT, or a low technology method such as clinical examination of the skin, is by definition a method designed to identify for intervention lesions which have previously been ignored. The natural history of these lesions is unknown when the screening method is introduced. In a population group, each 'early' lesion detected is a progressive lesion (which if left alone would progress to an 'advanced' lesion); the number of early lesions removed will be matched by an equal reduction in the number of advanced lesions which are diagnosed. At the other extreme, if none is progressive, the increase in the number of early lesions removed will have no effect on the incidence rate of advanced lesions subsequently detected. The reality is likely to be that some but not all of the early lesions are progressive, so that the increase in early lesions detected is linked to a smaller reduction in the frequency of advanced lesions. Whether the proportion of all lesions which are non-progressive is very large or very small is at the root of the controversy over prostate cancer screening by PSA testing and similar issues in the management of various types of lesions detected by mammography or Pap smears. It should not surprise us that some early melanomas which we are detecting and removing may not be progressive. On a population basis, a randomised trial could establish what proportion of lesions detected and removed would be progressive. For the individual, we need a biological marker to distinguish potentially fatal melanomas from those that will not progress.

Evaluation of melanoma screening

There are no randomised trials of the effects of screening for melanoma on end points like mortality. Indeed, there are no non-randomised trials and no controlled cohort studies as there are for cervical cancer screening. The lack of good scientific evidence about screening for melanoma is a serious deficiency. The only controlled study which addresses this is a case-control study carried out nearly 10 years ago in the US[21] which showed that subjects who practised skin self-examination (defined as 'a careful, deliberate and purposeful examination of the skin') and were diagnosed with melanoma had a reduced risk of progression to advanced disease (risk ratio 0.58, 95% limits 0.31 to 1.11). This result has been confirmed recently in a survival analysis of the same group of melanoma patients, with 5.4 years' median follow-up; the mortality hazard ratio associated with 'skin awareness' was 0.5 (limits 0.3 to 0.9).[22] This is consistent with screening leading to earlier diagnosis of melanoma and producing an advantage in terms of survival, but is open to lead-time and other biases. However, the other results of the case-control study are more difficult to explain.23 There was a reduced risk of melanoma incidence in those doing self-screening (risk ratio 0.66, 95% limits 0.44 to 0.99), which is unexpected. The main mechanism by which incidence could be reduced is by self-screening leading to the recognition and removal of precursor lesions, but there is no direct evidence of this from the study.[23] By combining both effects, the authors estimated that self-examination may reduce mortality from melanoma by 63% (risk ratio 0.37, 95% limits 0.16 to 0.84). However the reduction in incidence could also indicate observation bias or uncontrolled confounding within the study, raising questions about the validity of the other results. There was also the opposite of the expected dose-response effect; those who practised self-screening most carefully had less benefit than those who used it only casually. Assessing screening by case-control methods is inherently difficult and while this is a well-performed study, alternative explanations of the results cannot be easily ruled out.

There have been economic assessments, but these are totally dependent on the assumption that mortality will be reduced by a reasonable amount, for example 20%, which is made by analogy to other cancer screening programs. These show that if such a mortality reduction was produced by screening, it would be cost-effective.

A randomised trial of screening for melanoma

A randomised controlled trial, with melanoma mortality as the endpoint, would be the definitive means of determining whether screening is effective. The pilot work for a randomised controlled trial of a community-based screening program for melanoma has been done in Queensland. The full trial design was based on 44 Queensland communities with an aggregate population of 560,000 persons aged 30 years or over. Communities were paired according to their size, broad geographic location and socio-economic status based on standard indicators and randomised within pairs into intervention or control groups. This design provides 85% power to detect a 20% reduction in mortality in the 15 years from the beginning of the intervention period.[12,24]

The pilot phase involved randomisation to select nine intervention and nine control communities, running the screening program in the intervention communities and the evaluation of its short term effects. In the intervention communities, the community-based melanoma screening program was delivered over three years, comprising a community education program to promote self-screening, encouragement of prompt medical attention for suspicious lesions, promotion of whole-body clinical skin examination by GPs and an education and support program for general practitioners. No program activities were conducted in control communities. The first hurdle was to see if the program would be acceptable to the communities and particularly to the general practitioners. The answer was a definitive yes, with almost all the 100 or so general practitioners in the intervention communities agreeing to be involved in the program, attending briefing and educational sessions and accepting the materials prepared for distribution by them. In each community, a lay coordinator was appointed. The program was based on established theories of behavioural change and designed to facilitate the uptake of skin self-screening and doctor screening and its diffusion through the community. General practitioner workload was an issue; in several communities the GPs requested that additional services be provided through other general practitioners who were contracted to organise supplementary skin cancer sessions, usually at the practice facilities of the regular GPs in the area. This showed that it would be unrealistic to introduce population screening for melanoma based on general practice without supplementation of GP resources, at least in smaller communities.

The primary goal of the pilot program was to ensure that during the three-year intervention period, the proportion of the adult population who have had at least one whole-body skin examination by a general practitioner was increased to at least 60%. The sample size calculations for the full trial were based on the assumption that 60% screening participation could be achieved and that in the control communities the amount of screening would remain at around 20%. In the full trial, deaths from melanoma, deaths from all causes, incident cases of melanoma and the thickness of melanoma at diagnosis would be monitored amongst all adults aged 30 years who were resident in the intervention or control communities from the start of the intervention period, during the three year intervention period and for another 10 years after. This could be done with routine mortality collections and state cancer registry notifications. Short-term outcomes were measured through pre and post-intervention surveys by telephone and postal methods in the intervention and control communities.

A trial like this is a complex endeavour. Planning began in 1991 and funding for the pilot program was given by the Queensland Cancer Fund in 1997. Despite much effort, it has been impossible to fully fund the trial. The original plan was for the intervention to be mounted and completed in all intervention communities by the end of 2005, with mortality and other clinical outcomes monitored through to the end of 2015. So even if the Queensland trial had gone ahead, we would still be many years away from having a definitive answer to the question of mortality benefit. It could well be argued that such a result would not be helpful as by the time it came, attitudes towards skin cancer screening would be even more entrenched than at present. For example, in Germany a publicly-funded program of screening for skin cancer is being developed in which all adults over age 30 can have a full body examination by a specially trained general practitioner. Those who have an abnormality detected are referred to a dermatologist for further assessment and follow-up. This program is justified on the current burden of skin cancer morbidity and mortality and on the argument that early diagnosis will be cost effective in reducing extensive disease. The lack of randomised trial evidence has not prevented this policy being instituted. Nor has it prevented the substantial uptake of screening and the growth of various screening facilities in Australia. This example raises the general question of whether large scale long-term prospective trials are essential to assess cancer screening. The same question is debated in regard to prostate screening, helical CT screening for lung cancer and other developments. We have in progress a case control study in Queensland that can certainly assess the relationship between screening and depth of invasion at diagnosis. It may be able to estimate the proportion of lesions detected by screening which are non-progressive. With follow-up, it could relate screening to recurrence of melanoma and death from melanoma in the same way as the previous case control study. However, a key issue is whether the results of a case-control study will be acceptable to policy makers and to clinicians, particularly if the results conflict with current perceptions?

Conclusions

Screening for cancer on a population basis should be based on good evidence. There is no rigorous evidence to show or disprove the value of routine skin cancer screening. There are no available results from randomised trials or cohort studies, the only analytical study result being a single case-control study. Despite this, screening is widely practised. The main argument for the effectiveness of screening is based on the assumption that earlier diagnosis will produce mortality benefits, which in turn is based on the large differences in post-diagnosis survival by depth of invasion, for patients diagnosed in normal clinical practice. The great increase in the excision of thin melanomas

has not been matched by a similar decrease in the diagnosis of thick melanomas. However, overall mortality trends are encouraging and a beneficial effect of early clinical diagnosis is likely. It is the particular contribution of screening which is difficult to assess.

Acknowledgments

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GENETIC RISK AND MELANOMA

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Abstract

This paper reviews current understanding of the role of genetic factors in the causation of melanoma. Three genes have a proven role in influencing melanoma susceptibility: CDKN2A (p16INK4A) and its alternative product p14ARF, CDK4 and MC1R. The former two genes are frequently mutated in the context of familial melanoma, though rarely otherwise, and can raise risk to extreme levels. MC1R regulates melanocyte pigment production and its variants contribute strongly to risk in European populations because they are very prevalent, modulating individual risk by two to three fold. There are many unanswered questions about the genetic epidemiology of melanoma and the place of genetic testing in melanoma risk assessment; these are the subject of intense international collaborative research.

In one sense all melanoma is genetic. The main causes of melanoma are mutations, ie. permanent DNA sequence changes, affecting key genes in melanocytes. Melanocytic naevi are also now believed to result from short-lived clonal proliferation of melanocytes after similar mutagenic events. These may be induced somatically by solar ultraviolet radiation, other mutagens or DNA replicative errors, or may be inherited in the germline. Over the last 10 years a gradual revolution has been under way in our understanding of how they contribute to risk of melanoma.

An average Australian's risk of melanoma is currently estimated as 3.5% for women and 4.5% for men, though it is twice as high in the tropics and lower by half in the far south. It is best to regard an individual's risk as lying on a continuum, with many separate risk factors cooperating to raise or lower the probability that melanoma will develop at some time during their life. Some of these risk factors are genetic in the sense that they have been inherited and are therefore likely to be shared with parents and other close relatives. For example, it has long been understood that skin colour is a heritable trait and that fair-red, easy burning skin is associated with an above average risk of all forms of skin cancer. The other major phenotypes strongly associated with melanoma are the number, size and density of normal and atypical melanocytic naevi; these are quantitative traits with complex genetic origins. Sun exposure itself can also be strongly shared among close relatives, especially early in life; this is because families share a common environment, such as geographic location, and often share patterns and habits of sun exposure and protection.

The upshot of these considerations is that many cases of melanoma will involve related individuals. In other words melanoma will show familial aggregation. In some cases this will be due to one or a few strong genetic factors, or the additive effects of several genes, each of modest effect. In others it will be largely due to a shared high sun-exposure environment. Finally, in any large population it is inevitable that some clusters will have occurred purely by chance.

There is a separate sense in which a person's susceptibility to melanoma may be hard-wired genetically, but not inherited: critical mutations or epimutations, ie. fixed gene expression abnormalities without DNA sequence change, may have occurred in a melanocyte progenitor during embryonic-fetal development. This is an important area for future research to define but will not be discussed further here.

Historically, attention was first drawn to familial melanoma by observations of familial clusters of melanoma-susceptible individuals. These were characterised by early age of onset, multiple primary melanomas and frequent presence of atypical melanocytic naevi. Because the cases described were on the "same side" of the family, ie. shared common ancestors, it was postulated that a single gene, autosomal dominant Mendelian trait causing both melanoma and the naevi was responsible. Further research has shown that this was an oversimplification. There is no evidence yet that a syndrome of multiple banal or atypical naevi is caused by a single gene, even though familial melanoma can be.

What do we know of the genes that influence melanoma risk and their effects? Can this knowledge be utilised clinically? What more do we need to know and how is local and international collaborative research meeting this challenge? Readers have been directed in the references to comprehensive recent reviews,[1,2] to original reports with essential reference data, especially if post-dating those reviews, and to policy statements and unpublished studies of the Melanoma Genetics Consortium.

Genes that influence melanoma risk – CDKN2A

Major genetic effects are most easily discovered in families with multiple cases of melanoma. A combination of genetic linkage analysis of such families in and fine mapping of DNA deletions in the region of peak linkage to familial melanoma eventually led to the identification of the CDKN2A locus ("p16") in 1994, which was soon found to carry germline mutations in many melanoma kindreds. CDKN2A was ultimately found to produce two unrelated proteins by alternative splicing, a situation unique in the genome. The product discovered first, p16INK4A, was a known cyclin-dependent kinase (CDK) inhibitor that regulated the cell proliferation cycle at the G1-S checkpoint. Subsequently, the p14ARF product was identified and its complex functions include regulation of p53 levels and therefore pathways mediating responses to DNA damage.

CDKN2A mutations have been found in hundreds of familial melanoma kindreds throughout the world. The proportion of these kindreds with mutations varies from close to 100% in the very largest kindreds in low-incidence countries such as the UK to less than 5% in clusters of only two related individuals in Australia. Worldwide, 40% of dense kindreds (three or more cases) carry CDKN2A mutations, whereas the rate in Australian kindreds of the same density is 20-25%. These proportions increase somewhat if any cases have had multiple primary melanoma.[3]

Other putatively predisposed individuals can carry CDKN2A mutations. In the limited number of studies of multiple primary melanoma so far, frequencies from 2-15% have been observed. A recent population-based analysis of cases of melanoma under 40 years in Australia yielded a frequency of 2%; most of these carriers did not have a strong family history of melanoma.[3] Based on these and other estimates, it is unlikely that more than 1/200 melanoma cases in Australia carry a CDKN2A mutation. These mutations are observed throughout the p16INK4A exons of the gene and most of them encode proteins with altered function: altered binding to CDKs, failure to inhibit CDK activity, abnormal trafficking in the cell, or evidence of protein instability. Some mutations can affect both p16INK4A and p14ARF proteins while others affect p16INK4A, or rarely p14ARF, alone.

Phenotypes caused by CDKN2A mutation

Mouse knockouts specific for p16INK4A yield melanomas at a low rate, but this is greatly enhanced by mutagens if they are bred on to a p14ARF heterozygous background. The combined p16INK4A/p14ARF knockout is melanoma-prone, especially in the presence of activating oncogenic mutations. Taken together, there is strong genetic evidence that inherited, inactivating mutations in both products of this dual-function locus contribute to risk of melanoma and other tumours. Certainly the locus is a major target of deletion events in melanoma formation and these usually inactivate both genes, causing deregulation of a key cell-cycle checkpoint and the loss of an activator of p53-mediated apoptosis.

Carriers of CDKN2A mutations within mutation-positive families cannot be recognised clinically, although there is an association with increased number of naevi and atypical naevi. The risk of melanoma to carriers of these mutations has so far only been estimated in the context of familial melanoma, but confidence limits are still very broad and the estimates vary across geographic regions. Australian carriers of CDKN2A mutations had the highest lifetime risks, averaging 90%, in contrast to carriers in Europe in which they were less than half as high, especially in middle age. These effects are presumably due to differing regional levels of sun exposure.[4]

CDKN2A mutations, as a class, cause a significant increase in the risk of pancreatic cancer, estimated at 17% lifetime risk in one study of a common Dutch founder mutation.[5] Interestingly, recent analysis of data from around the world has shown that familial melanoma kindreds in Australia do not exhibit this association, except perhaps for carriers of the same Dutch mutation.[3] In five melanoma families worldwide, a germline CDK4 mutation prevents p16INK4A binding. The phenotype of these families is so far indistinguishable from that of CDKN2A families, but the data are simply too few to be sure of this.[3]

Other genes influencing melanoma risk – MC1R

Progress has also been made in identifying so-called low-penetrance genes, notably the melanocortin-1 receptor (MC1R) which is highly polymorphic, especially in fair-skinned populations. Many of the variant forms of this protein favour production of red-yellow (phaeo) melanins over brown-black eumelanin and are therefore associated with red hair, freckling and fair, sun-susceptible skin types. These variants are also convincingly associated with risk of both melanoma and non-melanoma skin cancer in population-based studies. The extra risk produced is modest, approximately two-fold per variant

allele carried, and is independent of skin colour; individuals with only one variant allele will exhibit a darker, eumelanin-based skin type, but still have increased risk of melanoma. Due to the high frequency of MC1R variants in the population, their overall contribution to disease prevalence (attributable risk) will be much larger than for rare, high-penetrance alleles of CDKN2A. It is anticipated that genes influencing naevus number, once they are discovered, will prove to be equally important.

The exciting discovery in 2002 that the BRAF gene is mutated at high frequency in melanoma has not had an impact on our understanding of melanoma risk. As with the second most common activating oncogenic mutation target in melanoma, NRAS, these mutations occur almost exclusively during life and are not inherited.

Genetic assessment of melanoma risk

Individual risk assessment must take a comprehensive view of personal and family history of melanoma, other risk factors such as the number and type of melanocytic naevi, skin pigmentation and evidence of sun sensitivity and past and present sun exposure. Is there a role for CDKN2A mutation testing, ie. should the gene be screened, and if a family mutation has been discovered, should an individual be tested for it? The cited reviews and position papers canvas the issues more thoroughly than space permits here.[6,7,8]

The probability of detecting a CDKN2A mutation is only substantial (>10%) in the context of a strong family history of melanoma, ie. three or more relatives affected by melanoma on the same side of the family. Importantly, a family history of melanoma cannot be taken at face value but must be confirmed from medical or cancer registry records. Previous Australian studies have shown that up to 40% of reports of melanoma in close relatives cannot be substantiated and analyses of different cohorts 15 years later show little has changed.[3]

Within the restricted context of proven high-density melanoma kindreds, in Australia, it is clear that CDKN2A mutation carriers have a substantially increased risk of melanoma. However these estimates are very imprecise (more so than for BRCA1 carriers in familial breast cancer, for example) and are probably strongly modulated by both sun exposure and pigmentation. We also know little of the risk to non-carriers in such families, however there are grounds to believe that it would be elevated, albeit to a much lesser extent than for the carriers.

Crucially, the outcome of genetic testing is unlikely to alter the risk management of the patient. All members of familial melanoma kindreds must be regarded as at increased risk of melanoma, irrespective of mutation status, and ought to be enrolled in programs of heightened surveillance. This would suggest that genetic testing has little positive to offer. There is also potential for negative consequences such as abandonment of preventive and screening behaviours in the event of a negative test. However the decision to test for carrier status of a family mutation is one for patients to make after weighing up their options and preferences. This is best done in the context of a family cancer genetics clinic.

The current research agenda

The Melanoma Genetics Consortium (now known as GenoMel) has been supported by the US National Institutes of Health (2001-6), and has recently attracted a European Union network of excellence grant (2005-9), to study the genetic epidemiology of melanoma. Partners in the consortium come from 18 centres in 11 countries and include all Australian groups working in melanoma genetics. Recruitment of people with a strong family history of melanoma remains active in Australia.

Are there more melanoma susceptibility genes to be found? Genome-wide linkage searches of the majority of familial melanoma kindreds without CKDN2A or CDK4 mutations have established that a new high-penetrance locus exists on chromosome 1p and possibly more.[9] Efforts to map and identify these genes continue. Pigmentation, naevus, sun-sensitivity and DNA repair phenotypes remain largely undefined genetically and some of the genes regulating them will undoubtedly influence melanoma risk via medium/low-penetrance alleles. In addition to direct genetic analysis of those phenotypes, there is a need for well controlled genome-wide association studies of melanoma to map and identify the relevant genes directly.

How common are these genetic variants, how strong are their effects and how do they interact with sun exposure to cause melanoma? These are questions that ideally require two types of resources: large cohorts of carriers of high-penetrance mutations, largely recruited from familial melanoma kindreds, and population-based cohorts of cases of melanoma and their relatives. Provided the appropriate risk factors have been measured, modelling of risk to the cases and their relatives will enable the strongest independent predictors of risk to be identified. Several large studies of this kind have been mounted in Australia and are currently completing data collection and analysis.

What are the issues and best practice approaches in management of people at high risk of melanoma? Now that a group at extremely high lifetime risk can be identified, at least in the context of familial melanoma, it is essential that they and their relatives at putatively lower risk be followed prospectively to resolve the uncertainties over the relationship of carrier status to risk. Psychosocial research is also required to establish the issues and consequences of genetic risk assessment in melanoma, which may differ from those in other familial cancers. Most importantly, longitudinal studies are needed to determine which clinical measures are most effective and efficient in preventing, detecting and treating future melanomas in high-risk patients.

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Melanoma is not what it used to look like

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Abstract

Two relatively new methods have changed the way primary melanoma is diagnosed. Dermoscopy (surface microscopy, epiluminescence microscopy) is a technique that was introduced at the beginning of the 1990s with the advent of inexpensive hand-held instruments. Since then, the technique has been shown to increase the diagnosis of virtually all pigmented skin lesions. In practice, this is seen by reducing the benign to malignant ratio of excised pigmented lesions while improving the diagnostic sensitivity for melanoma. Digital dermoscopy monitoring was introduced at the beginning of the millennium. Here, melanocytic lesions are excised following morphological changes seen over time. Like dermoscopy, digital monitoring can reduce excision rates of suspicious melanocytic lesions. However, in addition to this, the technique allows the identification of dermoscopically featureless melanomas that can only be detected by visual changes in time. These lesions often have a very benign appearance. These diagnostic techniques and others showing early promise, are briefly reviewed.

Techniques in dermoscopy

This article will concentrate on two diagnostic techniques, dermoscopy and digital monitoring, which have transformed the way pigmented skin lesions are assessed in routine clinical practice. Dermoscopy has been used since the early 1990s when inexpensive hand-held devices were developed in Germany. Digital monitoring is a later phenomenon, with most of the literature providing guidance for clinical practice occurring at the beginning of the new millennium.

Dermoscopy (surface microscopy, oil epiluminescence microscopy) is a simple technique that utilises an incident light magnification system (usually x10) with the addition of a liquid at the skin-microscope interface. This liquid eliminates the normal scattering of light at the stratum corneum, thus allowing the epidermis to become translucent. The result is the identification of morphological features not seen with the naked eye.[1]

In both expert hands and those of trained general practitioners, there is a significant increase in diagnostic accuracy for melanoma using dermoscopy.[2,3] This increase in accuracy is reflected in a lower benign to melanoma excision ratio and decreased excision rates.[4,5] Currently, there is a suggested two stage procedure for the diagnosis of pigmented skin lesions using dermoscopy.[1,6,7] The first stage allows the differentiation of melanocytic lesions (mainly moles and melanoma) from non-melanocytic lesions (seborrheic keratoses, pigmented basal cell carcinoma (BCC) and haemangioma). Once a diagnosis of a melanocytic lesion has been made, then the second stage allows differentiation of melanoma from benign moles.

A number of methods for differentiating melanoma from benign melanocytic lesions have been compared. The dermoscopy scoring systems for melanoma have been designed to be used by inexperienced clinicians. Such systems include the ABCD method,[8] the Menzies' Method[1,9] and the 7-point checklist.[10] Among experts of dermoscopy, pattern analysis,[11] which avoids rigid rules of the previous methods, allows an overall impression of multiple dermoscopic patterns and is probably the most widely-used. In a direct comparison of these methods by experienced dermoscopists, pattern analysis gave a superior specificity (proportion of correctly diagnosed non-melanomas) and the Menzies' Method a superior sensitivity (proportion of correctly classified melanomas).[6,12]

To illustrate how a diagnosis is made using dermoscopy, the Menzies' Method utilises 11 dermoscopic morphological diagnostic features.[6,12] For a lesion to be diagnosed as melanoma two negative features cannot be found (symmetry of pattern or a single colour). If neither of these features are present then to diagnose melanoma at least one of nine positive features must be found. These positive features are radial streaming, pseudopods, blue-white veil, multiple brown dots, peripheral black dots or globules, scar-like depigmentation, multiple blue-gray dots, broadened network and multiple (five-six) colours.

Digital monitoring

Digital (computerised) monitoring devices are usually instruments that take digital dermoscopy images and allow tiling on the computer screen for comparison of melanocytic lesions for change over time. The technique can be divided into two forms: long-term and short-term monitoring.[1]

Long-term monitoring allows comparison of atypical nevi over standard surveillance periods (generally 12 months).[13-19] Such monitored nevi, while atypical, are not considered suspicious for melanoma at the time of imaging. This technique is generally restricted to patients with the dysplastic naevus syndrome. Four to five per cent of monitored pigmented lesions will show significant changes over the surveillance period. Of those changed lesions, around 12% will be melanoma.[15] In contrast to long-term monitoring, short-term monitoring over a three-month period is used to make a clinical judgment about suspicious melanocytic lesions that do not have conclusive dermoscopic features of melanoma.[20] In short-term monitoring, any morphological change over the three-month period requires excision of the lesion. Of those changed lesions, as in the case of long-term monitoring, 12% will be melanoma. Eighty-three per cent of monitored benign atypical nevi will not change over this time. It is believed that the sensitivity is 100%, ie. all melanomas will change.[20]

What is becoming clear is that digital monitoring, both long and short-term, is identifying banal appearing melanomas that can only be detected by morphological change. In a recent prospective study of patients with dysplastic nevus syndrome, 44% of melanomas detected were found exclusively using

long-term digital monitoring.[17] None of these melanomas had diagnostic features using dermoscopy. These dermoscopy featureless melanomas are even better demonstrated with short-term monitoring.[20,21] It now seems clear that in the past melanomas were being identified at a later stage in tumor development, when dermoscopy or clinical ABCD features of melanoma (asymmetry, border irregularity, color variability and diameter greater than 6mm) became more apparent.

Future developments

The future in melanoma diagnosis probably resides heavily with automated diagnosis. Here, an instrument diagnoses a lesion without input from the clinician. Such technologies have been initially investigated in the early to mid 1990s and are now being released as clinical aids for diagnosis.[22 23] In general, studies are finding that automated diagnostic instruments have a diagnostic performance equivalent to specialist clinicians. However, to date, results of formal clinical trials are lacking. Nevertheless, it seems clear that such instruments will be a fundamental aid for diagnosis in the future.

Finally, in vivo confocal scanning laser microscopy is a technique that allows visualisation of single cells in the epidermis and upper dermis of lesions while on the patient's skin. While depth of penetration is a limiting factor with such instruments, melanoma in the epidermis seems to be visualised with gold standard histological accuracy. However, while holding much promise, such studies are in their infancy.[24]

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Magnetic resonance spectroscopy in the management of melanoma

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Abstract

The surgical treatment of melanoma has been progressively rationalised during the last two decades. Radical excision of primary tumours and elective (prophylactic) resection of regional lymph nodes have been replaced with more selective procedures that reflect improved understanding of the metastatic potential of individual tumours. Magnetic resonance spectroscopy (MRS) is an evolving technology which has the potential to diagnose many tumours and to characterise their metastatic potential. The Institute for Magnetic Resonance Research and the Sydney Melanoma Unit have developed MRS techniques to diagnose, stage and aid in the clinical management of melanoma. It is anticipated that these techniques will ultimately be used as clinical tools to provide non-surgical diagnosis of metastatic disease in sentinel nodes, either by MRS examination of a simple outpatient fine needle biopsy specimen or by use of an entirely non-invasive in vivo MRS assessment. Experience with MRS of primary breast cancers indicates that it may also be possible to predict the metastatic potential of melanoma by spectroscopic analysis of the primary tumour and to distinguish naevi from melanomas thus better selecting patients for surgery.

The last decade has seen the introduction of lymphatic mapping and sentinel node biopsy in an effort to rationalise the management of patients with intermediate and thick melanomas and stage them more accurately. While in the past an elective regional node dissection was recommended for such patients by many melanoma treatment centres around the world, currently only patients with a positive sentinel node are subjected to a complete field clearance at the time of their presentation. Thus many patients are now spared this procedure and its inherent risks and associated morbidity. Although sentinel node biopsy is generally associated with low rates of significant morbidity,[1,2] the development of non-surgical techniques that could determine the disease status of mapped sentinel nodes, and indeed other relatively inaccessible lesions in melanoma patients, would represent a significant advance. Experience with proton magnetic resonance spectroscopy (MRS) in the diagnosis of several primary human cancers has demonstrated that this technology is potentially capable of being developed both to identify metastatic malignancy and to predict those individual primary tumours which have a metastatic phenotype. In the case of MRS examination of a fine needle aspiration biopsy from a primary breast tumour, the method can determine pathology, nodal involvement (without direct biopsy of the nodes), tumour vascularisation, tumour grade and oestrogen and progesterone receptor status.[3,4] A collaborative project has now evolved to explore these and other applications related to the diagnosis and staging of melanoma with MRS.

MRS provides information on the chemical composition of cells and tissues, the changes that occur in the disease process, the host response and the aging process.[5] Proton MRS (on biopsy specimens, ie. ex vivo) provides an adjunct to current morphological methods for the diagnosis of human tumour pathology with sensitivities and specificities of at least 95%. Accuracies as high as 99% are obtained when mathematical classifiers are used to analyse the data.[6,7] MRS can also detect changes during tumour development and progression, including altered cellular chemistry ie.not morphologically manifest.[5] The sensitivity of the MRS method was exhibited in a study of a rat model for lymph node metastasis where malignant cells in lymph nodes were detected with a greater sensitivity than histology.[8] Micrometastases were detected that were not apparent even when the entire node was serially sectioned for examination by histology. The MRS diagnoses were confirmed to be correct by growth of the tumour in nude mice following xenografting of nodal tissue.[8]

In vivo MRS yields the chemical information from spectroscopy in one of two forms; single voxel spectroscopy (SVS), where a single area of interest is located by MRI[9] or 2D or 3D magnetic resonance spectroscopic imaging (MRSI) where a 2D or 3D grid of spectra is overlaid on an MR image.[10] A variety of applications, including diagnosis of prostate and breast cancers, has been demonstrated using whole-body magnets and MR spectroscopy at 1.5 Tesla (T) and 3T to monitor altered chemistry. For a review of these applications see Mountford et al. 2004.[5]

Diagnosis of metastatic melanoma in lymph nodes by MRS (8.5T) of fine needle aspiration biopsies (FNAB)

Elective lymph node dissection has now been replaced by sentinel node biopsy (SNB) in most major melanoma treatment centres around the world with blue dye and radioactive tracers used to identify the node/s that receive lymph directly from the area of skin bearing the primary tumour. SNB thereby allows patients with micrometastatic nodal disease to be accurately identified. It is however an invasive surgical procedure with a 5-15% complication rate whilst the histological examination of SLNs requires labour-intensive (expensive) serial sectioning and the use of immunohistochemistry. Patients with intermediate thickness and thick melanomas are known to have metastatic tumour in their related sentinel nodes at rates ranging upwards from 15%.[11]

A reliable method of determining regional lymph node status without a need for surgery would reduce patient morbidity and conserve the resources currently applied to surgical SNB

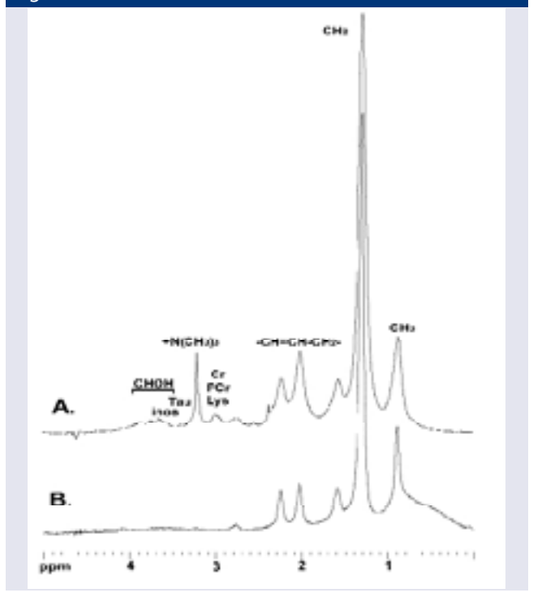
and pathological assessment. Our group commenced its experience with MRS and melanoma by undertaking a study that performed MRS on fine needle aspiration biopsies (FNABs) of sentinel nodes (SNs) procured by conventional surgery. A statistical classifier was then utilised to determine the accuracy with which MRS could identify metastatic tumour in the SNs.

FNABs were obtained from 118 lymph node tissue specimens from melanoma patients undergoing regional node surgery for suspected metastatic melanoma. Each FNAB was assessed using 1D proton MRS analysis at 8.5T.[12,13] Diagnostic correlation was performed between the MRS and histopathological data using a Statistical Classification Strategy (SCS) pattern recognition method designed specifically for biomedical spectroscopy databases.[7,14] The primary data set comprised MR spectra of FNABs from 56 samples containing metastatic melanoma and 62 samples free of metastatic disease. A secondary validation set of duplicate FNABs from a subset of the same tissue samples as the primary data set (24 melanoma-containing, 38 free of metastatic disease) were also classified with the classifier developed from the primary data set to test the variability of FNAB samples from the same tissue, variability in sample handling and storage and variability within the proton MRS measurement procedure.

Typical proton MR spectra of FNABs from histologically benign and malignant specimens are shown in Figure 1. Resonances in the spectra include those consistent with lipid, choline metabolites, creatine, phosphocreatine, lysine, taurine, inositol and carbohydrates.

Pattern recognition analysis was applied to the two histopathological categories, ie. free of metastatic disease tissues and tissues containing metastatic melanoma. In the primary data set, the presence of metastatic melanoma was predicted with a sensitivity of 92.9%, a specificity of 90.3% and an accuracy of 91.5%. Six false positives and four false negatives were identified. In the secondary validation set (utilising second FNABs from a subset of the same tissues) the presence of metastatic melanoma was predicted with a sensitivity of 87.5%, a specificity of 90.3% and an accuracy of 89.1%. These results are summarised in Table 1.[13]

Figure 1:



1D proton MRS (8.5 Tesla) of FNABs of lymph nodes from melanoma patients. A) Node containing metastatic melanoma; and B) Benign node. Reprinted from Annals of Surgical Oncology 2005: In press. Stretch JR, Somorjai R, Bourne R, Hsiao MD, Scolyer RA, Dolenko B, Thompson JF, Mountford CE, Lean CL. Melanoma Metastases in Regional Lymph Nodes Accurately Detected by Proton Magnetic Resonance Spectroscopy of Fine Needle Aspirate Biopsies, with permission from Springer.
Abbreviations:
CH_3 - methyl; CH_2 - methylene; $+N(CH_3)_3$ - N-trimethyl of choline and choline-based metabolites; $-CH=CH-CH_2-$ - acyl chain protons, N- or O-acetyl groups at 2.0 ppm; Cr – creatine; PCr – phosphocreatine; Lys – lysine; Tau - taurine; inos – inositol; CHOH - carbohydrate residues.

Table 1:

SCS-based classification of MRS data of FNABs from regional lymph nodes of melanoma patients. Reprinted from Annals of Surgical Oncology 2005: In press. Stretch JR, Somorjai R, Bourne R, Hsiao MD, Scolyer RA, Dolenko B, Thompson JF, Mountford CE, Lean CL. Melanoma Metastases in Regional Lymph Nodes Accurately Detected by Proton Magnetic Resonance Spectroscopy of Fine Needle Aspirate Biopsies, with permission from Springer.

	Sensitivity%	Specificity%	Crispness%	*Accuracy%
Primary data set				
Metastatic vs Benign	92.9	90.3	93.2#	91.5
Second data set				
Metastatic vs Benign	87.5	90.3	92.7#	89.1

* Accuracy for the test was obtained using the crisp data, ie. When specimens classified as fuzzy were excluded. A class assignment was fuzzy if the class probability was less than 75 per cent.

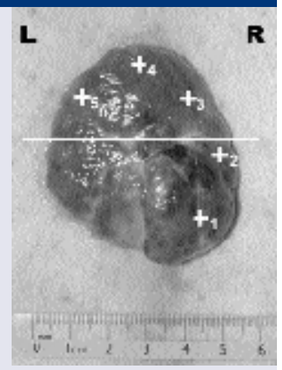
For the primary data set 8 of 118 samples were classified as fuzzy. For the second data set 4 of 62 samples were classified as fuzzy.

MRS diagnosis of primary and secondary melanoma on tissue biopsy at 8.5T and in vivo at 1.5T

In a study of punch biopsies of benign skin lesions and melanomas, proton MRS at 8.5T distinguished the two pathologies based on the presence of choline based metabolites in the spectra of malignant tissues. Similarly, using tissue biopsies, lymph nodes containing metastatic melanoma have been distinguished from uninvolved nodes based on the presence in the MR spectra of resonances consistent with choline based metabolites. For both primary lesions and lymph nodes this information has also been shown to be obtainable using MRS in vivo at 1.5T.

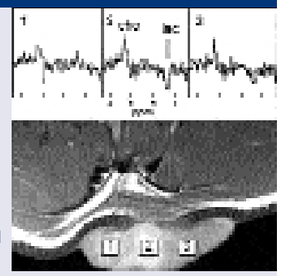
Reporting on a series of case studies, in vivo MRS at 1.5T was used to assess a large polypoid cutaneous melanoma (Figure 2) and two enlarged lymph nodes containing metastatic melanoma. Spectra were acquired in vivo from voxels wholly within the primary tumour (Figure 3) or metastatic lymph node (Figure 4) and were thus uncontaminated by signals from adjacent tissue. Tissue biopsies (Figure 5) taken after resection of the primary tumours and metastatic lymph nodes were examined by 8.5T MRS and the results compared with the in vivo spectra and with spectra from normal skin and a benign skin lesion. There was good agreement observed between the dominant features of 1.5T spectra acquired in vivo and 8.5T spectra acquired from resected tissue. However, less intense resonances observed at 8.5T in malignant biopsy tissue were not consistently observed at 1.5T in vivo. In vivo spectra from primary and metastatic melanoma showed high levels of choline metabolites. An intense lactate resonance was also present in the in vivo spectrum of primary melanoma. All 8.5T spectra of biopsies from primary and secondary melanoma showed high levels of choline metabolites and lactate, and additional resonances consistent with elevated levels of taurine, alanine,

Figure 2:



Clinical photograph of primary melanoma (Case 1).
The heavily pigmented quadrant can be seen on the inferior right of the tumour. The white line shows the approximate centre of the axial CSI slice shown in Fig. 2. Biopsy sites are marked 1-5. Reprinted from European Journal of Radiology, 53/3, Bourne R, Stanwell P, Stretch J, Scolyer R, Thompson J, Mountford C, Lean C. In Vivo and Ex Vivo Proton MR Spectroscopy of Primary and Secondary Melanoma.:506-513. Copyright (2005), with permission from Elsevier.

Figure 3:

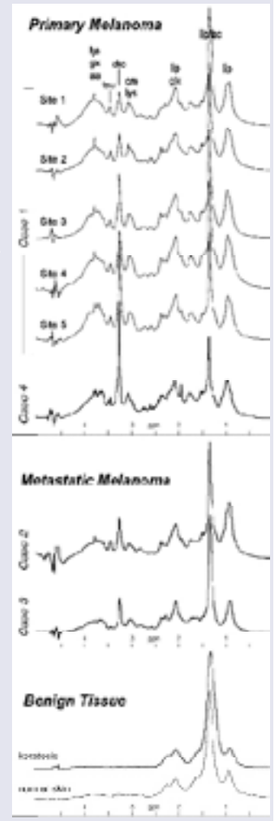


Axial plane CSI of primary melanoma (Case 1).
Spectra interpolated from three separate volumes (boxes labelled 1-3) within the tumour are shown. Note the choline resonance (3.2ppm) and inverted lactate resonance (1.3ppm). The approximate centreline of the slice (12mm thickness) is indicated by the line in Fig. 1. Field of view 16x16cm, matrix 16x16, TR=1200ms, nominal voxel size 1.2x1x1cm, global water shim ca. 11Hz, spectral width 1kHz. Reconstruction matrix 32x32. Interpolated voxel size (shown in figure) = 1.2x0.5x0.5cm. Reprinted from European Journal of Radiology, 53/3, Bourne R, Stanwell P, Stretch J, Scolyer R, Thompson J, Mountford C, Lean C. In Vivo and Ex Vivo Proton MR Spectroscopy of Primary and Secondary Melanoma.:506-513. Copyright (2005), with permission from Elsevier.

Figure 4:

Axial plane CSI of metastatic melanoma in lymph nodes (Cases 2&3).
The figure shows interpolated spectra acquired from a 0.3cm3 volume within A) a 5 x 3.5 x 3cm inguinal node, and B) a 5 x 6 x 3.5cm axillary node. Note the intense choline resonance at 3.2ppm. Acquisition details as for Fig. 2. TE=130ms. Interpolated voxel size (inner rectangle shown in figure) = 1.2x0.5x0.5cm. The outer (white) rectangle represents the CSI volume of interest (VOI). Reprinted from European Journal of Radiology, 53/3, Bourne R, Stanwell P, Stretch J, Scolyer R, Thompson J, Mountford C, Lean C. In Vivo and Ex Vivo Proton MR Spectroscopy of Primary and Secondary Melanoma.:506-513. Copyright (2005), with permission from Elsevier.

Figure 5:



8.5T 1D MR spectra of malignant and benign biopsy tissue.
The figure shows: five biopsies from different parts of a large primary melanoma (Case 1) and a single biopsy from a smaller primary (Case 4); two biopsies from two patients with metastatic melanoma (Cases 2&3); and two types of benign tissue (normal skin and keratosis). Note the general similarity of spectra from biopsies of the primary and secondary tumours and the intense choline and creatine resonances relative to the spectra from normal skin and a benign squamous keratosis. The approximate positions of the biopsies from Case 1 are indicated in Fig. 1. 360.1MHz, TR=1s, time domain=8k, 256 transients, pulse angle=60o, spectral width 3600Hz. Reprinted from European Journal of Radiology, 53/3, Bourne R, Stanwell P, Stretch J, Scolyer R, Thompson J, Mountford C, Lean C. In Vivo and Ex Vivo Proton MR Spectroscopy of Primary and Secondary Melanoma.:506-513. Copyright (2005), with permission from Elsevier.

Abbreviations: glx = glutamine/glutamate; tau = taurine;
lip = lipid; cho = choline compounds; ala = alanine; lys = lysine, cre = creatine; lac = lactate.

lysine and glutamate/glutamine relative to normal and benign tissues. Elevated levels of choline, lactate, taurine and amino acids thus appear to be clinically useful markers for identifying primary and metastatic melanoma.

Conclusions

Proton MRS of FNABs obtained from surgically procured SNs enables accurate diagnosis of metastatic disease in melanoma patients. Proton MRS (on biopsy specimens) has the potential to rapidly and objectively determine the lymph node status of patients with melanoma. Combined with lymphoscintigraphy and ultrasound guided fine needle biopsy of lymph nodes, this MRS technology offers the promise of accurate and minimally invasive assessment of regional lymph node status with high accuracy.

MRI and MRS in vivo have the potential to provide preoperative pathological diagnosis of primary and secondary melanoma. In particular, MRI may provide detailed information about primary melanomas including morphological parameters such as tumour depth and satellitosis, while MRS holds potential for determining the malignant potential of a lesion and the status of regional lymph nodes with high accuracy without biopsy.

The maturation of ex vivo and in vivo MR methodologies to provide reliable non-invasive preoperative diagnosis of melanoma and non-invasive or minimally invasive assessment of lymph node involvement would undoubtedly improve and simplify the clinical management of melanoma patients.

Acknowledgements

We thank Roger Bourne, Peter Stanwell, Chitra De Silva, Ling-Xi Li, Fiona Sutherland, Susan Dowd and Uwe Himmelreich for their contributions to the MR melanoma program. We gratefully acknowledge the contributions made by our colleagues at the National Research Council, Winnipeg, Ian Smith, Ray Somorjai, Brion Dolenko, Slawek Tomanek, Scott King and Sascha Nikulin. Thanks also to Sinead Doran and Kaye Oakley for invaluable help in preparing this manuscript.

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Collaboration between clinicians and pathologists: a necessity for the optimal management of melanoma patients

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Abstract

Pathological assessment of a tissue biopsy is a critical aspect in the multidisciplinary management of melanoma patients because it not only establishes a definite diagnosis in most cases but also provides information that to a major extent influences patient prognosis and directs initial further management. For the pathological report to be as accurate as possible, it is important that the clinician provides the pathologist with an adequate tissue sample and appropriate clinical details. If circumstances permit, an excision biopsy with narrow clearance margins is the most appropriate biopsy of a melanocytic tumour. This will enable an accurate assessment and allow definitive treatment to be planned appropriately if a diagnosis of melanoma is confirmed. Incomplete biopsies (such as shave, punch or curetting biopsies) may impair the accuracy of pathological diagnosis and the assessment of some important parameters and should be avoided if possible. Clinical factors that influence pathological assessment of melanocytic tumours include patient age and sex, the site of the lesion and others factors (such as prior biopsy, other trauma, surface irritation, pregnancy, topical treatment and recent strong sunlight exposure) should be communicated to the pathologist. The latter features may induce atypical pathological features and lead to a misdiagnosis of melanoma. The prognosis for patients with localised primary cutaneous melanoma depends principally on tumour thickness, but other factors such as the presence or absence of ulceration, mitotic rate, Clark level, anatomical site, age and sex are also important. The distance of the tumour from the excision margins and the presence of desmoplasia, neurotropism, regression, satellites or vessel involvement are other features that may affect prognosis and management. It is therefore important that the pathology report details all these factors. The use of a synoptic format pathology report can facilitate this.

Cutaneous melanoma is a major public health problem in European-derived populations around the world. In such countries, the incidence of melanoma has increased by about 5% per year over the past 40 years.[1] In 2003 in New South Wales, melanoma was the second most common cancer for both men and women.[2] Mortality from melanoma is lower than for other common cancers and is stable or declining slowly, but it has a disproportionately heavy impact on productive years of life because melanoma is the commonest cancer in young adults.[2] For these reasons, those involved in the diagnosis and treatment of patients with melanocytic lesions need to know the optimal methods for diagnosis, potential pitfalls in diagnosis and the important features that influence prognosis and direct management.

Patients with primary cutaneous melanocytic lesions rely on the knowledge, skills and experience of both their treating clinician and their pathologist for accurate diagnosis and appropriate management. Especially if the clinical diagnosis of a skin lesion is uncertain or suspected to be malignant, pathological assessment of a tissue biopsy is necessary. In such circumstances it is important that the clinician provides the pathologist not only with an adequate tissue sample, but also with clinical details that will assist in establishing a diagnosis. For patients with melanoma, their prognosis and further management will depend to a major extent not only on the pathological diagnosis, but also on other pathologically assessed/measured parameters. These parameters include the thickness, ulcerative state, Clark level of invasion and dermal mitotic rate of the tumour, as well as its microscopically measured proximity to the resection margins. Clinicians should know the important factors that should be included in every pathology report of a melanoma and ensure that their pathologist provides this information. The use of a synoptic format for pathology reporting of melanomas can facilitate this.

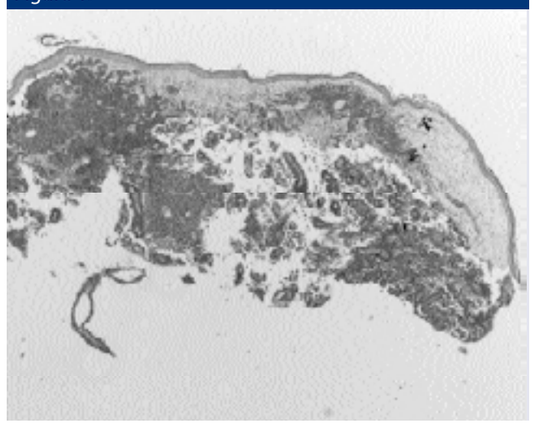
Biopsy techniques for cutaneous melanocytic lesions

If there is concern about the nature of a skin lesion and the possibility of melanoma cannot be excluded clinically, the lesion should be entirely excised for histopathological examination, with a 2mm clearance margin, when circumstances permit.[1] Such excision biopsy is recommended for reliable pathological diagnosis and to allow definitive treatment to be planned appropriately if a diagnosis of melanoma is confirmed. For melanomas, pathological examination of the specimen will provide details of the thickness of the primary tumour and any unfavourable prognostic features such as ulceration or a high dermal mitotic rate. Even if a confident clinical diagnosis of melanoma is made, it is important to perform an initial excision biopsy with narrow margins, so that subsequent definitive treatment options are not compromised. If an excessively wide margin is taken, or if complex flap reconstruction is undertaken, subsequent wider excision with adequate margins might be difficult to plan and lymphatic mapping (with a view to sentinel lymph node biopsy or simply to guide follow-up) may be inaccurate.[1]

Following excision, the specimen should be placed in 10% neutral buffered formalin for approximately 24 hours for adequate fixation prior to tissue processing. Small biopsies can be allowed less fixation time if the result is required urgently. Cytology and frozen sections for the diagnosis of primary cutaneous melanocytic lesions should be avoided because the risk of misdiagnosis is unacceptably high and changes induced by these techniques will compromise subsequent pathological assessment.

For large lesions, particularly those on cosmetically sensitive areas such as the face, or for lesions at sites that are difficult to biopsy (such as a subungual location), incision biopsy or punch biopsy may be performed with an aim of establishing a definite diagnosis. While clinical reasons dictate the need for this approach, it is important that clinicians are aware of the limitations of such procedures and the potential for misdiagnosis with the use of incomplete biopsies of melanocytic lesions. Incomplete biopsies, particularly punch biopsies, may provide unrepresentative sampling of a heterogeneous lesion so that a focal area of melanoma may be missed by the biopsy. Because the pathological diagnosis of melanocytic lesions relies on assessment of a range of architectural and cytological features of the lesion, including those at its deep edge and peripheral margins, incomplete biopsy specimens of melanocytic lesions may cause difficulties in diagnosis. In addition, for a lesion in which a definite diagnosis cannot be made on the initial partial biopsy, the assessment of a subsequent complete excision specimen may be compromised by reparative and regenerative changes in the lesion. Residual banal naevi may regenerate following incomplete removal and display pathological features mimicking those of melanoma ("pseudomelanoma").[3,4] For this reason, the use of such limited biopsies may lead to misdiagnosis by pathologists. The risk of misdiagnosis is greater if the pathologist is unaware of this phenomenon, is inexperienced or is not informed of the prior biopsy by the clinician. Even if a diagnosis of melanoma is established with confidence on the basis of a shave or punch biopsy, it may be impossible to establish the true thickness of the lesion (Figure 1). Knowledge of the thickness of the lesion is currently critical in determining appropriate definitive management, such as the width of excision margins[5] and the appropriateness of sentinel lymph node biopsy[1]. It is also an important prognostic feature. The potential for misdiagnosis when assessing incomplete biopsies is also highlighted by the fact that in one recent study it was found that up to 80% of medical malpractice claims in relation to melanoma involved incomplete biopsy specimens.[6]

Figure 1:



It is not possible to accurately determine the thickness of the melanoma in this ragged superficial biopsy specimen as the deep aspect of the tumour is not included. Knowledge of the depth of the tumour is critical in determining appropriate definitive management, such as the width of excision margins and the appropriateness of sentinel node biopsy. Incomplete biopsies of melanocytic lesions may at times compromise the accuracy of pathological diagnosis and should be avoided if at all possible.

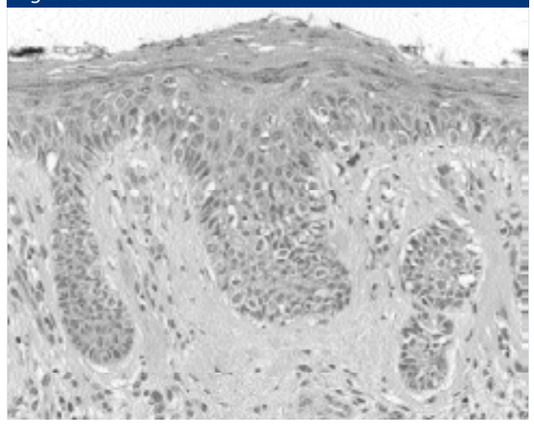
Clinical information necessary for optimal pathological assessment of melanocytic tumours

A definitive pathological diagnosis of a primary cutaneous melanocytic lesion should not be made without knowledge of the age and sex of the patient and the site of the lesion. The age of the patient is important in determining the significance of any atypical features such as the occurrence of dermal mitoses. Naevi occurring in unusual sites, such as the external genitalia or acral locations, may resemble melanomas pathologically and if the site of the lesion is not identified they are readily misdiagnosed. A lack of awareness of the other clinical details may also result in misdiagnosis in a variety of situations because some factors may induce changes in naevi that are usually associated with melanomas. Such factors include prior biopsy (Figure 2), other trauma, superficial irritation, pregnancy, recent strong sunlight exposure, topical treatments or co-existent blistering disorders.[3,7-10] A pathologist unaware of such clinical scenarios may misdiagnosis a naevus as a melanoma. Alerting the pathologist to unusual or changing foci, such as light or dark areas is also important. Light areas may represent regression and while most dark areas represent benign foci of hyperpigmentation, a small percentage represent melanoma.[11] The presence of the dark foci should prompt the pathologist to examine deeper tissue sections of the specimen if the cause of these foci is not identified microscopically in the initial tissue sections.

For wide excision specimens, it is also important for pathologists to be made aware of the histological subtype of a previously biopsied melanoma and involvement of the margins in any previous biopsy, since these factors may influence how the specimen is examined pathologically and therefore the accuracy of the pathology report. For example, the pathological features of a desmoplastic melanoma may be extremely subtle and difficult to distinguish from scar tissue.[12] Very careful microscopic assessment of the tissue sections, including sections stained immunohistochemically for S100 protein are usually necessary for accurate diagnosis.

For those lesions in which assessment of surgical margins is critical in determining the need for further surgery, or its extent, orientating specimens with marking sutures (or other techniques) at the time of surgery can be very useful. In such circumstances, the pathologist can assist the clinician by providing a specimen diagram or photograph that illustrates the extent of the tumour and its proximity to the resection margins. Photography can also be very useful when assessing clinically heterogenous lesions by enabling the clinician to direct the pathologist to any areas of particular concern. Careful clinicopathological correlation in this manner may be especially helpful in the develoment of new techniques for clinical diagnosis or when clinicians are acquiring new skills, such as dermoscopy.[11]

Figure 2:



Pagetoid epidermal invasion (upward extension within the epidermis) of melanocytes induced by surface irritation from scratching in a junctional naevus. Pagetoid epidermal invasion in melanocytic lesions is usually associated with a diagnosis of melanoma, but may sometimes occur in other settings (see text and reference 10 for a more detailed discussion of causes). By providing the pathologist with an appropriate clinical history, such as a history of previous biopsy or irritation to the lesion, the clinician may assist in establishing the correct diagnosis.

Predictors of prognosis for patients with primary cutaneous melanoma

In the absence of detectable metastatic disease, the prognosis for a patient with a primary cutaneous melanoma depends principally on the thickness of the primary tumour. Other features, such as the presence or absence of ulceration, dermal mitotic rate, Clark level of invasion and the anatomical site of involvement and patient characteristics, such as age and gender, are also important.[13] To enable an accurate estimate of prognosis to be made, it is important that the pathology report details all these factors.

The 6th edition of the American Joint Committee on Cancer (AJCC) staging system for melanoma was introduced in 2002 and an outline of it is presented in Table 1.[14] It was based on the details of 17,600 patients from 13 melanoma treatment centres around the world.[13] The staging system is used to define risk groups with regard to metastatic risk and survival rates, criteria for patient stratification and reporting of clinical trials, to allow comparison of treatment results from different centres and as a valuable tool for clinical decision making. It is important that pathology reports include all the information necessary for accurate staging of patients.

Table 1: Outline of the 2002 AJCC staging system for melanoma

Stage	Criteria
0	Melanoma in situ
IA	Tumour thickness ≤1.0 mm without ulceration and Clark level II/III.
IB	Tumour thickness ≤1.0 mm with ulceration or Clark level IV/V, or tumour thickness 1.01-2.0 mm without ulceration.
IIA	Tumour thickness 1.01-2.0 mm with ulceration, or tumour thickness 2.01-4.0 mm without ulceration.
IIB	Tumour thickness 2.01-4.0 mm with ulceration, or tumour thickness >4.0 mm without ulceration.
IIC	Tumour thickness >4.0 mm with ulceration.
IIIA	Any tumour thickness with no ulceration and 1-3 microscopically positive LNs.
IIIB	Any tumour thickness with ulceration and 1-3 microscopically positive LNs or any tumour thickness without ulceration and 1-3 macroscopically involved LNs or any tumour thickness with or without ulceration and either satellite(s)/ in transit metastasis(es) without metastatic node(s).
IIIC	Any tumour thickness with ulceration and either 1-3 macroscopically involved LN(s) or satellite(s)/ in transit metastasis(es) without metastatic LN(s) or any tumour thickness with 4 or more metastatic LNs or satellite(s)/ in transit metastasis(es) with metastatic LN(s).
IV	Any tumour thickness, any number of involved LNs and any distant skin, subcutaneous, nodal or visceral metastases.

Abbreviations: LN = lymph node

Although not included in the recent AJCC melanoma staging system, mitotic rate (MR) is a powerful prognostic factor for melanoma patients, both by its influence on overall survival[15-19] and its influence on SN positivity[20,21] and positivity of non-SNs in completion lymph node dissection specimens (Sydney Melanoma Unit (SMU), unpublished data). One of the aforementioned studies was an SMU analysis of 3661 patients,[18] in which it was found that MR was more important than ulceration and ranked second only to Breslow thickness in prognostic significance.[18] In that study, highly statistically significant differences in patient survival were found between each MR group ($p < 0.0009$), irrespective of whether the MR was grouped according to either of two methods (method A : 0, 1-4, 5-10, and >11 mitoses/mm^2 or method B: 0-1, 2-4, and >5 mitoses/mm^2). In a subsequent SMU study, the prognostic significance of MR was determined in a separate series of 1317 patients in whom the primary lesion pathology had been assessed by the late Dr Vincent McGovern.[22] In these patients, stage (according to the 2002 AJCC Staging System) was found to be the most predictive factor for survival ($p<0.0001$). However, MR still proved to be an important independent predictor of survival ($p=0.008$). The methods used to determine the MR pathologically were different in these two recent SMU studies and this may explain why MR was a somewhat less powerful independent predictor of survival in the latter study. In our initial study,[18] MR was assessed as the total number of mitoses per mm^2 in the dermal area of the tumour with the highest MR (as per recommendations of the 1982 International Pathology Workshop),[23] whereas the method used by Dr McGovern was to determine the average number of mitoses in at least 10 high power (x300) fields across the entire lesion and to express MR as the average number of mitoses per high power field (HPF) (as per the 1972 recommendations of the International Pigment Cell Conference).[24] In contrast to the method used to determine the MR in our initial study and current recommendations, no endeavour was made by Dr McGovern to find the area with the highest MR.

In view of these results, we recommend that the MR of a melanoma should be determined by commencing the mitotic count in the microscopic field with most mitoses and then counting in successive fields (over a 1mm^2 area). As the number of mitotic figures often varies greatly between different parts of a tumour, unless a standardised method is used to determine the MR, there is likely to be poor interobserver reproducibility between pathologists in their assessment of MR. As the field diameter of different microscopes is known to vary greatly,[25] it is also important that the MR is expressed as mitoses per mm^2 rather than per high power microscopic field.

Given these findings, it is important that MR be assessed by a standardised method and documented for all primary cutaneous melanomas. Including MR in future revisions of the AJCC/UICC melanoma staging system may improve its accuracy and should more rigidly define risk categories for patients entering clinical trials.

The reproducibility between pathologists of important histopathological prognostic variables, including MR, is another important question. In a further study, therefore, the inter-observer reproducibility among pathologists for these variables was assessed. It was found that there was excellent inter-observer agreement for assessment and measurement of tumour thickness (intraclass correlation coefficient (ICC) = 0.96), ulcerative state (kappa score (k) = 0.83) and MR (ICC=0.76) and fair to good agreement for Clark level (k=0.60).[26] This is despite the fact that the pathologists involved in the study had widely differing experience in the assessment of melanocytic lesions and included specialist dermatopathologists and general and trainee pathologists.

Features that should be included in the pathology report of a melanoma

It is critically important that the pathology report includes information that allows the most appropriate management recommendation to be made to the patient and also allows the determination of a reliable estimate of prognosis. The latter is important not only so that the patient can be informed of this estimate, but also so that assessment of clinical trial eligibility can be determined and stratification into a risk category subgroup within the trial can be performed accurately. Ultimately the results of these trials have the potential to significantly affect the treatment and management of melanoma patients.

In addition to the important prognostic features described above, there are other features that have an important influence on patient management and therefore must be documented in the pathology report. Such features include the microscopically measured distance of the tumour from the excision margins. The recommended appropriate margin of excision for a primary cutaneous melanoma depends on the thickness of the primary tumour. Most authorities currently recommend that melanomas <1mm thick should be removed with a 1cm margin, melanomas between 1 and 2mm thick should be excised with a margin of either 1cm or 2cm and melanomas that are >2mm thick should be excised with surgical margins of 2cm.[5,27] The thickness of the tumour is also used to determine which patients are most suitable for a

sentinel lymph node biopsy.[1]

The presence of neurotropism or desmoplasia in a melanoma is associated with an increased risk of local recurrence.[28,29] The presence of these features in a melanoma will usually prompt a wider margin of excision to be performed or may prompt the administration of postoperative radiotherapy. The degree of desmoplasia within a melanoma may correlate with its risk of metastasising to regional lymph nodes and with patient prognosis. Recent reports suggest that regional node field metastases are less frequent in "pure" desmoplastic melanomas and that such tumours are associated with a more favourable prognosis than non-desmoplastic melanomas.[29,30]

Other features of primary melanomas that should be included in the pathology report include its histological type, growth phase, predominant cell type, presence of lymphatic or vascular invasion, presence of satellites and any evidence of regression.

Traditionally, melanomas are classified into different histological subtypes: superficial spreading, lentigo maligna/Hutchinson's melanotic freckle, acral lentiginous and nodular.[23,24,31] Although it appears that assignment to one of these subtypes does not have significant prognostic relevance, it is recognised that they define well-known clinicopathological entities.

The concept of tumour progression is based on the assumption that a melanoma develops the potential to metastasise by going through a series of evolutionary steps. Melanomas in the "radial growth" phase have no capacity to metastasise and are therefore cured by adequate local excision. Definitions have been proposed to histologically determine the growth phase of the tumour.[15] Some studies have shown that the histologically defined growth phase correlates with the metastasising capability of the tumour.[15,32]

Table 2: An example of a synoptic pathology report for a primary cutaneous melanoma

Pathologic Feature	Example
Sex	Male
Site	Left shoulder
Diagnosis	Melanoma
Histological subtype	Superficial spreading
Vertical growth phase	Present
Breslow thickness	2.4mm
Ulceration (diameter in mm)	Present (3.6mm)
Dermal mitotic rate (per mm2)	9
Clark level	IV
Vascular or lymphatic invasion	Absent
Neurotropism	Present
Desmoplasia (% of dermal invasive tumour)	Absent
Satellites	Absent
Features of regression:	
Early (TILs)	Mild and focal (non-brisk)
Intermediate (angiofibroplasia +/- TILs)	Absent
Late (fibrosis and loss of rete ridges)	Absent
Predominant cell type	Epithelioid
Associated naevus	Dysplastic compound naevus
Nearest lateral margin to insitu component	1.2mm
Nearest lateral margin to dermal invasive component	4.2mm
Distance from tumour to deep margin	6.5mm

Abbreviations: mm = millimetres; % = percentage; TILs = tumour infiltrating lymphocytes

The presence of satellites[13] and of vascular or lymphatic invasion[15] are correlated with reduced survival in melanoma patients. A predominance of spindle cells has been associated with a more favourable prognosis in some studies.[33,34] The relationship between the presence of regression and prognosis in melanoma patients has been the subject of some controversy. Most studies assessing the relationship have been limited by lack of standandised definitions of criteria for diagnosis, small sample sizes and limited follow up. However, some studies have shown that thin melanomas with regression are associated with a higher incidence of metastases than tumours of similar thickness not associated with regression.[35]

For every disease, it is possible to compile a list of pathological features that are of agreed importance and to incorporate them into a synoptic report format. It is our view that both the pathologist and clinician benefit from the discipline of respectively reporting and reading reports in a synoptic format, an example of which is provided in Table 2.

Conclusions

The pathological diagnosis and assessment of various pathological parameters are key initial elements in the multidisciplinary care of melanoma patients. The accuracy and reliability of diagnosis are enhanced by clinicians and pathologists who possess a sound knowledge of diagnostic criteria, an awareness of potential pitfalls and good judgement. They should also communicate appropriately with each other. The clinician should provide the pathologist with a suitable biopsy specimen and an appropriate clinical history to assist in establishing a diagnosis. The pathologist, in turn, should provide the clinician with a report containing sufficient information to allow an evidence-based management plan and a reliable estimate of prognosis to be made. The use of a synoptic report format will ensure that potentially important information is not overlooked.

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Current strategies for the surgical management of melanoma

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Abstract

Over the past 25 years, surgical strategies for the management of primary cutaneous melanoma have changed considerably. In the 1970s and 1980s, most melanomas were widely excised with 3cm-5cm margins and regional lymph nodes were often treated by elective dissection. Today, excision margins rarely exceed 2cm and elective lymph node dissection has been almost completely replaced by selective sentinel node (SN) excision, with completion lymph node dissection only in the small proportion of patients found to have micrometastatic disease in a SN. These major changes in the surgical approach to primary melanoma management have occurred because large clinical trials have indicated that little or no benefit is achieved by excising melanomas with very wide margins, or by performing elective lymph node dissections. The other important factor has been the introduction and validation of the SN biopsy procedure, guided by preoperative lymphoscintigraphy. In the absence of effective forms of systemic therapy, the place of surgery in the management of metastatic disease has become more firmly established and it has become apparent that an aggressive surgical approach in patients with apparently limited metastatic disease, even at systemic sites, is fully justified.

Management of the primary melanoma

The role of surgery in the management of melanoma begins with excision-biopsy of the suspect lesion. Even if a confident diagnosis of melanoma is made on clinical grounds, preliminary excision of the entire lesion with around 2mm clearance margins is recommended, so that appropriate definitive treatment can be planned. Details such as the thickness of the primary tumour and whether any unfavourable features are present, such as ulceration, regression or a high mitotic rate, will determine the definitive excision margins that will be recommended and whether the likelihood of metastasis to regional lymph nodes is sufficiently high to warrant sentinel node (SN) biopsy as a staging procedure. The problems associated with partial biopsies (incision, punch and shave biopsies) of melanocytic lesions are described elsewhere in this issue of Cancer Forum.

There is universal agreement that complete surgical excision of a primary cutaneous melanoma is required, but there is continuing debate about the clearance margins that should be employed. Some have argued that complete excision of the tumour is all that is necessary,[1] whereas others have suggested that wide clearance margins are required, particularly for thick primary melanomas (>4mm). It is clear that the 5cm clearance margins generally regarded as standard treatment for all melanomas in the 1960s and 1970s can no longer be considered appropriate, because they do not affect long-term survival, nor do they achieve lower local recurrence rates than more conservative margins. Indeed, several large retrospective studies reported in the 1980s indicated that local recurrence was most uncommon in patients whose melanomas were excised with margins of 2cm or more. Rather, these studies made it clear that the risk of local recurrence was principally dependent on the thickness of the primary melanoma. In a 1985 review of the Sydney Melanoma Unit experience,[2] recurrence rates in 1839 patients with five years of follow up were reported. For thick tumours (defined as ≥ 3mm) the local recurrence rate was 21% when the excision margin was <2cm and 9% when the excision margin was ≥2cm. For thin tumours (defined as 0.1-0.7mm in thickness), the recurrence rates were two% when excision margins of <2cm were used and less than 1% when excision margins of ≥2cm were used.

Because of continuing uncertainty about the excision margins that were necessary to minimise the risk of local recurrence and to avoid an adverse effect on survival outcome, several large, prospective, randomised trials were undertaken. One of these trials, undertaken by members of the World Health Organisation (WHO) Melanoma Group,[3] compared results for patients with primary melanomas <2mm in Breslow thickness who had their tumours excised with margins of either 1cm or 3cm. For the 612 patients in this study, disease-free and overall survival rates did not differ for the two groups, but it was clear that melanomas ≤1mm in thickness were adequately treated by excision with a 1cm margin. Another important study was undertaken in the United States,[4] in which patients with intermediate thickness melanomas (1-4mm) were randomised to be treated with either 2cm or 4cm excision margins. For the 486 patients in this study, local recurrence rates were similar for the two groups and there was no significant difference in overall five year survival. As expected, however, treatment morbidity and length of hospital stay were significantly greater in the 4cm margin group.

Two subsequent European trials compared the results of treating primary melanomas with 2cm and 5cm excision margins. One of these, undertaken by the Swedish Melanoma Study Group, involved 989 patients with melanomas 0.8-2.0mm in thickness.[5] The other, undertaken by the French Group for Research on Malignant Melanoma,[6] involved 326 patients with primary melanomas <2.1mm in Breslow thickness. Both these studies failed to produce any evidence that 5cm margins reduced the local recurrence rate or improved survival outcome. The most recently reported large trial examining the question of excision margins was a 900 patient study undertaken in Britain.[7] Excision margins of 1cm and 3cm were compared for patients with melanomas ≥2mm in Breslow thickness. It was found that a 1cm margin was associated with a slightly greater risk of local recurrence than a 3cm margin, but with a median follow-up period of 60 months there was no difference in survival outcome for the two groups.

What conclusions can be reached about excision margins on the basis of all the information currently available? For invasive melanomas that are ≤1mm in Breslow thickness, a 1cm minimum clearance margin should be adequate and there is general consensus about this.[8] For tumours between 1mm and 2mm in thickness, there is some evidence that excision margins >1cm are desirable, but this evidence cannot be regarded as conclusive.[9] For melanomas that exceed 2mm in Breslow thickness, available evidence suggests that an excision margin of at least 2cm is required, to minimise the risk of local recurrence, but whether this margin is adequate or a margin of 3cm is required remains uncertain, because the appropriate trials have not been conducted. A further consideration is that most of the available clinical trial evidence has been based on patients with tumours located on the trunk or a proximal extremity, with exclusion of patients who have melanomas in the head and neck area or on a distal extremity. It is possible that different guidelines are required for the management of primary tumours in these sites.

Surgical morbidity and cosmetic implications must also be considered. Even if excision margins of ≥2cm do achieve slightly lower local recurrence rates for patients with intermediate thickness and thick melanomas, this small benefit must be weighed against the increased surgical morbidity and disfigurement that will inevitably be associated with wider excision margins. It could be argued that it is better to accept a slightly higher risk of local recurrence and avoid the additional morbidity and cosmetic deformity that a wider margin will produce, because if local recurrence does occur, it can usually be managed by simple surgical removal. And even though local recurrence is associated with a reduced survival outcome, it is scientifically inappropriate to assume that the process of performing a wider excision with the intention of reducing the risk of local recurrence will necessarily improve survival. Indeed, careful evaluation of all the available evidence suggests that it is tumour biology rather than the extent of local treatment that determines ultimate outcome. Some compromise on excision margins therefore seems reasonable in situations where the risks of surgical morbidity and cosmetic deformity are high.[10]

Management of regional lymph nodes

During the 1970s and 1980s, there was ongoing controversy about the value of elective lymph node dissection (ELND) for patients with intermediate thickness melanomas who presented with no clinical evidence of regional node metastasis. Although retrospective studies appeared to indicate a survival benefit,[11] randomised trials did not do so.[12-15] Particularly for patients with primary melanomas of the lower limb, the long-term morbidity of ELND was considerable and in any case only approximately 20% of patients were found to have metastatic disease in the regional nodes when ELND was performed.

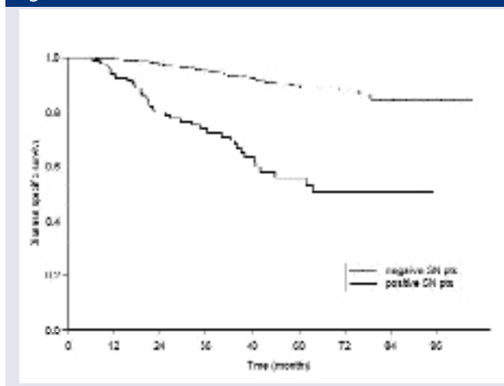
A potential solution was proposed at a meeting of the Society of Surgical Oncology in 1990 by Donald Morton and his associates from the John Wayne Cancer Institute.[16] They suggested that it was possible to assess the status of regional lymph nodes with confidence by performing lymphatic mapping to identify a SN in each patient and to then remove that node for histological examination. Technical details of the procedure were published in 1992[17] and it was proposed that SN biopsy would allow ELND to be avoided in 80% of patients, but identified the 20% of patients most likely to benefit from the procedure. Within three years of that initial publication describing SN biopsy, confirmation of its accuracy in identifying regional node metastases was provided by studies undertaken in the United States[18] and at the Sydney Melanoma Unit.[19] In both these studies lymphatic mapping and SN biopsy were performed, but with immediate completion ELND so that all remaining nodes in the node field could be assessed histologically. The results of the two studies were remarkably similar to those that had been reported by Morton and his colleagues and established conclusively that the sentinel node hypothesis was valid. In other words, if no evidence of micrometastatic disease was found in SNs, metastatic disease was not likely to be present in other nodes in that node field. Other validation studies with similar results were reported subsequently[20] and all confirmed that SN status accurately reflects the status of the entire node field in patients with melanoma.

Although the practical clinical importance of the SN concept had not been fully appreciated until the early 1990s, the SN concept was not new. Indeed, it had been very clearly described by the pathologist Virchow in the mid 19th Century.[21] The SN concept is remarkably simple. Lymph draining from a tumour passes first to a SN before passing onwards to other nodes in the regional node field. If tumour cells enter lymphatic collectors, they are thus most likely to be found in the SN. In the early studies undertaken by Morton and his colleagues, blue dye was injected intradermally at a primary melanoma site and blue-stained afferent lymphatics were traced to a blue-stained SN in the regional node field. This was a tedious and quite invasive process, but it soon became apparent that preoperative lymphoscintigraphy could not only provide valuable information preoperatively, but could also facilitate SN identification by intraoperative use of a hand-held gamma probe. A report from the Sydney Melanoma Unit was the first to suggest that it was possible to use residual radioactivity in the SN after preoperative lymphoscintigraphy for intraoperative SN identification with a gamma probe.[22] It was quickly recognised that the most rapid and confident identification of SNs was achieved if all three methods were used, ie. a preoperative lymphoscintigram, blue dye injection at the primary melanoma site immediately preoperatively and use of a gamma probe intraoperatively.

Knowledge of a patient's SN status has important prognostic implications and the results of several large studies confirming this have now been reported.[23-30] Irrespective of other prognostic variables, the five-year survival probability for melanoma patients who are SN positive is much lower than the five-year survival for those who are SN negative. Results for 991 patients treated at the Sydney Melanoma Unit are typical[31] and are shown in Figure 1; the five-year survival rate for patients who were SN positive was 56%, whereas for those who were SN negative it was 90%.

A detailed account of the technical details of SN biopsy is beyond the scope of this article, but full descriptions are given elsewhere.[32,33] It is important to note that although the SN concept is simple, the process of identifying and removing SNs can be technically challenging, particularly when more than one SN is present in a node field, as is often the case in patients with primary melanomas in the head and neck region.[34] The value of the technique clearly depends upon accurate identification and removal of every SN in each patient. It has become clear that metastatic disease can be present in any node that is truly a SN and not just in the hottest SN, or the SN that is most intensely stained with blue dye. False negative rates as high as 25% have already been reported,[32,35] where a false negative result is defined as recurrence in a node field following removal of a SN or SNs reported to be negative. Although some of these false negative results are likely to have been due to incorrect interpretation of the lymphoscintigram by the nuclear medicine physician and others are likely to have been due to failure by the pathologist to detect micrometastatic disease that was actually present, there can be no doubt that failure by the surgeon to identify and remove the correct node or nodes was responsible for the false negative result in some cases.[36]

Figure 1:



Disease-specific survival in sentinel node positive patients (n = 139) versus sentinel node negative patients (n = 836). (p < 0.001)

Although it is abundantly clear that SN assessment provides valuable prognostic information, there is no evidence at the present time that removal of these nodes, with complete regional node field dissection if a positive SN is found, will improve survival outcome. The results of large multicentre randomised trials will be required to answer this question. Preliminary results of one such trial, the Multicenter Selective Lymphadenectomy Trial[37,38] were presented recently[39] but have not yet been published. After a median follow-up period of 54 months, there was no statistically significant difference in overall survival between patients treated by wide excision only and those treated by wide excision plus SN biopsy, with immediate completion lymph node dissection if a positive SN was found. However, the survival outcome for patients who were found to be SN positive and who had an immediate completion lymph node dissection was much better than the survival outcome for patients who were initially treated by wide excision only and who subsequently developed clinical disease in the regional node field and had a therapeutic lymph node dissection at that time. Further results of this trial, after a longer period of follow-up, are awaited with great interest.

The next important question that will need to be answered is whether it is always necessary to perform a completion regional node field dissection when a positive SN is found. This question is of importance because no more than 20% of patients will be found to have metastatic disease in non-sentinel lymph nodes. A new multicentre, international trial (MSLT II) has recently been commenced to examine this question. SN-positive patients who enter the study will be randomised to receive standard treatment, ie. completion regional lymph node dissection, or to have no further surgery, but to have their regional nodes checked regularly both by clinical examination and using high-resolution ultrasound.

Preoperative lymphoscintigraphy has now been performed in over 4000 Sydney Melanoma Unit patients and has provided important new insights into cutaneous lymphatic drainage pathways.[40,41] These studies have shown that many long-held beliefs about cutaneous lymphatic drainage pathways, some dating back to the work of Sappey and his associates in the mid 19th Century,[42] are incorrect. It has been found, for example, that lymphatic drainage across the midline is common and that drainage to previously unrecognised lymph node sites such as the triangular intramuscular space on the back, just lateral to the scapula, can occur.[43] From the upper limb, direct drainage

not only to the axilla but also to supraclavicular SNs can occur, as well as drainage to epitrochlear SNs and to interval SNs in the arm. From the lower limb, drainage can occur not only to popliteal SNs and interval SNs in the thigh, but also directly to external iliac and obturator SNs, as well as to SNs in the femoral triangle. Sometimes, drainage from the lower back to SNs that are retroperitoneal and paravertebral can occur, and occasionally drainage is exclusively to these sites, with no drainage to the groin or axilla. Normal and abnormal lymphatic drainage patterns in patients with melanoma are discussed in greater detail elsewhere.[41,44-46]

The present role of sentinel node biopsy

Even if the results of clinical trials do not show a survival benefit for patients treated by SN biopsy, the value of the technique in providing prognostic information will remain. Knowledge of SN status provides a patient with the most reliable estimate of prognosis that is currently available and allows more accurate stratification for entry into adjuvant therapy trials. If effective adjuvant therapies are found, knowledge of SN status will be required to identify those at greatest risk of recurrence and therefore most in need of adjuvant therapy.

It has been suggested that the SN biopsy procedure should not be performed because it increases the risk of in transit metastasis.[47-49] However, no increased risk of in transit metastasis was found in two large single centre series[50,51] and the recently presented results of the Multicenter Selective Lymphadenectomy Trial demonstrate conclusively that the in transit metastasis rate is not increased in patients who have a SN biopsy procedure.[39] It seems likely that primary tumour biology alone determines the risk of in transit metastasis.[52,53]

Nevertheless, the concept of obtaining information about SN status in minimally invasive and non-invasive ways is already being investigated. For example, studies undertaken at the Sydney Melanoma Unit have already shown that rapid and accurate results can be obtained by examination of fine needle aspiration biopsies from SNs, using magnetic resonance spectroscopy.[54] This technology is discussed in another contribution to this edition of Cancer Forum. Studies are currently in progress to confirm the feasibility of completely non-invasive SN assessment, using surface coils to obtain magnetic resonance spectra from underlying SNs, which have been identified and localised by preoperative lymphoscintigraphy and ultrasound examination.

Surgical treatment of locally recurrent, in transit and nodal metastases

A detailed consideration of the role of surgery in the management of local melanoma recurrence. In transit disease and regional node disease is beyond the scope of this article. The important principle, however, is that whenever recurrent disease is localised and can be resected with an acceptably low risk of serious morbidity, this is the treatment of choice because it is likely to be the most effective way of preventing or relieving symptoms and may also extend survival.[55] It is a sad fact that presently available forms of systemic therapy rarely achieves complete disease remission. Therefore systemic therapy is generally reserved for patients with symptomatic or rapidly progressive metastatic disease. However, surgical techniques such as isolated limb perfusion and isolated limb infusion, in which high dose regional chemotherapy is administered to patients with extensive recurrent disease confined to a limb, can achieve complete remission rates exceeding 50%, with a low risk of serious side effects. These techniques and the results of treatment using them are described elsewhere.[56-59]

Surgical treatment of systemic metastases

More than 85% of melanoma patients who present with AJCC Stage IV disease have demonstrable metastases confined to a single organ site such as the lung or the gastro-intestinal tract, although metastases sometimes appear later at other sites. In recent years positron emission tomography (PET) scanning has been used to confirm that systemic metastases are genuinely isolated. When considering surgical resection of systemic metastases, several facts must be borne in mind. It has been shown, for example, that the most powerful predictor of survival in melanoma patients with systemic metastases is the number of organs or tissues containing metastases.[60-62] For patients with metastatic disease identified at only one site, median survival is around seven months, for two sites it is four months, and for three or more sites it is only two months.[63]

Consideration of these facts has led to a re-appraisal of the value of surgical resection in the management of patients with Stage IV melanoma. Complete surgical removal of a metastatic deposit can render patients disease free and substantially improve their survival probability. Even if survival time is not extended, resection of isolated systemic metastases can provide excellent palliation of symptoms and can also prevent the development of problems at a later date. In recent series, five-year survival rates of 20-27% have been reported following complete resection of lung metastases[64,65] and survival rates of 28-41% following complete resection of metastases in the gastrointestinal tract.[66-68] Even patients with melanoma metastases in the liver can survive for prolonged periods after surgical resection; in a combined series of patients treated at the Sydney Melanoma Unit and the John Wayne Cancer Institute, the five-year survival was 29%.[69] Even when multiple systemic metastases have been resected, long-term survival has sometimes been achieved.

Present evidence suggests that complete or near complete cytoreduction by surgery improves survival by reducing the overall tumour burden, allowing the host's immunological defence mechanisms to function more efficiently. The other systemic site where surgical removal of an apparently isolated metastasis can be highly effective in relieving symptoms is in the brain, where surgical treatment alone was associated with a median survival of 7.1 months and surgery plus adjuvant postoperative radiotherapy a median survival of 9.2 months.[70]

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Medical management of advanced melanoma

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Abstract

Despite major advances in the treatment of many solid tumours, metastatic melanoma remains stubbornly resistant to therapeutic attack with systemic agents. Much of the resistance of melanoma to immunotherapy and cytotoxic treatment is due to an impressive array of molecular defences that derive ultimately from the essential molecular structure of the melanocyte and its biological requirement for defence against apoptosis. Patients with metastatic disease should be cared for by a multidisciplinary team with a coordinating clinical nurse consultant playing a central role. In selected patients observation remains the best initial management. All eligible patients should be entered on clinical trials of new treatments. Standard systemic therapy consists of chemotherapy with dacarbazine, but response rates are less than 10% in recent Phase III trials. The Ras-RAF signalling pathways are commonly constitutively activated in melanoma and newly tested inhibitors of these, like sorefenib, may sensitise melanoma cells to cytotoxic attack. Considerable hope is also provided by recent Phase II trials with immunotoxins. These provide novel opportunities for targeted therapy in the treatment of melanoma.

Despite continuous research endeavours in chemotherapy, immunotherapy and biological therapy, there is no cure for disseminated melanoma and only rarely do systemic treatments appear to modify the natural history of the disease. Advanced melanoma is a tumour with a vast number of genetic alterations, conferring cellular proliferative advantages, coupled with resistance to apoptosis and apoptosis-inducing agents like chemotherapy and radiotherapy.[1]

Against this background of relative therapeutic impotence, the management of patients with metastatic melanoma presents a special set of challenges which are best met through the type of multidisciplinary approach pioneered at Sydney Melanoma Unit by Gerald Milton and William McCarthy. Central to this is the timely intervention with surgery and radiation therapy, even in patients with substantial metastatic burden, the early involvement of palliative care expertise and the coordination of care by a clinical nurse consultant.

Natural history of metastatic melanoma

Melanoma is notoriously variable in its pattern of spread. In selected patients the disease has a propensity to remain confined to loco-regional lymphatics for extended periods and some such patients have achieved long-term remissions even after hind-quarter amputation.[2] In others, haematogenous dissemination occurs early and widely. In certain patients, years may pass between the primary presentation and the development of metastases. Certain patients may display serial presentations, each with relatively isolated metastases, remaining in clinical remission for many years between episodes of local (usually surgical) treatment of these exacerbations. Others will suddenly develop fulminant disease in many organs simultaneously with a very rapid demise. In some patients, the disease displays particular affinity for a particular organ or organs. Thus, certain individuals may develop extensive pulmonary involvement without ever developing liver metastases. Others will succumb to cerebral metastases without any extra-cranial disease. This wide spectrum of variability confounds the ability to make accurate prognosis. However, some broad guidelines may be drawn from statistical analyses of large numbers of patients who have died from metastatic melanoma.

The most common initial sites of metastasis are skin, subcutis, distant lymph nodes, lung, liver, bone, small intestine and brain.[3] Approximately 4% of patients present with widespread metastases as the initial manifestation of metastatic disease.[4] In a recent revision of the AJCC Staging System for Melanoma,[5] Stage IV melanoma has been subdivided into three prognostic groups. The M1 category includes those patients with lymph node and/or subcutaneous metastases and has a median survival of >12 months and a two year survival of 15-20%. The M2 category has pulmonary metastases +/- subcutaneous or lymph node involvement and has a median survival of 9-12 months and a two year survival of 10%. The M3 category has other visceral involvement or any site with an elevated LDH. M3 patients have a median survival of four-six months and a two year survival of 5%.

Non-metastatic manifestations of malignancy

Melanoma is associated with a wide range of paraneoplastic phenomena. The majority of these occur in the context of established metastatic disease. Many are presumed to be the result of cross-reactivity between novel expressed melanoma cell surface antigens and normal cellular epitopes.

Some of the paraneoplastic clinical conditions that have been reported more commonly include retinopathy, melanosis and melanuria, hypercalcaemia, cachexia-pyrexia, vitiligo, dermatomyositis, Sjogren's (sicca) syndrome, inflammatory neuropathy and marantic endocarditis.[3]

Assessment of the patient with disseminated disease

The entire history of the patient's melanoma and its treatment should be carefully documented. The original histology should be reviewed as the prognostic features may influence the decision to biopsy metastatic disease. The occurrence of locoregional recurrence and the disease-free interval are relevant to the prognosis of metastatic disease and possibly to the likelihood of response to systemic therapy. Previous normal X-rays and scans may be useful in determining the pace of disease progression.

Careful emphasis should be placed on the patient's current major problems and the symptomatology most urgently calling for relief. Those with poor performance status are most unlikely to benefit from systemic anti-tumour therapy.

Cerebral metastases are so common in patients with advanced melanoma that it is mandatory to enquire about symptoms of raised intra-cranial pressure. Co-morbities should be reviewed in the light of their impact on therapeutic intervention and a survey of regular medications performed to seek those, such as corticosteroids, that may interfere with systemic therapies with, for example, immunostimulants and cytokines.

Physical examination should include careful palpation of all lymph node sites and palpation of the entire skin surface with the palms of both hands seeking the presence of cutaneous or subcutaneous metastases. Special attention should be paid to the neurological system, including the fundi and exclusion of the early signs of spinal cord compression.

Investigations should only be performed if they are to contribute to clinical management.

The full blood count and blood film are simple and informative. Anaemia is common in melanoma and most commonly shows the features of acute or chronic blood loss, the site of which is usually the gastrointestinal tract. A normochromic normocytic picture may also occur in the presence of extensive metastatic disease, without blood loss or marrow involvement. Occasionally, a leukoerythroblastic blood film may indicate bone marrow replacement.

Serum biochemistry should include an assessment of the hepatic and renal function. The serum LDH, although non-specific, is an independent prognostic indicator in metastatic disease.[6] The serum calcium should be routinely measured, particularly in patients with known extensive bone metastases.

Positron emission tomography (PET) scanning may be particularly useful if extensive surgery is contemplated for metastatic disease, but has minimal role outside this. Computerised tomographic (CT) scanning of the abdomen and pelvis is a simple staging manoeuvre. Head CTs should be reserved for those in whom cerebral metastases are clinically suspected or major extracranial metastasectomy planned. Magnetic resonance imaging (MRI) scanning is the most sensitive test for the presence of cerebral metastases and is routine prior to planned cerebral metastasectomy. MRI is also the investigation of choice in screening for spinal cord compression and leptomeningeal metastases. Bone scans should be performed in patients with relevant symptoms. Hot spots in long bones should be subjected to plain X-ray examination to determine the extent of cortical bone erosion, a determinant of the need for prophylactic orthopaedic intervention.

Approach to the patient with metastatic melanoma

Frequently, the patient is a young adult, with the financial, career and family responsibilities and aspirations of mid-life, mid-career and parenthood to teenage children. The devastation of diagnosis is compounded by the gloomy predictions of prior medical attendants and whatever factual material might have been frantically retrieved from the internet.

The initial consultation therefore requires particular attention and skill. A carer or relative should be present. In Sydney Melanoma Unit it is customary for the oncologist to be accompanied by an oncology nurse specialist who will take a key role in follow-up and coordination of care that often involves multiple professionals and the general practitioner. A principal objective of the initial consultation is to establish an environment of confidence and trust.

Some useful concepts in sustaining patients at this time of devastating news are: the idea that the oncology medical and nursing team are joining forces with the patient in fighting a battle; the news that certain vital organs are spared on the CT scans; optimistic anecdotes referring to the successful outcome of the treatment of a similar patient in the past; the rapid rate

of progress in medical research and the speed with which new treatments are being developed; the fact that the team of melanoma clinicians are experienced, expert and informed and that patients will immediately receive the benefit of advances in knowledge.

The explicit delineation of a plan of management will do much to allay the fears and anxieties of patients and carers. The importance of symptom control and the objective of rapid absolute relief of pain requires particular attention and time. An emphasis on symptom control and on early engagement of community nursing support will facilitate smooth transition to palliative care at a later stage of the illness.

Choice and evaluation of treatments

The heterogeneous nature of melanoma and its patterns of spread and progression, together with the fact that no existing form of systemic treatment has been shown to prolong survival in prospective randomised controlled clinical trials,[1] means that for certain patients observation may be the most humane and rational choice. Patients best suited to observation are those with relatively low bulk disease who are without symptoms, whose disease has a slow rate of progression, who do not yet display constitutional features of anorexia, weight loss and decline in performance status and whose temperament is suited to such a plan. Typically, metastatic disease has been detected in these patients by the performance of routine staging investigations. Such patients may be eligible for clinical trials of new anti-melanoma drugs and immunotherapy. Patients may be reassured on observation programs by the knowledge that there is no evidence that delay of initiation of chemotherapy for melanoma jeopardises response, providing that deterioration in weight and performance status have not intervened. Supportive programs of counselling, diet and exercise may be useful adjuvants in maintaining morale in this group of patients.

Surgery and radiotherapy play a major role in the management of metastatic melanoma and are covered elsewhere in this issue of Cancer Forum.

Where possible, patients with metastatic melanoma should be entered on clinical trials. Given recent advances in the rational design of agents which may overcome inherent defences in the melanoma cells against apoptosis, together with major inroads into the molecular abnormalities common to melanoma cells, clinical trials will prove essential in refining the utility of a battery of new treatments.

Frequently, the eligibility criteria for participation in Phase II and Phase III trials for melanoma select out a small group of patients with good prognosis. The outcome of this is that, even in units with a high level of commitment to clinical research, there will be a number of patients who are ineligible for treatment with new agents. These patients are necessarily treated “off study”.

Metastatic melanoma is relatively resistant to treatment with cytotoxic drugs. No form of systemic therapy prolongs overall survival. Single agent treatment with dacarbazine (dimethyl triazeno imidazole carboxamide, DTIC) has been standard best systemic therapy since the late 1960s and its use in Australia was pioneered by Gerald Milton and William McCarthy at Sydney Melanoma Unit.[7] Partial responses to dacarbazine and two other commonly used single-agent cytotoxic drugs, temozolamide and fotemustine, occur in less than 25% of treated patients, and complete responses in less than 5%.[8-10] However, in recent Phase III prospective randomised trials, in which dacarbazine has been standard therapy, response rates have been less than 10%.[11,12] The use of combinations of cytotoxic drugs, even with the addition of potent cytokines like interleukin-2 and interferon-alpha,[13] produces slightly higher transient response rates, but at considerable cost in toxicity and with no survival benefit.[1]

Predictors of response to dacarbazine include good performance status and disease confined to the skin, subcutis, lymph nodes and lungs.[14,15] The median duration of response is five-six months.[9] Only 1-2% of patients treated with dacarbazine sustain long-term complete responses, but those in complete remission more than two years after treatment tend not to relapse.[16,17]

A major advantage of dacarbazine is that it is simple, ambulatory and associated with minimal toxicity when administered with 5-HT(3)-antagonist anti-emetics. Alopecia does not occur with dacarbazine therapy and the drug is minimally myelosuppressive. Acute photosensitivity reactions may occur.

For certain patients, the prospects of response to chemotherapy are so low and/or the risks of toxicity so high that attempts at anti-tumour therapy are better abandoned and replaced with a policy of best supportive care. Patients who fall into this category include those with very poor performance status and extensive or rapidly progressing metastatic disease in multiple visceral sites. Patients who have failed initial chemotherapy may also fall into this group, as a recent review of the efficacy of salvage chemotherapy for metastatic melanoma in the Sydney Melanoma Unit revealed a response rate of less than 5%.

There have been highly encouraging recent advances in treating metastatic melanoma with immunoregulatory molecules. This subject is reviewed by Peter Hersey in this issue of Cancer Forum.

New approaches with biological therapy and chemotherapy

The molecular pathways so far identified as being central to melanoma are the subjects of intense investigation for their potential as targets for strategically directed therapy.

Growth factors, such as SCF, FGF and TGF-alpha are produced by the action of solar radiation on melanocytes and surrounding keratinocytes and fibroblasts. Resulting signals are transduced via the Ras and RAF signalling pathways and subsequently MEK-ERK-Mitf, or PI3K-Akt-mTOR. The transcription factor Mitf triggers the transcription of a suite of genes involved in cellular proliferation and migration. mTOR promotes the translational efficiency of growth regulatory gene products. Constitutive activating NRas and BRAF mutations are very common in melanoma and physiological “brakes” to this oncogenic activity, provided by the protein products of the CDKN2A gene, p16 and p14ARF, are also frequently disrupted in advanced tumours (reviewed in (1)). When defective, p16 is unable to inactivate CDK4 and 6, which phosphorylate Rb, leading to cell cycle progression. The molecule usually central to protection against DNA damage, p53, is rarely mutated early in melanoma, possibly one of a number of adaptations to permit survival of the cells responsible for generating sun-protective pigment[18]. However, mutations in p14ARF permit degradation of p53 by releasing its binding partner hdm2. As a further defence, melanoma cells frequently express high levels of the anti-apoptotic molecules bcl-2 and bcl-x.[19] These are proving important targets for modern therapeutic attack on the tumour.

Targets undergoing experimental inhibition in melanoma therapy include antisense oligonucleotide to bcl-2 (oblimersen), CDK inhibitors (flavopiridol), receptor tyrosine kinase inhibitors (imatinib, bevacizumab), farnesyl transferase inhibitors, RAF inhibitors (sorafenib) and mTOR inhibitors.

Oblimersen is an antisense oligonucleotide to the anti-apoptotic molecule bcl-2 which is over-expressed in many melanomas. Phase III testing of DTIC plus oblimersen versus DTIC alone showed incremental benefits in progression-free survival but no overall survival benefit.[20] The RAF inhibitor sorafenib has minimal activity as a single agent, but a combination of this agent with the cytotoxic drugs carboplatin and paclitaxel gave 14/35 partial responses (Flaherty, K.T. oral presentation, 40th Ann Meeting Amer Soc Clin Oncol, New Orleans, June 5-8, 2004) and response did not depend upon the presence of an activating RAF mutation.[21] The prospect of using a number of targeted inhibitors in combination with chemotherapy provides some optimism and is the subject of planned Phase III trials.

Spontaneous regressions

In certain patients melanoma metastases fluctuate in size spontaneously. This is most frequently seen in subcutaneous deposits, lymph nodes and pulmonary metastases and may be due to immunological and inflammatory responses, necrosis induced by out-growth of blood supply and haemorrhage into highly vascular deposits. This behaviour, so characteristic of metastatic melanoma, is one particular reason for the rigorous control necessary in assessing response in clinical trials of new agents. Very rare complete spontaneous regressions of metastatic melanoma are also described.[22]

Dealing with alternative therapies

Motivated by their own despair, confronted with apparent helplessness and occasional negativity in health professionals, fuelled by the exaggerated and frequently bogus claims of the evangelical or unscrupulous in the popular press and on numerous websites and harassed by the well-meaning attentions of family and friends, patients with metastatic melanoma frequently seek alternative therapies.[3]

Patients and their carers may be assisted by a number of highly informative resources on alternative therapy, such as those available from the American Cancer Society (www.cancer.org/docroot/ETO/ETO_5.asp) and those contained in websites such as “Quackwatch” (www.quackwatch.com). Certain patients may also be fortified by the provision of safe supportive programs of sensible dietary and exercise advice, relaxation therapy, meditation and massage, aimed principally at improvement in quality of life and symptom control.

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Immunotherapy of melanoma – past, present and future

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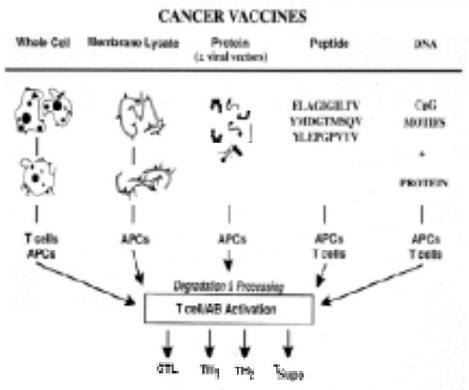
Abstract

Treatment of melanoma by immunotherapy remains a topic of much interest. Initial studies were based on stimulation of immune responses by immunisation with whole cells or lysates of whole cells. Some of these trials are still in progress but results with these or purified melanoma antigen vaccines have not been particularly effective. Recent approaches have been directed to overcoming inhibitory homeostatic mechanisms by use of antibodies which block the CTLA-4 receptor involved in downregulation of cytotoxic T cells and the activity of regulatory T cells. Adoptive immunotherapy after immunodepletion of recipients is also showing promise. Future trials that combine immunotherapy with agents that overcome resistance to apoptosis of melanoma cells may provide the breakthrough being sought in treatment of melanoma.

Treatment of melanoma by immunotherapy has been of much interest to clinicians and scientists for at least the past three decades. Such endeavour has been stimulated by evidence suggesting that immune responses against the tumour have an important role in evolution of the disease. This includes partial or complete regression of cutaneous melanoma usually associated with lymphoid infiltration into the primary tumour and more rarely spontaneous regression of advanced metastatic disease. In vitro studies have also shown abundant evidence of antibody and T cell responses against autologous tumours and more recently studies have shown that adoptive transfer of tumour infiltrating lymphocytes (TILs) may be associated with regression of metastatic melanoma.[1]

The source of antigens in vaccines include whole melanoma cells, melanoma lysates, whole protein antigens, peptide epitopes and RNA or DNA coding for the antigen. In addition, various vaccine "platforms" have been utilised in the studies, such as administration with adjuvants, dendritic cells or direct injection of antigen into skin. The antigen sources and types of vaccines are summarised in Figure 1.[2]

Figure 1:



The hypotheses being tested in vaccine studies have evolved over the years as follows.

Hypothesis 1 – "The immune response against melanoma is too weak to control melanoma growth. Immunisation with vaccines will increase strength of response and control tumour growth."

This hypothesis has now been tested in several relatively large randomised trials. The first of these was by Wallack et al, who used vaccinia viral lysates from three melanoma cells. The result showed a non-significant trend in favour of the vaccine. The second and so far largest of the randomised trials was that conducted by Hersey et al in Australia.[3] The vaccine was a vaccinia viral lysate of one melanoma cell and vaccines were given over a three year period to patients with stage IIB or III melanoma in the old AJCC staging system.

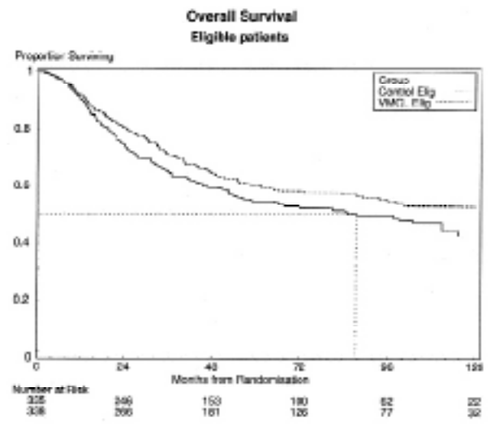
Table 1:

Summary of VMCL Trial

- 700 patients, median follow up 8 years
- Trend in favour of VMCL.
  - HR for OS=.81 CI=.64-1.02 P=.068
  - HR for RFS=.86 CI=.7-1.07 P=.17
- Median survivals 100 months overall
  88 months for Controls
  151 months for VMCL

The results summarised in Table 1 indicated that there were 20 more deaths in the control group and that the hazard of dying was reduced to 0.81 compared to control untreated patients. Nevertheless, the confidence intervals were wide (.64 – 1.02) and the P value of 0.068 was just outside the accepted .05 value. All patients in the study survived very well with an overall

Figure 2:



median survival of 100 months (see Figure 2).

The third trial was conducted by the South West Oncology Group (SWOG) in the US in 689 patients with AJCC stage II disease. The vaccine was a sonicated lysate of two melanoma cells given in an adjuvant called Detox. The results for all patients showed a small effect on disease free survival (DFS) but no effect on overall survival. However, when the patients were stratified according to their HLA-A2 and/or C3 status it was found that the vaccine induced a significant increase in survival in patients who were HLA-A2 and/or C3 positive.[4] A follow-up study with the vaccine has not yet been commenced.

The fourth trial used a vaccine made from three whole viable irradiated melanoma cells (Canvaxin) given initially with BCG as an adjuvant. Trials in patients with resected stage IV disease were discontinued in April 2005 by the Data Monitoring Committee because of no detectable effect on survival. A total of 496 patients had been accrued after entry of 1160 patients. A larger trial in patients with resected stage III disease was closed to accrual in September 2004 and results are awaited.

Hypothesis 2 – "Vaccines made from peptide epitopes or purified proteins will be more effective than use of whole cells or whole cell lysates."

As information about the specific melanoma antigens recognised by the immune system became available, it was possible to produce vaccines containing only well-defined antigens, such as peptide epitopes recognised by T cells. Such vaccines were relatively cheap to produce and were shown to be effective in inducing T cell responses against the antigen concerned. In practice however, such vaccines have proved relatively ineffective in inducing clinical responses in patients with melanoma. Our experience is shown in Table 2. In studies on 36 patients the best response was stabilisation of disease in six patients defined as no progression over a 12 week period.[5] Similar experiences have been reported by other investigators[6]

Table 2:

RESULTS OF MELANOMA PEPTIDE TRIAL

	Peptides Alone	Peptides +GM-CSF	Peptides + Montanide	Pep + Montanide +GM-CSF
NMU	2	1	5	1
SMU	3	5	4	0
RAH	3	4	2	7
Totals	**8**	**10**	**11**	**7**
Best Resp	**1SD**	**0**	**2SD**	**3SD**
%	13%		18%	43%

so that there is now little enthusiasm for purified peptide vaccines in treatment of melanoma.

Hypothesis 3 – "Melanoma antigens given on dendritic cell vaccines will be more effective than direct cutaneous injections of the vaccine."

This approach was based largely on the view that dendritic cell (DC) antigen presenting cells (APCs) were non-functional or present in low cell numbers around tumours. Therefore if DCs were produced in vitro and injected into patients after incubation with melanoma antigens the immune responses to melanoma would be stronger and result in regression of melanoma. Again, the results from a number of trials have not lived up to expectations. The results of our first phase II trial on 33 patients shown in Table 3 resulted in three partial responses, one mixed

Table 3:

Dendritic Cell Vaccines in Stage IV Melanoma

	DCs + Lysates	DCs + Peptides
Number Entered	**19**	**14**
Completed 6 vaccines	**18**	**13**
Complete Response	**0**	**0**
Partial Response	**3 (16%)**	**0**
Mixed Response	**1 (5%)**	**0**
Stable Disease	**4 (21%)**	**5 (35%)**
PD	**11 (58%)**	**9 (65%)**

Table 4:

Summary of Dendritic Cell Vaccine Trials Against Melanoma

Investigator	Antigen	DCs	Matured	Route	No. of Patients	Response (%)
Smithers et al., 2003	Lysates	Mono	N	im.	22	1 CR, 2 PR (41)
O'Rourke et al., 2003	Lysates	Mono	Y	id.	19 (17)	3 CR, 3 PR (32)
Hersey et al., 2003	Lysates Peptides	Mono Mono	N N	Intranodal Intranodal	19 14	3 PR, 1 MR (21) 5 SD

response and nine with stabilisation of disease.[7] Similar results were reported by Smithers et al but studies by O'Rourke et al[8] were more impressive, resulting in 3 CR and 3 PR (Table 4).

Hypothesis 4 – "Immune responses against melanoma are inhibited by physiological down-regulatory mechanisms in the immune system." "Taking off the brake approach."

The immune system has a number of homeostatic mechanisms which return activated lymphocytes to a resting state. One such mechanism is the presence of signal pathways that inhibit the activation signals resulting from contact with antigen and co-stimulatory receptors. The inhibitory pathways are activated by ligands on APC that interact with receptors on T cells. One of the most important of these is the cytotoxic T lymphocyte antigen 4 (CTLA-4) receptor which interacts with CD80 (B7.1) and CD86 (B7.2) on APC. Studies by Allison and colleagues[9] have shown that antibodies against CTLA-4 allow the activated T cells to persist and proliferate, resulting in a more prolonged vigorous T cell response. Blockade of the CTLA-4 receptor may also inhibit a subpopulation of regulatory T cells that act to inhibit immune responses by down-regulation of stimulatory signals from APC. Regulatory T cells constitutively express the CD25 (IL-2Ra) IL-2 receptor and CTLA-4 and MAb against CTLA-4 may limit their production of inhibitory cytokines such as IL-10 and/or TGF-b

These studies have been commercially exploited by Medarex/ Bristol Myers Squibb, which is testing the MDX-010 monoclonal antibody (MAb), and by Pfizer, who are testing another MAb, CP-675206. The phase I dose finding studies by Pfizer (shown

Table 5:

PHASE 1 STUDY WITH CP-675206

Dose mg/kg	Patient number	Clinical response	Duration mths
3	8	1CR,1 SD	24
10	11	1PR, 3SD	15
15	6	2CR,1PR, 1SD	14,13,14
	25	3CR,2PR, 5SD	

in Table 5) were very promising in that durable CR and PR were seen at the higher dose levels in patients who had failed other treatments. Overall the response rate was 20%. A large phase II study at the 15mg/kg dose level each three months is now planned.

MDX-010 has been tested in combination with peptide vaccines by the NCI group[10] and by Weber et al.[11] Again, impressive durable CR and PR were seen (Table 5). A large international randomised three arm study in previously treated patients is now in progress. Treatment with MDX-010 has been complicated by severe side effects, particularly diarrhea which can require admission to hospital and fluid replacement. Skin rashes are common and rarely hypophysitis may occur.

Hypothesis 5 – "Lymphocyte depletion will allow selective expansion of tumour specific lymphocytes produced by vaccines or adoptively transferred after expansion in vitro."

Homeostatic mechanisms control lymphocyte numbers at surprisingly constant levels and are believed to limit the proliferation of lymphocytes activated against tumours. Rosenberg and colleagues have depleted lymphocytes from patients with cyclophosphamide and fludarabine, and then adoptively transferred T.I.L.s that have been expanded in vitro. The results (Table 6) have been most impressive, with durable

Table 6:

LYMPHOCYTE DEPLETION AND TRANSFER OF AUTOLOGOUS ANTI TUMOUR LYMPHOCYTES

- 35 patients. Many previously treated.
- 50% response rate.
- 4 CR
- 14 PR
- Long term persistence of transferred Tcells

- Rosenberg et al PNAS 101:14639-45 2004

CR and PR seen in 50% of a series of 35 patients so treated.[12] The in vitro cultivation of T.I.L. requires considerable laboratory resources and other groups (Urba, Fox, et al) are testing whether immunisation with vaccines following lymphocyte depletion may achieve the same outcome.[13,14]

Hypothesis 6 – "Immune therapy alone is limited by resistance of melanoma cells to apoptosis. Combination with agents which reduce resistance to apoptosis is required for optimal results."

Studies over the past few years have shown that lymphocytes kill tumour cells by induction of apoptosis (Table 7) and consequently mechanisms which reduce the sensitivity of melanoma to apoptosis limit the effectiveness of immunotherapy. The resistance mechanisms involved are the subject of intensive research but available evidence suggests that activation of MAP kinase extracellular receptor kinase (ERK1/2) and Akt signal pathways are responsible at least in part for resistance to apoptosis. We and others have shown that the ERK1/2 pathway is activated in advanced melanoma[15] and that inhibition of this pathway sensitises melanoma to killing by immune mediators of apoptosis such as TNF related apoptosis inducing ligand (TRAIL).[16] Phase II studies using an inhibitor of this pathway produced by the Onyx/Bayer companies were associated with impressive responses (in previously treated patients) to chemotherapy. A randomised trial in Australia is now in progress to further test this combination. Inhibitors of the Akt

Table 7:

CELL KILLING MECHANISMS USED BY LYMPHOCYTES DEPEND ON INDUCTION OF APOPTOSIS

1. Granzyme – Perforin Mediated Killing

CD8 CTL (CD4 CTL)

NK Cells and ADCC

2. TRAIL (FasL, TNF-α) Mediated Killing

CD4 T Cells

Monocytes, Dendritic Cells

pathway are also becoming available. One such inhibitor is the geldanamycin derivative (AAG) which inhibits the heat shock protein (HSP) 90, which chaperones several signal pathway proteins, including those in the Akt pathway.[17] Phase II studies with this agent in stage IV melanoma patients are planned to commence soon in Australia.

The search for agents which sensitise melanoma cells to apoptosis is a fertile area of research and includes not only signal pathway inhibitors, but agents which target anti-apoptotic proteins in melanoma. The next few years will see many of these agents tested in clinical trials and may open the way for significant advances in treatment of this disease not seen over the past 30 years.

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The role of radiation therapy in cutaneous melanoma

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Abstract

Melanoma is an aggressive skin cancer with an increasing incidence worldwide. It is particularly common in Australia and New Zealand, where it is a major health issue that is responsible for the deaths of patients of all ages. Although melanomas are cured by surgery alone if they are detected at an early stage, many are diagnosed at more advanced stages. It is in the management of these more advanced melanomas that radiation treatment (RT) has an important role. The commonly-held idea that melanomas are resistant to radiation is an over-simplification, as many melanomas respond well to RT. The role of RT applies to patients treated both for cure and for palliation. In the curative setting, RT is usually combined with surgery, to improve local control at either the primary site or the regional lymph nodes. The precise uses of RT are still being refined, using clinical trials. For patients who have incurable melanoma and receive palliative treatment, RT is used in a wide range of clinical settings to improve quality of life. This review will illustrate some of these situations.

As described elsewhere in this issue of Cancer Forum, the incidence of melanoma is increasing globally. Fortunately, as a result of greater public awareness, many melanomas are detected at an early stage and are treated adequately by surgery alone, without the need for locoregional adjuvant treatment. These thin melanomas have an excellent cure rate[1] and will not be discussed further.

This review of the role of radiation therapy (RT) mainly concerns patients whose melanomas have spread beyond the confines of the primary site. These patients fall into two distinct categories, being i) those for whom cure remains the goal of treatment and ii) those for whom cure is no longer a possibility and whose treatment is aimed at symptom reduction and improvement in quality of life (QOL).

Before describing the roles of RT in various stages of the disease, it is appropriate to consider briefly the radiation response of melanoma. This will provide an explanation of both the previous controversies regarding the value of RT for melanoma and the (apparently) unusual fractionation schedules that have been used.

Radiation response of melanoma

As mentioned above, melanoma has a reputation as a tumour that does not respond to radiation. This idea derived from selective use of clinical data[2] and was supported by early laboratory work using irradiated melanoma cell cultures.[3] In retrospect, it is clear that the irradiated tumours were generally large recurrences that had failed surgical treatment. Good outcomes would be unlikely for any of the common malignancies under these circumstances.

Although the clinical and in vitro cell survival curve responses were generally poor, analysis suggested that the best response was obtained when the total radiation dose was divided into a small number of large fractions (termed hypofractionation), instead of the usual schedule of a larger number of smaller-sized fractions (termed conventional fractionation).[4,5] However a large in vitro study of human melanomas showed a wide range of radiation responses among xenografts and cell culture lines.[6]

Conventional fractionation is the standard fractionation schedule for curative treatments of most cancers, as hypofractionation tends to increase the risk of serious, late complications

caused by RT. In the case of melanoma, however, a number of well publicised clinical series have shown benefit using hypofractionated schedules (see below).[7-10] Despite the results from these reports, which are discussed below, the case for the superiority of hypofractionation in melanoma treatment remains uncertain, as the single randomised clinical trial comparing conventional versus hypofractionated RT showed equivalence of response.[11]

In summary, the radiation responses of human melanomas show a wide range of radiosensitivities, with some indication of better responses using hypofractionated RT schedules.

Role of RT in management of primary melanoma

In most cases, primary melanomas are managed surgically, with wide excision as the sole treatment. This results in high local control rates if clear margins of excision are obtained. Cure rates are dependent on well documented features including tumour thickness, ulceration and mitotic rate.[1]

Postoperative RT should be considered when the risk of local recurrence increases. This includes close or positive margins when re-excision is impractical (eg.close to critical structures); multiple recurrences; and desmoplastic melanomas, for which recurrence rates exceeding 20% have been reported following surgery. The use of adjuvant RT in these settings reduces local recurrence significantly.[12,13]

RT has been used also for the definitive treatment of large lentigo maligna and lentigo maligna melanomas. Adequate resection of these large lesions is frequently difficult, particularly in the context of an elderly patient with co-morbidities. The results of RT alone for these lesions has shown high rates of local control.[14,15]

Role of RT in management of locoregional melanoma

The value of RT and its appropriate use as an adjunct to surgery in the management of regional lymph nodes represents the most uncertain aspect of the role of RT in melanoma. Quite apart from the misconceptions regarding the sensitivity of melanoma to radiation (discussed above), there are other considerations mitigating against RT. First, there is a strong correlation between nodal involvement with melanoma and survival[1]. Thus, patients with sufficient indication for postoperative RT to the regional nodal basin have a poor prognosis due to development of systemic metastasis. Second, the morbidity of lymph node dissection followed by postoperative RT may exceed the potential gain in local control. Third, there is no indication that any improvement in local control impacts on survival. On the other hand, uncontrolled locoregional melanoma is frequently an irretrievable and devastating condition.

Currently there are no data from randomised clinical trials (RCTs) to assess adequately the merit of adjuvant RT following regional lymph node dissection. The sole reported RCT used an unusual RT schedule and did not report on local control.[16] A RCT addressing this issue is being conducted as an intergroup study by the Australian and New Zealand Melanoma Trials Group (ANZMTG) and the Trans Tasman Radiation Oncology Group (TROG). The trial was opened in 2003 and has accrued approximately half of the 270 patients required. The randomisation is between surgery alone versus surgery plus postoperative RT for patients with fully resected nodal regions in which the histopathology report indicates nodal involvement with melanoma. Inclusion criteria include the number of involved nodes, nodal size and the presence of extracapsular spread.

In the absence of high level evidence, current practice outside the clinical trial is based on the available published data. Many surgical series over the past two to three decades have provided a good indication of factors influencing regional recurrence. Most of these factors are adverse histopathological features, the dominant ones being number of involved nodes, maximum size of involved nodes and the presence of extracapsular extension of melanoma into connective tissue. Regional recurrence rates averaging 20-30% have been reported for any of these adverse findings, with higher recurrence rates for combinations.[17-20] Not surprisingly, these adverse features tend to occur together. Non-histological factors influencing regional recurrence include the indication for lymph node dissection (therapeutic versus elective)[17-19] and the site of the nodal basin (higher recurrence rates for cervical nodes versus axilla or groin).[18]

The addition of adjuvant postoperative RT to lymph node dissection has been reported in retrospective or prospective non-randomised studies by a number of groups.[8,10,21-25] These include series in which limited neck dissections were performed.[8] The RT fractionation schedules in these studies have varied considerably, although most investigators have used hypofractionated schedules. These include 30 Gray in five fractions (treating twice weekly),[8] 33 Gray in six fractions (treating twice weekly)[10] and 48 Gray in 20 daily fractions.[9]

Despite the large range of recurrences reported in surgical series and the differing fractionation schedules used in the RT series, the local relapse rates following post operative RT fall close to 10% in all series. These local relapse rates are markedly less than the historical surgical series and imply that RT is effective in controlling microscopic deposits of melanoma. By contrast, local recurrence rates of dissection and postoperative RT increase to approximately 50% following incomplete surgery and gross residual disease.[10,26,27]

Patients are referred for postoperative RT on the basis of adverse pathological features. This places them at high risk for metastatic disease. However, survival was 37% at five years in the Sydney Melanoma Unit (SMU) series, attesting to the benefit of local control for one third of patients at least.[10]

Similarly, the late effects and complications of combined dissection and postoperative RT are important to evaluate. The anticipated late effects are soft tissue fibrosis and induration within the radiation field, with the potential for lymphoedema following irradiation of the axilla or groin. For anatomical reasons, the risk of serious complications is less for neck irradiation than for treatment of other nodal regions. Although the radiation fields in neck irradiation often extends from the temporal region to the clavicle, the depth of treatment is limited to several centimetres. However, when treating the axilla and groin, larger volumes of tissue are irradiated, including the lymphatics draining an entire limb. To minimise the risk of complications, careful attention to radiation field placement is mandatory, to ensure maximum sparing of normal tissues without compromising the target volume. Lymphoedema rates ranging 20-50% have been reported.[10,21,28]

Role of RT in management of metastatic melanoma

Despite the trend to earlier diagnosis, many patients develop metastases from melanoma. The spectrum of metastatic presentation is wide, with regard both to the location(s) of metastasis(es) and to the rate of progression. As systemic treatments have limited efficacy in metastatic melanoma, local treatments, including RT, become important for palliation of distressing symptoms. A brief assessment of the value of RT in various scenarios follows.

The incidence of brain metastases in patients with metastatic melanoma is high, reaching 75% in autopsy series.[29] Clinically, the diagnosis of brain metastases is highly variable, from the initial presentation of melanoma to the final episode of widespread metastatic disease. Diagnosis is made by CT or MRI brain scans. Irrespective of the time of onset, the median survival from the diagnosis of brain metastases is several months.

The initial management of patients with multiple brain metastases is immediate commencement of high dose steroids. In many cases this will settle the presenting symptoms. This is followed by whole brain irradiation (WBRT) if the patient's condition is adequate. The usual RT schedules are 20-30 Gray in 5-10 daily fractions. Response rates are generally poor, with the addition of WBRT adding one to two months to the median survival compared with steroids alone.[30,31] Of patients with multiple brain metastases, subgroups with minimally different survivals have been identified from an analysis of prognostic factors.[32]

Despite the dismal prognosis for most patients, small subgroups should be considered for more aggressive treatment. This includes patients with single or oligo brain metastases without extracranial metastasis or with minimal, slowly progressive extracranial disease. Surgical resection of a single cerebral metastasis improves survival compared with WBRT alone.[33] Conversely, addition of WBRT to surgical resection reduces dramatically the incidence of further intracranial relapse, although survival is unchanged.[34]

Stereotactic radiation (SRT) is a non-surgical alternative for aggressive treatment of metastases. SRT is a high precision technique that utilises a number of radiation beams that focus on the metastasis. This produces a very high radiation dose in the target, with a sharp dose fall-off outside the target volume. These characteristics are well suited to the treatment of brain metastases. SRT is usually delivered in an outpatient setting and does not require a surgical procedure or general anaesthetic. In general there are few side effects and patients are able to walk out of the treatment room and resume their pre-treatment activities immediately.

Limitations on the use of SRT are a maximum tumour diameter of approximately 3cm. Many centres offering SRT also impose a limit of approximately three metastases, all of which may be treated at the same episode. Multiple reports indicate that single doses of approximately 15-20 Gray lead to control of a metastasis in approximately 90% of cases. It is often possible to repeat the procedure if new brain metastases develop at a later date. Although surgical resection and SRT have not been compared in a RCT, case matching suggests that both methods have similar results. SRT has an advantage for lesions that are deeply placed and surgically inaccessible. Conversely, surgical resection provides pathological confirmation of malignancy. This is essential if doubt exists regarding the diagnosis, as clinical and radiological suspicion is incorrect in approximately 10% of cases.[33]

The skin is a common site of both locoregional and distant metastasis. RT is used extensively for isolated lesions which are inappropriate for local excision. However toxicity limits RT in the treatment of extensive areas of infiltrated skin.

Short courses of palliative RT are used for bone metastases causing pain and for stabilisation following orthopaedic intervention and internal fixation of bone metastases. Vertebral metastases that threaten or cause spinal cord compression should be considered for initial surgical decompression followed by RT. If surgery is not possible, due to either the patient's condition or extensive vertebral metastases that preclude internal fixation, RT is delivered under steroid cover.

Palliative RT is used to shrink masses causing a variety of symptoms. Large, dominant mediastinal masses causing vascular, oesophageal and bronchial obstruction often respond to RT. Nodal masses and soft tissue masses in unusual sites (eg. muscle, tongue, etc) may respond also. Unfortunately, responses tend to be transient, although occasional responses are durable.

Melanoma spreads commonly to lung, liver and the gastrointestinal tract. RT is useful for individual symptomatic lung lesions, but is of limited value for infradiaphragmatic metastases.

The future

The science and technology of RT are advancing rapidly. This is most evident in the fusion of developments in the accuracy of treatment delivery and radiobiological knowledge of tumour cell killing. These developments are enabling the concepts of intracranial SRT to be extended to the remainder of the body. Real time imaging during delivery of radiation, coupled with techniques for gating and/or tumour immobilisation, enable higher doses to be delivered with greater safety. Methods for tracking and targeting tumours during treatment are being developed. The importance of dose inhomogeneity within the tumour is being explored. The ability to increase the radiation dose to regions of hypoxia or decreased radiation sensitivity, due to intrinsic genetic variability, is being investigated. This is possible due to the integration of advanced treatment delivery techniques and sophisticated imaging such as positron emission tomography, using molecular probes.

Conclusion

It is evident that RT has a significant role in all phases of the management of melanoma, from the primary tumour to widespread metastatic disease. When melanoma is localised, RT has its main role as a surgical adjuvant, to decrease the risk of local recurrence. Until definitive evidence is available from RCTs, the finding of adverse pathological features should guide the use of postoperative RT to the primary site and regional nodal basin.

RT has an indispensable role in palliation. In particular, the development of stereotactic techniques has had a dramatic impact on the management of many patients with brain metastases. Current developments in RT, combined with developments in imaging, should improve the efficacy of RT and increase its scope and role to encompass visceral metastases.

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Developments in melanoma management – success and failure

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Abstract

Melanoma is a high priority cancer in Australia with a lifetime risk of occurrence of 1 in 30. However the incidence rate rise is stabilising and survival now exceeds 90%. The improvements in melanoma survival are mostly based on mostly early diagnosis. The management of melanoma has gone from radical surgery to a conservative individualised approach based on new and better understandings of the biology and behaviour of the malignant melanocyte. Despite many "unknowns" and many earlier inappropriate management approaches, the outlook for melanoma patients has steadily improved over the last 50 years.

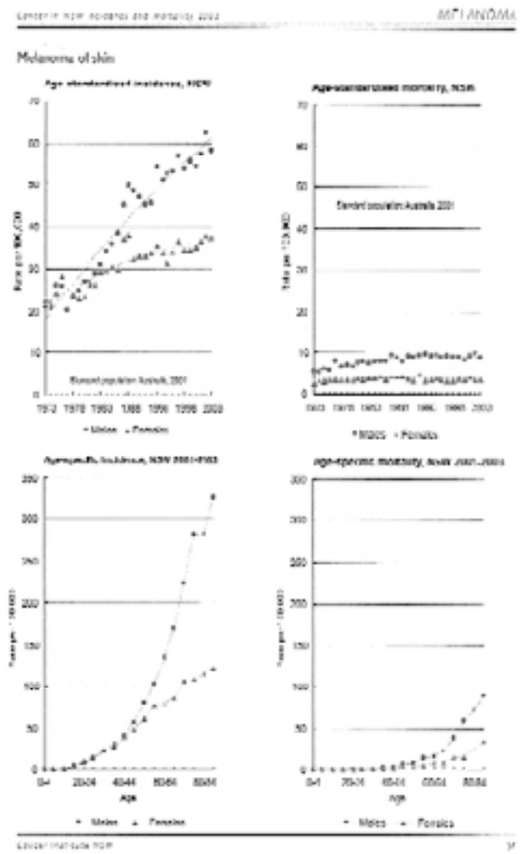
Melanoma is known abroad as the Australian cancer. In Australia, its prevalence and community educational programs have given it high priority in the minds of most Australians, even though it now has the best survival (more than 90%) of all major cancers and for the majority of patients who develop melanoma, only relatively minor surgery is curative.

The high profile of melanoma in Australia is mainly due to its association with the perceived lifestyle of the Australian citizens, with sun, sand and surf dominating both local and international views of Australians. However, while it is certainly true that melanoma is very much more common in Australia than anywhere else in the world, its mortality is generally overestimated by the Australian populace. NSW is the largest state in Australia, with approximately five million people and the most recent data on melanoma comes from Cancer Institute NSW, which has recently reviewed melanoma in NSW from 1994 – 2003.[1] In 2003 there were 3239 new cases of melanoma and 407 deaths in NSW. The lifetime risks for melanoma were 1 in 24 for males and 1 in 35 for females.

In Australia the incidence of melanoma is between 36.9 to 51.1/10^5/year for males and 25.9 to 38.1/10^5/year for females (world standardised rates). Queensland has the highest incidence. These rates are more than three times the US rates for whites (15.4 for males and 11.6 for females per 100,000) and six times the UK rates of 5.8 males and 7.4 females per 100,000.

The dominant feature in Australian melanoma incidence data is a high incidence in older males and this is reflected also in mortality (Figure 1). There is a virtual stabilisation of mortality for patients under the age of 40.

Figure 1:



Age standardised incidence and mortality NSW 2004.
Source: NSW Central Cancer Registry

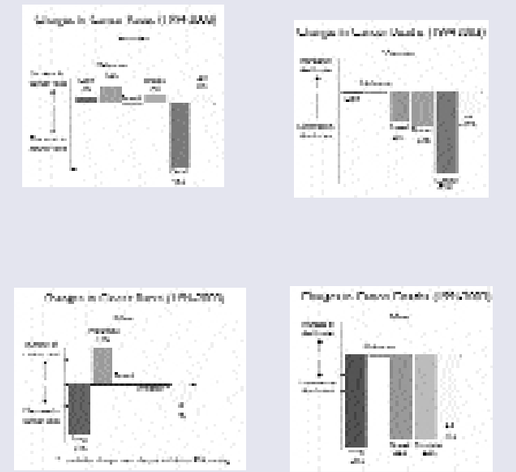
The management of melanoma in Australia has been influenced by general worldwide interest in the disease and research both here and elsewhere. In Australia a large emphasis is placed on melanoma prevention by The Cancer Council Australia and the state-based Cancer Councils, non-government foundations, such as the Melanoma Foundation, the Skin Cancer Foundation and clinical melanoma units in every state in Australia and in New Zealand. Australian clinicians and researchers can take credit for many contributions to the increasingly successful management of melanoma. However, there have been many blind pathways during the development of the management of melanoma, with much time and effort spent pursuing pathways which have not led to substantial improvements in outcome.

Primary prevention

Australian skin cancer preventative programs have an enviable reputation throughout the world. No other nation has comparable emphasis on the prevention of melanoma.[2] All Australian states have state-specific educational programs and one program, "Slip, Slop, Slap" which originated in Victoria, is used nationally as the basis for national public education programs on the prevention of sunlight damage to the skin.[3]

A degree of success can be claimed for these programs. From 1984 to 1993 in NSW, melanoma incidence rates increased by 54% in males and 17% in females. From 1994 to 2003 the age standardised incidence rate rose by only 15% in males and 12% in females and mortality rates are now almost stable. (Figure 2) Furthermore much of the incidence rate rise in males can be attributed to the older male population who receive the majority of their skin sun damage prior to the great emphasis on skin cancer prevention that began in the decade 1980–1990. For younger cohorts preventative programs now show a satisfying stabilisation in incidence rates and in mortality (Figure 2). The obvious failure to date of these preventative programs is concentrated particularly on one specific community group, older males. This is unlikely to be changed in the near future because sun damage to the skin is essentially irreversible and for this group the predisposition to skin cancer has been established by earlier sunlight exposure.

Figure 2:



Changes in Cancer Rates and Mortality 1994-2003 (NSW)
Source: Cancer Institute NSW – Statistics and Data 2004

Causation

The basic premise of melanoma causation is that ultraviolet light damages melanocytes in the skin, particularly those in naevi, causing a transformation to a malignant phenotype. This occurs in the basement membrane of the skin (in-situ melanoma), which then becomes invasive, cells are released into the surrounding tissue fluid with subsequent invasion of the lymphatics, involvement of the lymph nodes and, with or without lymph node involvement, systemic metastatic disease. Ultraviolet light is known to promote malignant change by a direct mutagenetic effect on DNA, stimulation of growth factors, reduction in cutaneous immunity, promotion of reactive oxygen species which damage DNA and suppress apoptosis and

cumulative damage, which selects for a malignant phenotype that has the ability to stimulate blood vessel growth and directly invade blood vessels and lymphatics. Melanoma synthesis, particularly involving pheomelanin, produces by-products, which may of themselves be carcinogenic. Detailed information is now available[4] on the metabolic pathways and on the immune-suppressive effect of ultraviolet light on the skin. Many of the metabolic pathways involved in the development of the malignant phenotype are known and the interaction of sunlight with skin cell genetics is under intensive investigation. Particular attention has been placed on the CDKN2A gene and its protein products, p16 and p14ARF. Details of these genetic pathways are reviewed elsewhere in this journal by Graham Mann.

It is clear that ultraviolet light does not cause melanoma. Ultraviolet light is specifically related to susceptibility and predisposition. Figure 3 lists the known predisposing factors for melanoma and these are clearly related to ultraviolet light and genetics, but there are many questions about the interaction of ultraviolet light on genetically susceptible skin. These questions include:

1. Given the excessive exposure to sunlight by the majority of white skinned Australians, why do so few get melanoma? One in 30 Australians will develop melanoma during their lifetime, whilst 29 others will not.
2. Australians have on average more than 40 naevi and many Australians have hundreds of naevi, yet on any individual melanoma patient only one, or sometimes two, become malignant.
3. Melanoma is quite common on areas of the skin not exposed to ultraviolet light and it also occurs on mucosal surfaces where ultraviolet light clearly does not play a role.
4. Many people have all the risk factors for melanoma but do not get it, while some people with no risk factors do get it.
5. Young people who get the majority of ultraviolet exposure get far less melanoma than older people who have much less exposure.
6. In southern Australia it is the recreational exposure of the affluent classes, which correlates with melanoma incidence, but this dose response relationship disappears in northern Australia where chronic exposure seems to be the predisposing factor.

Figure 3 – Clinical risk factors for melanoma [4]

	Relative Risk
Genetic Factors	
1. Strong family history	35-70
2. Weak family history	3
Naevi	
1. Multiple benign naevi (>100)	11
2. Multiple atypical naevi	11
Previous skin factors	
1. Previous melanoma	8.5
2. Previous non-melanoma skin cancer	2.9
Immunosuppression	
1. Transplant recipients	3
2. AIDS	1.5
Sun sensitivity	
1. Type 1 skin (sunburn easily)	1.7
2. Freckling	2.5
3. Blue eyes	1.6
4. Red hair	2.4
UV exposure	
1. History of blistering sunburn	2.5

Some of the anomalies in the ultraviolet story are attributed to the immunosuppressive effect of ultraviolet light on the skin. This could explain the lack of relationship between direct exposure and the development of melanoma, especially the site distribution of the melanoma, but there are many questions still unexplained about this immunosuppressive effect. The relatively low risk for immunosuppressed people and people with AIDS (Figure 3) is difficult to explain. Squamous cell carcinoma incidence is higher in most patients after immunosuppression, while melanoma incidence is only marginally increased. Recent studies have implicated ultraviolet A as a major cause of immunosuppression but this is yet to be generally accepted. The amount of ultraviolet light seems to be important with small doses improving skin immunity while large doses are depressant.

Clearly there is a yet undetermined factor involved in causation of melanoma. It is only possible to state that ultraviolet light and genetics play a role in predisposition to melanoma but certainly do not explain its occurrence. Diet, urban pollution, stress, viruses, radio waves and electromagnetic energy have all been suggested as the unknown factor X, but to date none of these has shown to have any significant association with melanoma incidence and mortality.

Sunscreens are a part of the recommended protection methods against melanoma, but debate on the effectiveness of sunscreens in melanoma protection has filled the literature for the last 10 years.[2] A consensus has developed that sunscreens do have a role in melanoma prevention provided they are used appropriately, contain UVA as well as UVB protection and are used as adjuvants to sun avoidance, particularly in the middle of the day ("11 to 3 stay under a tree").

Genetic susceptibility also has many unanswered questions. It is clear that many genetically susceptible people, eg. redheaded freckled people with light-coloured eyes do not all get melanoma while many people with type 4 skin, brown hair and brown eyes do get melanoma. One interesting anomaly is the fact that the occurrence of melanoma in one twin is virtually never associated with melanoma in the other twin despite identical genes and similar UV exposure.

Early diagnosis (secondary prevention)

Early diagnosis (secondary prevention) has been an outstanding success story, particularly in Australia. The risk of death from melanoma is dependent on tumour thickness, which is measured by the pathologists as the maximum vertical diameter of the melanoma from the granular cell layer of the skin to the deepest malignant cell excluding infiltration along natural tissue planes such as hair follicles and sebaceous gland ducts. The UICC/AJCC classification of melanoma thickness is now generally accepted worldwide and is as follows:

TIS – In situ melanoma (no invasion)
T1 – Melanoma – 1mm (thickness)
T2 – Melanoma 1.1-2.0mm
T3 – Melanoma 2.1-4.0mm
T4 – Melanoma > 4mm

(The full AJCC/UICC classification can be found in Reference 2)

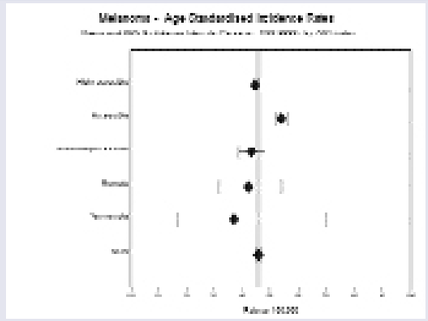
An important new biological characteristic of melanoma has recently been added to this classification system, surface ulceration. Surface ulceration is not traumatic ulceration but a histopathological finding where the skin surface over the melanoma is no longer evident. The UICC/AJCC classification has been modified with each category having an A or B sub-category. The A category means without ulceration and the B category indicates ulceration. The presence of this ulceration, the mechanism of which is unknown, significantly increases the risk that the melanoma will metastasise. Curiously enough the presence of ulceration of the primary tumour remains an important prognostic criteria, even when the patient already has lymph node involvement.

The largest increase in melanoma rates has occurred in early melanomas (T1). The thickness measurements in Australia have been falling every year since accurate measurement was available in the early 1980s and now the median thickness is around 0.7mm. In NSW, superficial spreading melanoma increased from 5.2/10^5/year in 1986 to 20.6/10^5/year in 1988, after which rates ranged from 19-23/10^5/year in 2002. Rates for nodular melanoma increased much more slowly, from 6.1 to 8/10^5/year between 1988 to 2003. A substantial peak in melanoma incidence occurred late in 1987 following a dramatic 60 Minutes program entitled "Goodbye Sunshine" (Figure 4). This program was generated by the Melanoma Foundation of the University of Sydney and led to the diagnosis of more than 500 new melanomas in the six months following the program.[5] The downside of television footage has been the development of an unrealistic fear of melanoma in the general populace, evidenced by excessive attendance at skin cancer clinics for "mole checks", even by people with no significant risk factors. The rates for all melanomas increased only marginally over the last 10 years, ie. by 15% in males and by 12% in females. These increases of less than 1.5% per year contrast dramatically with the 5-10% increases per year during the 1980s (Figure 5).

Figure 4:

Age Standardised Incidence Rates – NSW (1970-2005)
Source: NSW Central Cancer Registry

Figure 5:



Remoteness Variation Incidence and Mortality
Source: Cancer Institute NSW

Some epidemiologists have suggested this large incidence increase of very early melanoma is artefactual and is caused by a large number of lesions, diagnosed as melanoma by pathologists, being "non metastasising melanomas", ie. melanomas which would not progress and might even regress if they were not excised.[6] The most recent NSW data add some credence to this view in that people with little access to skin cancer clinics, dermatologists or major melanoma centres, have a lower incidence of melanoma than those for whom there is easy access for diagnosis of suspect skin lesions (Figure 5).

The clinical diagnosis of melanoma is based on the A (asymmetry) B (border) C (colour) D (diameter) system developed by the New York School of Medicine. However early diagnosis of melanoma has been substantially influenced by two recent developments. The first of these is the advent of surface microscopy or dermoscopy, which is detailed in this edition of Cancer Forum by Scott Menzies. Dermoscopy has demonstrated a significant improvement in the rate of diagnosis of early melanoma.[7] Recent research[7] suggests that automated diagnosis of melanoma on pigmented skin lesions may well be available in the near future.

The second influence on early diagnosis of melanoma has been the advent of skin cancer clinics staffed by general practitioners. Because of convenience, no necessity for referral and bulk billing, these clinics have been enthusiastically endorsed by the general population. This had led to a substantial increase in the number of pigmented lesions excised and has raised considerable difficulty for pathologists to determine what is actually a melanoma, so substantial over-diagnosis is possible. There is no doubt that the differentiation of early melanoma is difficult, even for more experienced pathologists. At the Sydney Melanoma Unit, reclassification of histopathologically diagnosed melanomas as benign and sometimes of dysplastic naevi as melanoma, is not exceptionally rare.

Unfortunately the appropriate clinical trial to answer the question of "non-metastasising melanoma" cannot be done. It is unlikely that any clinician would not excise these doubtful lesions given the consequences of failure to diagnose a potentially lethal lesion and the medico-legal complications of such an event.

Primary melanoma management

The management of primary melanoma has undergone substantial change since the disease was first described by William Norris, an English physician in 1820. Misconceptions about the behaviour of melanoma have led to substantial overtreatment of the disease. In 1857 Norris described an advanced melanoma and advocated extensive local surgery. Following that, in 1907 William Sampson Handley, on the basis of a single autopsy examination of a patient with advanced melanoma, advocated regional dissection and even amputation in selected cases. In 1908, Hogarth Pringle, also a prominent surgeon of that time, also recommended excision of the skin between the primary and the lymph node field (incontinuity dissection). These recommendations were accepted almost up to the present day, with wide local excision, radical node dissection and sometimes incontinuity resection being relatively standard approaches to melanoma up to the mid-1980s. By contrast, current therapy for 85% of patients is a limited local excision and, for only an additional 10% a lymph node; sampling by way of sentinel node biopsy is undertaken.

Radical surgery is now confined to patients with locally advanced tumours and proven nodal metastatic disease. It must, of course, be conceded that Norris, Handley and Pringle and the many surgeons who followed their recommendations were dealing with melanoma patients presenting for treatment at a locally advanced stage. Survival in the first few years of the 20th century was around 15%. Survival at the present time in Australia exceeds 90%, clearly indicating the advanced nature of the disease being treated by the surgical pioneers.

The margins of excision of primary melanoma has decreased regularly since the turn of the 20th century, when "dinner plate" excisions measuring at least 5cm in diameter requiring an extensive skin graft were standard practice. At that time it was felt that flap closure, although cosmetically more acceptable, might delay diagnosis of local recurrence and therefore was not recommended, so many patients had large unsightly skin grafts. However, subsequent research has shown that flap closure does not facilitate local recurrence. The necessity for wide excision was based on a high local recurrence rate, evident in early reviews of melanoma management and a hypothesis that melanocytes in the vicinity of a melanoma were unstable and recurrence was due to these melanocytes becoming melanomas following the removal of the clinically visible lesion.[9,10,11] In the last 20 years this theory has lost credence. It is now known that local recurrence is essentially due to "satellitosis", ie. the tendency of melanomas, as they invade deeper into the dermis, to release cells into the surrounding tissue fluid. These cells invade local lymphatics outside the excision margin. This phenomenon is clearly related to tumour thickness. A further theory has been propounded[12,13] that some of the local recurrences are due to metastasisation back to the primary melanoma site from an as yet undeclared systemic metastasis. However this is unlikely to be the cause in very many patients given that more than 50% of patients with local recurrence survive the disease. It is more likely that the systemic disease that does occur in many patients with local recurrence is the result of metastases from the recurrent tumour as it develops.[14] Death from metastatic disease in these patients is correlated with tumour thickness of the locally recurrent nodule.

An unexplained fact about locally recurrent melanoma is that it can recur many years after the primary melanoma has been excised, without any evidence of systemic recurrence.

Most recent studies show that the margin of excision is related to local recurrence rates but survival is not influenced. A large recent study[15] revealed that the loco-regional recurrence, including nodal recurrence, was related to width of excision but not to survival. This suggests strongly that intransit recurrence and nodal recurrence is due to melanoma cells in lymphatics outside the primary excision margin, which are removed when a wider excision is done but not excised with the narrow excisions.

Intransit recurrence

The development of the recurrence of melanoma between the primary melanoma and the lymph nodes is a difficult and devastating problem for the melanoma patient. Untreated, the disease may progress relentlessly to a situation in which the entire limb can be almost completely replaced by melanoma. This sometimes occurs in the absence of systemic disease. Standard treatment for this type of recurrence is isolation perfusion, which was pioneered in the US by Krementz almost 50 years ago. It remained the treatment of choice until the last 10 years when a much less aggressive, but almost equally efficacious treatment of isolation infusion was pioneered in Europe and Australia. It is now the method of choice for intransit recurrence. The outcome of this treatment modality is reviewed by John Thompson in this edition of Cancer Forum. Because of the accessibility of the tumour to local therapies, many other techniques have been tried for the treatment of intransit metastases. These include simple surgical excision of the recurrence, injection of cytotoxic into the nodules, cryotherapy for superficial recurrences, injection of immunotherapeutic substances into the nodules, electroporation, a technique utilising electrical energy to open tumour cell pores to increase absorption of cytotoxic agents, local radiotherapy and, of course, amputation. None of these techniques has yet been successful to a level at which they can be recommended in place of isolation infusion.

Lymph node management

The management of the lymph nodes of patients with melanoma has undergone the same correction of misunderstandings of tumour behaviour as occurred with primary melanoma. Elective lymph node dissection was debated for almost 100 years without conclusive proof of its efficacy and, in many cases, without precise knowledge of the lymphatic drainage pathways. With the advent of good lymphatic mapping (lymphoscintigraphy) it has become apparent that many of the earlier clinical trials of elective lymph node dissection, particularly axillary and neck dissections, were flawed by the selection of inappropriate node fields for excision. The selection of node fields was based on the long admired work of Sappey[16], which determined lymphatic pathways by injection of mercury into cadavers. Modern lymphoscintigraphy, using a radioactive labeled antimony trisulphide, has shown that at least 18% of melanomas on the trunk and many melanomas on the head and neck have lymph node drainage to nodes not predicted by clinical assessment, based on Sappey's rather dogmatic lines![17]

Elective lymph node dissection disappeared when sentinel lymph node biopsy was introduced by Donald Morton in the early 1980s. Sentinel node technique is detailed in this edition of Cancer Forum by John Thompson. However, even sentinel node biopsy, an elegant and technically challenging procedure, has not yet been shown to have survival value, although it is clearly the best prognostic indicator of melanoma behaviour. In this and other trials, the outcome for patients with positive sentinel nodes, which is followed by completion lymph node dissection, is statistically better than the outcome for patients who have dissection for clinically apparent nodal involvement but, this is not a randomly selected group comparison.

The important question now is to determine which patients with a positive sentinel node should have completion lymphadenectomy. In the recent interim analysis of the Multicenter Selective Lymphadenectomy Trial (MSLTI), less than 20% of patients had nodes other than the sentinel node involved in the completion lymphadenectomy. A new international trial (MSLTII) has been set up to answer this question.

One of the other unanswered questions about malignant melanoma is the significance of reverse transcriptase polymerase chain reaction (RT-PCR) positive lymph nodes. Up to 30% of nodes negative to routine histopathological examination will contain RT-PCR positive cells. This fact mitigates against unqualified acceptance of the previous selective lymph node dissection trials and also of the recent MSLTI trial outcomes. RT-PCR was not included in the MSLTI trial design. However, RT-PCR is included in the MSLTII protocol. The prognosis for RT-PCR positive patients is slightly worse when these cells are detected in their nodes.

No studies to date have confirmed that melanoma cells in lymph nodes are necessarily progressive. It remains possible that, in some people, nodal metastatic disease may be protective and this could explain the lack of survival value for nodal surgery when compared to observation regimens. A clinical trial to assess this possibility is unlikely.

Adjuvant therapy

Immunotherapy of melanoma is reviewed elsewhere in this edition of Cancer Forum by Peter Hersey. The concept that the body's natural immunity to melanoma can be harnessed to prevent recurrence of locally advanced and nodal melanoma is attractive, as is the view that immunotherapy may be effective even for systemic disease. Unfortunately, to this date adjuvant therapy for thick primary melanomas and nodal disease has been disappointing and for systemic metastatic disease even less satisfactory. The Sydney Melanoma Unit began immunotherapy trials more than 20 years ago using a variety of immune stimulants such as bisdiazobenzadine and gamma globulin coupled with irradiated melanoma cells, and a variety of approaches using Bacillus Calmette-Guérin (BCG). BCG was also used as an adjuvant in a large international adjuvant trial undertaken by the WHO Melanoma Group. None of these earlier trials had any significant success. Over the last 20 years a large number of immunotherapy and chemotherapy adjuvant trials have been undertaken but, to date no regimen has substantially altered the prognosis for this group of patients. At the present time all adjuvant regimens are only justified in the context of a clinical trial. Similarly, immunotherapy in the presence of established systemic disease has so far been successful only in a small number of individual patients.

Disseminated melanoma

Therapy for disseminated melanoma is reviewed in this edition of Cancer Forum by Richard Kefford. In summary, the management of disseminated melanoma remains unsatisfactory. Despite a multitude of studies with single agent chemotherapy, multiple agent chemotherapy and biochemotherapy, the outcome for patients with disseminated melanoma remains poor. The best survival for patients with disseminated melanoma occurs where the disease manifestation is a solitary nodule in a single organ or where a small number of metastatic nodules can be resected. In this instance, particularly in the lung, a long-term benefit can be achieved. For this reason most major melanoma centres encourage an aggressive surgical policy and metastatic melanoma is resected where the tumour burden is low. This is often followed by an experimental immunotherapy protocol within the clinical trial setting.

At the present time in the absence of a worthwhile standard therapy for melanoma, most centres encourage patients with disseminated disease to enter clinical trials of new agents.

Conclusion

Despite many journeys down the wrong pathway, the outlook for melanoma patients has improved steadily since the days of Norris, Handley and Pringle. The situation at the present time is moderately satisfactory with 90% of patients presenting with primary melanoma being cured by surgery. This is a 70% improvement since the early 1900s. Most of these patients (80%) will be cured by local surgery only. A further 15% will undergo biopsy of a lymph node, 15% of these will have a positive node and more than 50% of node positive patients will be cured by node dissection. The remaining patients are the major problem for melanoma management worldwide. However, there is a large and increasingly active research effort into finding a cure for disseminated melanoma. With the passage of time these efforts will undoubtedly lead to the desired outcome for most these patients.

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Medical education at the University of Sydney - the last 40 years

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Abstract

Medical education in Sydney was initiated in 1883. Designed for undergraduates and based on the highly regarded Scottish system of medical education, it was scientifically rigorous, progressing from basic science to clinical work. Those fundamental principles of the curriculum did not change substantially in 90 years. Changes introduced in the 1970s (reducing six years to five) and 1980s (returning to six years) were designed to enhance and integrate the scientific and clinical content, but the basic structure remained similar. New subject areas were progressively included, but teaching methods were basically didactic, with few exceptions. Clinical contact was delayed. Departmental budgets were based on contact hours, leading to competition for curriculum time. The consequence was an overloaded curriculum, punctuated by largely written examinations; students had only a limited sense of a progression in knowledge, understanding and skills. One medal-winning student characterised the program as "doing the Higher School Certificate six times". Radical change was instituted during the 1990s, with the development of a four-year, graduate-entry program that is integrated and problem-based. The role of the Australasian and New Zealand Association for Medical Education is discussed.

The first curricula

The Medical School at the University of Sydney was founded in 1883 when the 26-year old Professor TP Anderson Stuart arrived as Dean. He instituted a curriculum based on the rigorous Scottish model of the time, considered then to be "state-of-the-art".[1] Students first enrolled in a year of Arts, studying the basic sciences and clinical subjects for three years. The Arts requirement was abandoned early 1889 and the program extended to five years. In 1922 it was lengthened a little and in 1926 it was extended to a full six years. The underpinning philosophy did not change, although the curriculum was shortened during World War II. A small number of early subjects were later removed (eg. latin, materia medica, botany), but new scientific disciplines were progressively included, eg. physiology and biochemistry were separated in 1948 and neuroscience was introduced in the 1960s, combining neurophysiology and neuroanatomy.[2] The growth in knowledge was relatively slower in the 1950s than now. Eg.a classmate of ours in first year at that time comfortably used his father's zoology notes; the lectures (and even the drawings carefully done on the blackboard) had not changed in any substantial way.

Up until about 40 years ago, few academic staff were salaried. Major departments had a tenured professor as head, but lecturers – often medical practitioners – worked part-time. Departments that offered practical work usually had a full-time demonstrator, but the classes tended to be repetitive, traditional and uninspiring. By no means all staff undertook research. Clinical teaching was idiosyncratic as it depended on unpaid tutors and needless to say they exhibited a wide range of abilities in teaching; their levels of enthusiasm (and competence) varied considerably. Medical education was just starting to become a recognised area of study. Forty years ago, Australian medical schools were still accredited by the General Medical Council of Great Britain, nothing like as rigorous or supportive a process as that later developed by the Australian Medical Council.

Curriculum change in the 1970s and 1980s

A major systematic reform started from 1969 with the planning of a five-year curriculum, which was introduced in 1974. The reasons for the reduction to five years remain somewhat obscure. Staff in both medical schools in Sydney apparently thought they needed to make the change because the other was doing it. At that time, two interfaculty workshops for the medical faculty of Sydney and NSW on evaluation and curriculum development were convened and conducted by Bill McCarthy, which were influential. These workshops led subsequently to the development of the Australasian and New Zealand Association for Medical Education (ANZAME).

Bill McCarthy was Subdean for Medical Education at the University of Sydney from 1975 to 1989. In that role, he was a member of the Dean's advisory committee on curriculum and was active in the progressive implementation of the five-year curriculum, although he was not the originator of the idea for the reform. Bill had gained a Masters degree in medical education at the University of Illinois with medical educational pioneers George Miller and Thomas King. In 1973 he prepared a crucial faculty paper encouraging evaluation of teaching by students. This issue was vigorously debated and some staff felt it was inappropriate for students to comment on experienced teachers. In 1975 a faculty committee of students and teachers successfully developed an effective process which was subsequently endorsed and has been consistently implemented since that time. Indeed, enhanced and better resourced, it remains a centrepiece of the current curriculum. A Staff- Student Liaison Committee was established for ongoing face-to-face discussion of these issues.

David Madison, the Dean of the Medical Faculty at that time was an enthusiastic educator and, with Bill McCarthy as convenor, initiated a workshop on curriculum change which facilitated the curriculum developments. Several educational papers were published, including a comparison of the Australian and American systems[3] and surgical clerkships.[4] Other papers on the examination process[5,6] and the techniques of teaching[7,8,9] followed.

Curriculum planning provided a major opportunity to review the Sydney program, remove redundancy and introduce some clear improvements. In 1974, faculty summarised six key aims of the new curriculum: horizontal integration between preclinical disciplines; the introduction of behavioural sciences; the development of integrated clinical sciences; the introduction of general practice; the inclusion of specific teaching in history-taking and physical examination; and the development of a strategy for progressive assessment.

Some of the difficulties in developing a new curriculum arose because, at the time, Sydney was by a considerable margin the largest medical school in Australia, with the most daunting student-staff ratios. Statistics from the Australian Universities' Council in 1975 recorded figures for Sydney Medical School of 1804 students enrolled, 159 equivalent full-time staff and a student-staff ratio of 11.3. These figures compared unfavourably with the next biggest, Melbourne, with 1625 students, 216 staff and a ratio of 7.5. It was noted at the time that a continuing problem for Sydney had been that the great majority of clinical teachers were generally unpaid, unlike their counterparts in some other states.

Other major educational initiatives occurred after the arrival of Michael Blunt in 1973 to the Chair of Anatomy who had a long commitment to enhancing the teaching of anatomy. Dissection was no longer mandatory but available as an option. Students studied in discussion groups with a tutor, using prosected specimens to meet defined objectives. The method was very popular with students and many staff; it was demonstrated to be educationally superior, with better long-term retention of knowledge.[10] The program was also time-efficient and cost-effective.

Despite some effective initiatives, strains soon developed in the new curriculum, reflected in faculty minutes. Without agreed goals (which had not been developed), there was no effective way to manage the curriculum. Despite the faculty's commitment to integration, individual departments vied to include yet more material because their funding depended on contact time and the numbers of students. The students were vocal in their complaints of overload, overlaps and redundancy. Material was not integrated, the levels of detail were often inappropriate for undergraduates and some of the information was largely irrelevant. Thus in 1980 discussions were held about extending the curriculum again to six years. A report recommended extension, but it was not implemented at that time.

In 1983, for the first time, clinical students completed a questionnaire that sought their views on the whole medical course. Half of the students in each of the last two years (four and five) completed the questionnaire. They generally felt that most of their subjects were providing appropriate preparation for practice. Nevertheless, 79% supported lengthening the program. Also in 1983, the Australian Medical Council was established in December, to start the process of accreditation from 1985. It was to become the major force for curriculum review and development across all Australian and New Zealand medical schools, but Sydney was not listed for its first accreditation visit until 1993.

After a faculty retreat, it was agreed that a small, effective "curriculum committee with teeth" should be established to develop a six-year curriculum. A "core plus options" approach was suggested, with integration to be a key element. The paramount need for faculty development in teaching was recognised. The report was adopted in 1984 and the new curriculum was to be developed and overseen by interdepartmental committees. Some time afterwards, objectives were agreed, but inevitably too late to drive curriculum design. Nevertheless, initiatives included logbooks and journals, a wider use of multiple-choice questions and clinico-pathological discussions.

During 1988, as the new program was being implemented, it was recognised that one of the difficulties in the curriculum lay in the lack of "vertical integration" between basic and clinical learning. A lively workshop was held, with M Field, J Harris and A Sefton elected as sub-deans. Their final report recommended mechanisms to encourage discussion across all six years of the curriculum within "vertical streams" – topic areas that extended throughout all years of the curriculum. While many themes were designed to link related basic and clinical sciences (eg.heart and circulation, nutrition, neuroscience), other issues (eg.growth and development, ageing) were included. After much discussion and activity, it became apparent that existing departmental structures made it impossible to implement such a "vertical" curriculum. Undoubtedly, the most valuable legacy of those discussions was a greater awareness of shared interests between basic science and clinical teachers. Not only did those meetings provide an invaluable basis for the collaborative development of the next curriculum, a number of cross-disciplinary research projects were born and new friendships were generated.

Another long-running issue was that of student selection. In the 1950s, any applicant could enrol in any faculty providing he or she had achieved a minimum of five Leaving Certificate B passes. Subsequently, entry requirements were tightened, until medicine at the University of Sydney was the most difficult university program in NSW to enter. There was substantial evidence that many lacked any specific motivation. They enrolled because they "got the marks" or as a result of pressures from families and schools. Failures and discontinuations were common. The faculty compensated to some extent by opening up places for internal transfers and for a small cohort of graduates and others with health professional qualifications.

Genesis of the Graduate Medical Program (now the Sydney Medical Program)

By the early 1990s, an increasing sense of frustration developed. All the educational effort so far had not resulted in significant change in the curriculum, which remained overloaded and traditional in approach. There was by then an increasing literature on medical education; many academic and clinical staff were reading about alternative ways of educating medical students. Some had experienced other systems while on sabbatical leave or had visited Newcastle (NSW) Medical School. Nevertheless, each department or unit approached their educational tasks from an independent perspective, leading to duplication and gaps. Worse, the educational approaches were inconsistent or even conflicting.

Professor John Young, as the new Dean from 1989, was strongly aware of these issues and tensions, although his predominant interests had previously centred in research. During a visit to Harvard in 1991, he arranged for Ann Sefton to attend an intensive week-long educational leadership course there. By chance, Stephen Leeder , who was undertaking a sabbatical, was one of the faculty for the week. They both agreed that there was no real reason why Sydney could not make a similar change, despite the lack of Harvard's immense financial resources. In following years, the Dean arranged for a number of other key academic staff members to attend the Harvard program.

In October 1991, the faculty determined to explore the possibility of moving to a four-year, graduate entry program. Committees were formed to write reports which were presented to a meeting of faculty for final decisions in one

year's time. Committees were established with nominated chairs; members of faculty and students were encouraged to join one or more of them. Goals were to be developed and made explicit (Chair: Stephen Leeder), a curriculum would be outlined (Ann Sefton); modern assessment methods would be designed (Bill McCarthy); new strategies for admission were prepared (Ian Fraser) and a blueprint for the development of clinical schools was prepared (John Stewart). In the event, the total contributions to the planning committees came from 98 members of staff and 17 students, some contributing to more than one committee. It was a time of intense but creative activity; new alliances and friendships developed and those who contributed gained a greater understanding of different viewpoints. The previous work on vertical streams had provided a very useful foundation by initiating and supporting communication between individuals and departments. The charismatic Professor Dan Federman, Dean of Education at Harvard Medical School visited during the year and provided strong support.

At the biggest faculty meeting ever held, a vote was taken. The final decision was made on the basis of the detailed report, with one caveat: the Dean had to be assured that resources were sufficient. The result was 166 in favour of a four-year goal and theme-based graduate entry program, a focus on problem-based learning, new assessment strategies and early clinical contact. Six voted against the motion; some (not all) of those later participated willingly and creatively in developing the program. Michael Field and Ann Sefton were appointed as Associate Deans (curriculum).

Unfortunately, soon afterwards, planning activities had to be put on hold for well over six months as we prepared the documentation for the essential accreditation by the Australian Medical Council of the existing program. Although notice had been given of a radical change, Sydney was still required to complete the full formal accreditation of a program that would only be accepting a few more intakes. After that experience (which was shared with Flinders Medical School whose program was accredited in the previous year), more realistic arrangements have been put in place when medical schools give notice of a change in curriculum.

A most valuable source of support came from the realisation during the planning year that two other Australian medical schools were thinking of a similar move - Flinders and Queensland. A consortium of the three universities was formed; it provided mutual support and significantly eased the burden of development by sharing the responsibility for leading on specific issues[11,12]. Many Sydney staff also attended a range of consortium meetings, as well as educational conferences and courses locally and internationally. A number visited other problem-based learning (PBL) schools, including MacMaster (the "home" of PBL), Newcastle NSW (which generously provided strong support particularly in admissions and in introducing Sydney staff to PBL), Harvard and Maastricht, amongst others.

Key features of the new program include graduate entry on the basis of academic performance in: a first degree; aggregate performance in a Graduate Australian Medical Schools Admission Test (GAMSAT) developed by the Australian Council for Educational Research[13] to include reasoning in the sciences, and in the social sciences, as well as a writing task. On the basis of their results, applicants are invited to a structured interview which is currently undergoing modification.

At the heart of the curriculum are the goals which define four themes that extend throughout the program: basic and clinical science; patient and doctor; community and doctor; and personal and professional development. The themes form the basis for the organisation of the program and the integrated assessment. Problem-based learning extends throughout, designed to stimulate discussion, critical thinking and problem-solving in all of the themes in each weekly problem. Clinical contact starts from the first week; students spend a day each week in their clinical school, learning the skills of communication, examination and procedures, as well as observing and interacting less formally with patients and clinical staff. A Medical Education Unit, now the Office of Teaching and Learning in Medicine, was established on campus to manage the program with Jill Gordon as Associate Dean and Head. Its expert tasks include: ongoing systematic development; managing assessment; extensive program evaluation; and supporting and leading the development of scholarship and research in teaching and learning. The office also continues to train PBL and clinical tutors as well as interviewers for the admissions process and offers seminars on educational issues. Staff publish regularly in the literature of medical education. Last year, a Masters in Medical Education degree (partly online) was developed and it is proving popular. Notably, the Department of Surgery established its own educational unit, led by Bill McCarthy between 1994 and 1996. From that unit have come studies on formative assessment[14] and competency based education[15] amongst others.

Perhaps the most innovative aspect of the program has been the development of a unique learning management system supported by information technology (IT), under the leadership of Simon Carlile and Stewart Barnet.[16] Providing a framework and supporting many aspects of the students' learning, the system is used to provide the triggers for the problem-based learning discussions (an image and a short statement). It allows the timed release of data on the patient including images and clinical information. Staff prepare resources relevant to each problem and the librarians have been invaluable in ensuring access to high quality materials on-line; they also help to develop the students' bibliographic searching and critical appraisal skills for evidence-based medicine. Students can access recommended websites, communicate with staff and each other. The function most used provides access for the students to online questions for formative self-testing; they use it at all hours of the day and night. In the future, a project is under way to transfer written examinations to online delivery. Evaluation of all aspects of the program, a key feature, is also carried out online. With the development of distant rural clinical schools, distant teachers and students have access to the same resources as their city-based colleagues. Further, the ongoing development of sophisticated teleconferencing facilities encourages interaction between disparate sites. The expertise in educational IT developed during the development of the program has enabled a very successful unit, the Centre for Innovation in Health Professional Education, to be established. It currently successfully bids for educational contracts from various sources, including some of the postgraduate medical colleges and government organisations.

Continuing a theme initiated by Bill McCarthy, evaluation of the program and of the students' learning experiences is vital to the continuing and future quality of the program. Newer methods make this process simpler and more effective, but the underlying philosophy has not changed. All aspects are open to review: tutorials, quality of materials and resources (including library and IT), effectiveness of tutors and teachers, perceived relevance and clinical experiences.

One measure of the impact of a program is evidence of its adoption by other institutions. In Sydney, the first two years of the medical program have been adopted and adapted by the Faculty of Dentistry. That faculty uses a similar method of selection from among graduates and shares almost all of the problems studied by the medical students in the first two years, but in separate tutorial groups. Both programs have been attractive to international students from a range of countries, including the US, Canada, and Singapore. Perhaps the most obvious evidence of success, however, comes from the fact that the Sydney medical program has been adopted and adapted for use internationally – in places as diverse as Johannesburg (South Africa), Derby (UK), Riyad (Saudi Arabia) and locally by the Australian National and Bond Universities. Other initiatives, including a partnership in Vietnam, are future possibilities.

Additional measures of success cannot be ignored. The program has attracted and graduated more Indigenous students in eight years than in the previous 104 years, although numbers are still too small. Faculty data indicate that a significant number of students in the previous program withdrew or failed, with only around 85% at best graduating within minimum time plus two years after enrolment. Currently, very few of the graduate entry students fail or discontinue. They are strongly positive in their responses to the national course experience questionnaire and graduate surveys, as well as to local evaluations. Students in the previous program were resoundingly negative in their responses to the same questionnaires. In terms of output measures, in a recent study of intern performance, Sydney graduates have performed above graduates from the other two NSW medical schools on six of eight items, and no differently on two.[17]

Australasian and New Zealand Association for Medical Education (ANZAME)

Australia is now generally recognised as a leader in medical education. One of the major drivers has been the Australasian and New Zealand Association for Medical Education (ANZAME). As noted earlier, Bill McCarthy initiated the idea in the early 1970s, with a number of colleagues largely from the Universities of Sydney and NSW, following the two successful workshops referred to earlier. It was established when World Health Organisation was looking to establish a Regional Training Centre for Asia and the Western Pacific in Sydney, although that centre was ultimately located at the University of NSW.

Bill was the foundation President of ANZAME and held that office for six years. Other early committee members included Gerry Milton and Fred Katz (the latter from UNSW). It all started from a discussion in 1972 in Canberra (at which I was also present). There was hot debate about what to call the planned organisation. The title was chosen to ensure that not only New Zealand, but also Western Pacific nations could be included. It formally started in 1973, again at a meeting in Canberra. From humble beginnings, initiated by small cast of enthusiasts, it has become a widely respected organisation which now attracts not only hundreds of local participants to its conferences, but also highly respected medical educators from around the world as speakers. The annual meetings, which have been held continuously since, are invariably interactive, of high quality, but uniquely friendly and lively. Students have always been welcomed and many make outstanding contributions.

One of the undoubted strengths of the organisation has been the inclusion of all the health professions. Overseas, educational organisations are often specific to medicine, or to nursing or the therapies. The broad umbrella of ANZAME provides real opportunities for interaction and broad inter-professional discussion. At least in part, that inclusiveness was probably due to both of the McCarthys – Bill as a medical and Mavis as a nursing educator. Both served on Council and together, for many years, they edited and produced the ANZAME Bulletins, which provide an interesting record of the growth and development of thinking about medical, nursing, health science, medical science and even veterinary education.

The formats of the conferences provide opportunities for real interaction and discussion. Examples of issues that arose in the 1980s included learning for understanding, early patient contact, continuous curriculum development, as well as a more specific inclusion of social and preventive medicine. Educational expertise was encouraged for all teachers.

Ken Cox from University of NSW provided a comment from the early days of ANZAME:

"I think my most powerful memory of that time was not any specific incident, but of Bill's tenacity in the face of overt and covert opposition and the blocking of change. Without Bill, educational development in medicine would have been very much later, and slower. The activities he nourished gave education a legitimacy in daily practice, instead of the insincere lip service of the time."

Other educational aspects

In their teaching, Bill and his colleagues have drawn attention to the need to communicate effectively and empathically and to explain clearly the nature of the illness or disability. Indeed, they have studied a number of issues in effective communication in their clinical work[18,19]. Bill and Mavis also wrote a paper for Nursing Times with the intriguing title of "Egotistical specialists and nursing students", but it has proved difficult to locate. The Melanoma Unit has been a striking example too, of educating the broader public about sun exposure and sunscreens. Walking past primary school playgrounds in different parts of Sydney, it is very easy to see that the "no hat, no play" message is effective.

Conclusion

Medical education at the University of Sydney has come a very long distance, from a traditional, discipline-based, passive and didactic curriculum to problem-based, interactive and integrated learning. The new programs are based on increasing evidence of effective educational practice: active and interactive learning; early clinical contact; and explicit training in skills, critical appraisal, effective communication, all supported by new assessment strategies. Medical education is now taken seriously by all Australian medical schools, although not necessarily with the level of support now provided in Sydney. Bill McCarthy has made a significant educational contribution to that development. He has also been influential within Australia and our region more generally through ANZAME.

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The integrated, multidisciplinary clinic: a new model for the ongoing management of women at high genetic risk for breast and ovarian cancer

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Abstract

An important minority of Australian women have a strong hereditary predisposition for the development of breast and/or ovarian cancer. Evidence-based cancer risk reduction strategies for this group are complex and need to be tailored to individuals and refined as new evidence emerges. In Australia, risk management services for these women are largely unidisciplinary. Here we describe the development, feasibility and cancer and screening outcomes for the first two years of an Australian multidisciplinary Risk Management Clinic (RMC). Data on screening test results and risk-reducing surgery were collected prospectively using standardised forms. Data on clinical and genetic characteristics were collected by medical record review. A total of 98.8 years of follow-up were available on the 92 clients. The average age of clients was 36 years and 20 (22%) carried a documented mutation in BRCA1 or BRCA2. One interval breast cancer had been diagnosed and screening investigations resulted in three investigational operative gynaecological procedures for non-malignant disease. Forty-three (47%) clients were participating in at least one research project. It is feasible in the Australian setting to run a multidisciplinary risk management clinic, with integrated clinical research programs, within the setting of a Family Cancer Centre.

In Australia, approximately one in 12 women will develop breast cancer and one in 100 will develop ovarian cancer by the age of 75.[1] For an important minority of Australian women, the risk is much higher because they have a strong family history of breast and/or ovarian cancer.[2] Two important genes have been identified that are associated with an increased risk for breast and ovarian cancer, namely BRCA1 and BRCA2.[3] A woman who has inherited a mutation in BRCA1 or BRCA2 has a 60% to 80% risk of developing breast cancer[4,5] and a 15% to 66% risk of ovarian cancer by age 75 years.[6,7] There is also growing evidence to suggest that individuals with a BRCA1 or BRCA2 mutation have an increased risk for other cancers.[7,8] Other much rarer gene mutations known to cause hereditary breast cancer are p53 (Li-Fraumeni Syndrome) and PTEN (Cowden's Syndrome).

Family Cancer Centres were established to provide genetic counselling and testing to individuals with a strong family history of cancer. These centres operate in most capital cities, many also providing an outreach service to rural centres. (www.nbcc.org.au/pages/info/risk/genserv.htm) These clinics have traditionally focused on assessment of risk rather than ongoing management of cancer risk. Risk assessment involves several steps including: reviewing family history (attempts are made to confirm all reported cancers), estimation of the client's risk for cancer development and genetic counselling and testing (if appropriate). For those ultimately determined to be at high risk, a discussion of risk management strategies is usually encompassed in the consultation. This includes both surveillance and prevention strategies (Tables 1 and 2).[9-16] National guidelines exist for the management of high-risk women (Table 2)[16] however, because this is a rapidly moving field, best practice may alter several times before updated guidelines are published.

After initial recommendations are made, ongoing multidisciplinary risk management is not generally undertaken as part of Family Cancer Centre activities, rather individuals are required to make their own arrangements for cancer surveillance, usually through individual private specialists. Consumers have identified this as problematic for a number of reasons. It can be difficult to identify breast and gynaecological specialists with particular expertise in the field of genetics and who are likely to be motivated to keep up with the large and emerging literature in this highly specialised area. Having to attend multiple different specialists and diagnostic facilities on different days and in different locations is inconvenient and results in a focus on ill health rather than wellness, which is inappropriate for women who are at risk but in fact have no personal history of cancer. There is a perception that a non-multidisciplinary, decentralised arrangement for cancer risk management may also result in a suboptimal level of coordination of care between the specialties and limited opportunities to participate in relevant clinical research. In Europe and North America the need for centralised multidisciplinary care of BRCA1 and BRCA2 mutation carriers and other women at very high genetic risk has been recognised and has resulted in recommendations for, and the development of, such clinics.[17]

Here we describe the initiation, feasibility and outcomes from the first two years of a centralised multidisciplinary Breast and Ovarian Cancer Risk Management Clinic (RMC), initiated at the Peter MacCallum Cancer Centre in September 2001 for women at very high risk for breast and/or ovarian cancer. To our knowledge this is currently the first clinic of its type in Australia.

Table 1: Breast and ovarian cancer risk reduction strategies for BRCA1 and BRCA2 mutation carriers

INTERVENTION OR STRATEGY	EFFECT ON BREAST CANCER RISK	EFFECT ON OVARIAN CANCER RISK
Risk-reducing salpingo-oophorectomy	53% reduction[9,10]	96% reduction[9,10]
Risk-reducing Mastectomy	90% reduction[11]	-
Oral Contraceptive Pill	20% increase*[12]	0-50% reduction[13,14]
Tubal Sterilisation	-	63%* reduction[15]

*Effect only seen in BRCA1 mutation carriers

Table 2: Surveillance guidelines for women at high risk of breast and/or ovarian cancer

BREAST CANCER	OVARIAN CANCER
• Maintain breast awareness. • Attend for 6-12 monthly clinical breast examination. • Report to GP promptly with any breast changes. • Attend for annual mammographic screening (and possibly ultrasound) commencing at age 40, and consider starting five years earlier than the youngest breast cancer case in the family, whichever is earlier.	• Discuss with woman that there are no data which conclusively demonstrate that surveillance has a favorable impact on either stage at diagnosis or the mortality of ovarian cancer in women at risk. • Unnecessary intervention can sometimes result after a false positive test and that interval cancers can develop between tests. • Attend for annual transvaginal ultrasonography (TVUS), preferably with colour flow Doppler, commencing at age 25-30 years, or at least five years younger than the age of diagnosis of the youngest ovarian cancer case in the family, whichever is earlier. • Annual CA125 measurement may be appropriate as an additional screening test after menopause (timed with TVUS).

From : Familial aspects of cancer: a guide to clinical practice, NHMRC, 1999[6]

Methods

Risk management clinic

With the aim of providing a centralised, multi-disciplinary, peer-reviewed specialist service for the ongoing management of women at high risk of breast and/ or ovarian cancer, the Familial Cancer Centre at the Peter MacCallum Cancer Centre, initiated a RMC in September 2001. An additional aim of the clinic was to enable such women access to clinical research programs. Breast surgeons, gynaecologic oncologists, medical oncologists with expertise in clinical cancer genetics and a clinical nurse specialist attend each monthly clinic. Dietetic, social work and psychology services are available on call. All women attending the clinic have no personal history of breast or ovarian cancer, but must have at least an estimated 30% risk for breast cancer to age 75 years. The 1999 NHMRC surveillance guidelines (Table 2) are used as a guide to determine the surveillance strategies to be used for each individual.

Women who require surveillance investigations, such as mammograms, transvaginal ultrasounds or CA125 testing, have these carried out on the morning of their visit to the RMC. During a multidisciplinary pre-clinic meeting all test results are reviewed and each individual is discussed with respect to any new information from the literature that might alter their personal risk management plan and any new research protocols for which they may be eligible.

Women are seen by the appropriate specialists in the afternoon clinic. Most women see the breast surgeon at every visit for a clinical breast examination, who also reviews their mammogram result (if done). Women who are undergoing gynaecological surveillance or who wish to discuss risk-reducing salpingo-oophorectomy or use of hormonal contraceptive or hormone replacement therapy also see the gynaecologic oncologist. When there is new information from the literature that might impact on a woman's personal risk and/or management plan, she is seen by the medical oncologist.

Long hand progress notes are written in the clinic, but there is also systematic recording by clinicians of key pieces of information on specially designed data forms, with a plan to ultimately enter those data into a prospective database. The clinical nurse specialist is essential to the functioning of the clinic. She coordinates appointments for surveillance investigations and the specialist consultations. In addition, she carries a pager and is the first point of contact for women who have concerns about symptoms that might occur between clinic visits. She assesses the symptomatology over the phone and contacts the most appropriate specialist to set up an urgent review appointment.

Data collection

Data on frequency and results of screening tests, such as breast examination, mammograms, CA125 tests and transvaginal ultrasound, were documented in each woman's medical record using the standardised forms which constitute the bulk of each woman's history (and are supplemented where necessary by hand-written notes). A copy of the pathology reports and surgical notes were obtained from the respective surgeon's records and filed with the patient's record. These data, along with relevant clinical and genetic data, were extracted from the records.

Statistical analysis

Descriptive statistics were used including the calculation of median and mean scores.

Results

Characteristics of attendees

To October 2003 there were 92 women, with no personal history of cancer, who had attended the RMC. All women had had at least one risk assessment consultation prior to attending the RMC. The median number of RMC visits was two (range one to four), representing a total of 98.8 client years of follow-up for the 92 women. The mean age of attendees at their first visit was 36 years (range 19 to 65 years). All women have at least an estimated 30% life-time risk for the development of breast cancer and 58 also have a substantially increased risk for ovarian cancer. Sixty-nine (75%) of the women live within the Melbourne metropolitan region, the remaining 23 (25%) travel to the clinic from rural centres. Three women have ceased attending the clinic; one because she moved interstate, one has had a subsequent negative predictive mutation test and is now considered at average cancer risk and one woman from a rural centre has subsequently developed breast cancer and is pursuing follow up with her local specialists.

Prior to their first appointment in the RMC, five patients had undergone risk-reducing salpingo-oophorectomy. One of these women has a known BRCA2 mutation, while for the others genetic testing is not currently possible. An additional woman who had not undergone genetic testing had previously had a unilateral salpingo-oophorectomy for investigation of cystic changes. No woman had undergone a risk-reducing mastectomy or tubal sterilisation for risk-reducing purposes prior to her first RMC attendance, although two women had previously had tubal sterilisation for contraceptive reasons.

Genetic testing

Twenty women of the 92 attendees (22%) are known to carry a genetic mutation, six in BRCA1 and 14 in BRCA2. One additional Jewish woman has had testing and was found to be negative for mutations associated with Ashkenazi Jewish families. Three attendees are yet to decide whether they wish to undergo predictive testing for family specific mutations in either BRCA1 or BRCA2. An additional patient is also yet to decide about testing for a p53 mutation, which has been found in an affected member of her family. There are 67 (73%) high-risk women who attend the clinic who have not been able to undergo genetic testing for BRCA1 or BRCA2. For 40 (43%) of these, another cancer-affected relative in the family has been tested but no mutation was found. This does not necessarily mean there is no underlying gene mutation in the family. It may mean that a mutation in BRCA1 or BRCA2 was missed (because testing is not 100% sensitive) or that there is an underlying mutation in another gene for which testing is not available, so in such cases the woman is still considered high risk. Eleven (12%) women have not been able to undergo testing because there is no living cancer-affected family member available for testing. In general, initial genetic testing in a family is commenced with a person who has had cancer, to maximise the chance of finding a genetic mutation. A person who has no history of cancer may be unaffected because they have not inherited a gene mutation that may have been found had an affected family member been tested. For five (5%) women, testing is not yet available because the cancer-affected individuals in their family have declined or are still thinking about mutation testing. For the remaining eleven women for whom a genetic test has not yet been possible, testing has been carried out in their cancer-affected relatives, but results are currently pending.

Clinical events

Cancer surveillance

At all visits either the breast surgeon or the medical oncologist has performed a clinical breast examination. Sixty-four women have undergone either a baseline mammogram or are having regular mammographic screening. Three of the 94 mammograms carried out to date have been reported as abnormal requiring further investigation. Two women had an additional ultrasound that confirmed that the noted abnormalities were benign cysts. In one woman the initial mammogram showed two small nodules, thought to be benign, this was repeated at six months with no interval changes noted. An additional five women have significantly increased overall breast density for their age, therefore reducing the sensitivity of mammography. Ultrasounds have since been added to their surveillance regimen.

Currently 31 women are undergoing regular screening for ovarian cancer. Four of 59 transvaginal scans have been reported as abnormal. Two of these showed increased endometrial thickening in postmenopausal women, both of whom underwent subsequent investigative hysteroscopy and dilatation and curettage procedures, with no malignancy detected. One of the abnormal scans was in a premenopausal woman who was found to have an ovarian cystic mass with septations and who subsequently underwent an investigative laparoscopy with unilateral salpingo-oophorectomy (physiological follicles were diagnosed at surgery). The other abnormal scan was in a perimenopausal woman. It showed a cystic mass, probably arising from the ovary, with a single septation. This had resolved at an arranged repeat scan. In one perimenopausal and one post-menopausal woman, at least one ovary was not identified on ultrasound using either a trans-vaginal or trans-abdominal approach. None of the 60 serum CA 125 levels that have been assessed have been reported as abnormal, including those women who have had abnormalities noted on their transvaginal ultrasound.

Risk reducing surgery

Since their first visit to the RMC, four of the 31 women (13%) at increased risk for ovarian cancer, for whom risk reducing salpingo-oophorectomy has been recommended as an option, have undergone bilateral risk reducing salpingo-oophorectomy. One of these has a mutation in BRCA1, two have a BRCA2 mutation and in one genetic testing has not been possible, but she is considered to be at very high risk for ovarian cancer because of her family history. No occult cancers were found at surgery, however one pathologist reported surface papillary changes in both ovaries for the woman without a BRCA mutation. No woman has undergone a bilateral risk reducing mastectomy.

New cancers

One 31-year-old woman has had an interval breast cancer diagnosed. Her surveillance recommendations had been for a clinical breast exam every six months and increased breast awareness. Mammography was planned to commence from the age of 35 years. The patient detected a small lump in her breast five months after her last clinic visit, at which time the clinical breast examination had been normal. The pathology after initial breast conservation surgery revealed an 11mm, axillary node negative, grade 2 tumour which was oestrogen receptor positive, progesterone receptor negative and strongly overexpressed HER2/ neu on immunohistochemistry. She declined the recommended adjuvant systemic therapy and has subsequently been diagnosed with metastatic disease. Mutation testing had not previously been possible for this patient (because there was no living cancer affected individual in the family to test). The patient elected to have genetic testing at the time of her diagnosis but no mutation was identified in either BRCA1 or BRCA2.

New information conveyed

Since the commencement of the clinic in September 2001, new data on genetic risk modifiers have been published.[9,10,12] These data and the implications they potentially have on women attending the clinic were discussed in detail at pre-clinic meetings. The clinicians have been able to relay the information to appropriate women and have assisted them, where necessary, in adjusting their ongoing personal risk management plans.

Participation in research

Since the clinic's inception three major research projects have been open for recruitment and participation offered to eligible women; a study comparing two methods of information to assist decision making about risk-reducing salpingo-oophorectomy, a cancer family cohort study ("KConFab") and a study of breast ductal lavage as a potential new risk refinement and breast cancer screening method. Forty three women are currently enrolled in at least one of these research studies. Future studies anticipated to soon also be available for women attending the RMC are the international chemoprevention study, IBIS II and a US Gynaecologic Oncology Group observational study of ovarian surveillance versus risk reducing salpingo-oophorectomy.

Discussion

The monthly RMC, a surveillance and management clinic for women at very high risk for breast and/or ovarian cancer,

commenced operation in September 2001 and has been running for two years. The multidisciplinary "one-stop shop" style of the clinic enables evidence-based, peer-reviewed, integrated specialist management of individuals and the opportunity to participate in research. Women attending the clinic anecdotally report high levels of satisfaction with this form of health care provision, the drop out rate is low and there is currently accrual of approximately three to four new women at each clinic. To date there has been one interval breast cancer and three surgical gynaecological interventions for abnormal ovarian screening results. Risk reducing mastectomy has not been used as a risk management strategy by any of these women to date, but risk-reducing salpingo-oophorectomy has been used by 13% of those to whom it has been recommended as an option.

Currently little is known about what cancer surveillance and management strategies are being undertaken by Australian women who have attended a Family Cancer Centre for a risk assessment consultation. Published data suggest reasonably high utilisation of breast screening but poor utilisation of ovarian screening, prior to the first visit to a Family Cancer Centre,[18,19] however there are no published studies regarding the subsequent screening habits of these women. We, in conjunction with many other Australian Family Cancer Centres, have recently conducted a large multicentre study addressing this question, which has shown that a large proportion of high-risk women do not follow screening guidelines recommended to them, often for logistical reasons (unpublished data).

We have demonstrated the feasibility of a multidisciplinary RMC running within the setting of a Family Cancer Centre. As the focus of breast cancer genetics moves away from merely categorising the risk level of women to actively attempting to reduce their risk of morbidity and mortality from breast and ovarian cancer, we anticipate that other Australian Family Cancer Centres may initiate similar clinical services.

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Cancer reporting award winners

Congratulations to Cathy O'Leary from The West Australian and Sheryl Taylor from National Nine News, winners of the 2005 Australian Awarding Cancer Enlightenment (ACE) Reporter Awards in the print and broadcast categories.

The ACE Reporter Award is open to consumer journalists from around Australia, rewarding those who provide the general public and cancer patients with independent, accurate, clear and timely information on advances in cancer prevention, treatment and care.

Marnie McKinnie (The West Australian), Jill Margo (Australian Financial Review) and Jane Worthington (The Australian/ New Idea) were recognised as finalists for their outstanding reporting efforts in print, along with Sophie Scott from ABC Television in the broadcast category.

Finalists in the print category will also be nominated for the European School of Oncology's international ACE Reporter Award.

The ACE Reporter Award is judged by a panel of representatives from cancer organisations in Australia including The Cancer Council Australia, the Brain Foundation, National Breast Cancer Centre, Prostate Cancer Foundation, Australian Lung Foundation, National Breast Cancer Foundation, European School of Oncology, Cancer Voices, Asbestos Disease Society of Australia (Inc), Leukaemia Foundation, Asbestos Diseases Foundation NSW and the Australian Medical Writers Association. The award is sponsored by Eli Lilly.

Cancer Forum is pleased to reproduce several of Cathy O'Leary's winning articles, The men who are dying of embarrassment; Tomatoes, tea hold hope; and Doubt over value of cancer test with the kind permission of The West Australian. These articles were published in The West Australian on 11 November 2003, pages 10 and 11.

The men who are dying of embarassment

Men need more facts to make informed decision

By Cathy O'Leary
Medical Editor

PROSTATE cancer does not behave in the way we have come to expect of cancers.

All the usual warnings about the need to diagnose and treat early do not necessarily hold true for this baffling and controversial men's disease.

It is the most common cancer in Australian men yet few die of it. Many more will die with it because although the cancer may have been present for many years, it will not have done any real harm.

For many men, it is heart disease or another type of cancer which ultimately claims their life.

But prostate cancer is not always so benign and invisible.

In some men, the disease strikes aggressively and needs to be stopped in its tracks, particularly if they are young by prostate cancer standards.

In WA, 200 men die each year because they have developed a fast-moving disease.

The problem is that experts cannot divide the two groups those who will have a very slow-growing tumour which is unlikely to harm their health for many years and those who face a quick-moving cancer which could cause premature death.

Research has not been able to help doctors work out the likely path of the tumour or whether screening all middle-aged men will extend lives.

One school of thought is that a slow growing disease in elderly men may be best left untreated while late middle aged men may benefit from treating the cancer, despite possible side effects such as impotence. But that raises the question of what age should be the unofficial cut-off point for treatment 75, 80, 85 or even later?

While the value of screening and aggressive treatment continues to be debated, researchers also are turning their interest to how to prevent the cancer in the first place.

While some lifestyle factors, such as diet, slowly are providing a few clues about what may help reduce the risk of prostate cancer, there still are few definitive answers and only a handful of maybes. What men end up with is a few snippets of information which ultimately they have to digest and weigh up.

Some men will opt for early testing, whether or not they have symptoms, and will want any cancer, no matter how small or innocuous, removed.

Others, particularly older men, may adopt the "don't fix if it's not broken" philosophy and be happy to live with something which is not bothering them and probably will not shorten their lives.

Men need the right information, and then some choice.

WHAT IS THE PROSTATE?

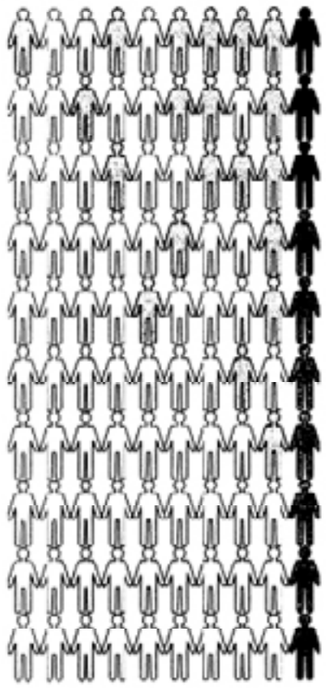
The prostate is a gland found only in males. About the size of a walnut, it is situated where the bladder joins the urethra, the tube through which urine is passed from the bladder to the end of the penis.

WHAT DOES IT DO?

The prostate is one of the glands of reproduction. It produces some of the nutrients on which sperm live once they leave the body. Secretions from the prostate make up a large part of semen.

WHAT CAN GO WRONG?

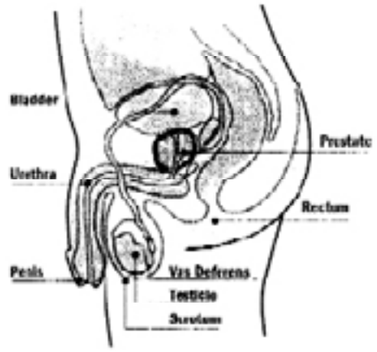
The most common problem associated with the prostate is the enlargement of the gland. This often occurs when men get older. If the prostate becomes so large that it presses on the urethra, men can have problems passing urine. This is usually caused by what is known as benign prostatic hyperplasia. Benign means non cancerous and hyperplasia means that it gets bigger. But sometimes the growth which obstructs the urethra can be malignant or cancerous and this is referred to as prostate cancer.



WHO WILL GET PROSTATE CANCER?

From a sample of 100 men:

- *30 will have some form of prostate cancer*
- *10 will get prostate cancer which will eventually lead to disability or death*
- *3 will die from prostate cancer*



Tomatoes, tea hold hope

■ **By Cathy O'Leary**
Medical Editor

DIETARY factors such as tomatoes and green tea as well as physical activity hold promise in preventing prostate cancer, according to researchers.

Men who eat at least one serving of tomato-based food a day are known to have a lower risk of prostate cancer because tomatoes contain an antioxidant called lycopene which can prevent cells from becoming cancerous.

Tomato-based foods include spaghetti sauce, salsa and pizza sauce, and one serving is the equivalent of half a cup of sauce.

A recent study at Curtin University also showed that drinking green tea significantly reduced the rate of prostate cancer in Chinese men. The benefits were likely to be similar for men who drank black tea.

Associate Professor Lin Fritschi, from the University of WA's school of population health, says research is in its early days and the jury is still out on prevention.

She is completing a three-year Healthway-funded study which has looked at factors such as diet, occupation, family history, smoking and physical activity.

So far the evidence suggests that while family history can double a man's risk of getting the disease, being bald or having a vasectomy are unlikely to affect it.

"There are still a lot of unknowns when it comes to preventing prostate cancer but we're starting to get promising signs, such as the value of tomatoes in the diet and physical activity," she said.

Terry Slevin, the WA Cancer Foundation's director of education and research, said it was difficult to advise men on how to reduce their risk.

Definitive advice could be given to prevent other cancers, such as advising people to give up smoking to reduce their risk of lung cancer or to use sunscreen to avoid skin cancer.

But although there were encouraging signs of possible factors to prevent prostate cancer they were not conclusive.

"We're still not at the stage where we can provide advice with a reasonable level of confidence so it would be wrong to push one line," he said.

Mr Slevin said reducing the amount of foods with animal fats could also lower the risk of prostate cancer.

► For more information on prostate cancer, including a free brochure, call the Cancer Helpline on 13 11 20.

Doubt over value of cancer test

■ **By Cathy O'Leary**
Medical Editor

THERE is no test good enough to warrant testing all men for prostate cancer, according to WA's main cancer groups.

WA Cancer Foundation director of education and research Terry Slevin said this was a controversial and hotly debated issue and urologists were divided over the value of early testing.

Some believed that all men should be screened from middle-age while others felt this could compel men to seek treatment which may not extend their life.

Debate centres on the use of prostate-specific antigen (PSA), a blood test that measures the amount of PSA in the blood. An elevated level can be due to presence of an abnormality, but not necessarily cancer. It is used with or without a digital rectal examination (DRE) which involves the doctor inserting a gloved finger into the rectum to feel for changes to the prostate gland.

Mr Slevin said neither of the tests was conclusive and further tests were often necessary in order to diagnose cancer. "We are not against men having the PSA but this test simply isn't good enough to be used to screen all men," he said.

"While we can't agree on the best way to detect prostate cancer and there are potentially harmful effects, men shouldn't be accepting a second-class test.

"We're not convinced we should be promoting a test to all men when we know of men who go on to regret their decision to have active treatment on the basis of the results of that test."

But Mr Slevin said some doctors strongly believed in the value of the PSA test and most men who had undergone treatment for prostate cancer supported population screening.

What compounded the debate about testing was that doctors found it difficult at the time of testing to determine which cancers could go on to be aggressive and which ones would be slow-growing. Yet their patients had to make a decision about how they wanted to be treated.

Associate Professor Lin Fritschi, from the University of WA school of population health, has recently reviewed the latest screening guidelines and says prostate cancer is more difficult to offer advice on than other forms of cancer. She said the tests for prostate cancer were not as good and most expert groups such as the Cancer Council of Australia and the Royal Australian College of General Practitioners did not support screening.

But the Urological Society of Australasia says men aged 50-70 with at least 10 years of life expectancy should be offered screening by annual PSA and DRE testing. The American Cancer Society and American Urological Association have similar views.

"Many experts do not think we currently have a good test with good outcomes, which is a hard message to get across when we've spent many years trying to tell people about the important of early diagnosis," she said.

"But we simply do not understand enough about prostate cancer, particularly about why some will sit there and do nothing while others will go wild, but that's a tricky message to get across.

"A lot of men like the idea of the PSA because they just want a simple, clean blood test but really it should be done in conjunction with a DRE and many men don't want that part of it."

Dr Harry Sheiner, chairman of the WA Clinical Oncology Group, said no one would argue against the view that the earlier diagnosis was made the better — provided the abnormality would be treated. "At the end of the day to justify screening men without symptoms you have to be able to show you can improve their outcome and urologists are divided over this," he said.

"Some say they are happy that the data suggests there has been a fall in the death rates but when you tease it out you see that there's been a reduction across the board, even in countries where they don't have PSA testing. It is fair to say any men under the age of 65 who have the test are highly likely to act on it but it is hard to justify offering PSA screening to men over the age of 80."

Mr Slevin argues that those who undergo testing should do so knowing the pros and cons.

Research published in 1999 showed that about 40 per cent of WA men tested had no discussion with their GP about the value of testing for the disease. "While there is uncertainty about the benefits of screening for prostate cancer, it is important men are informed about that uncertainty before going ahead with the test," he said.

Medical dilemma: The WA Cancer Foundation's Terry Slevin, who says most men who have treatment for prostate cancer support population screening.

REPORTS

Australian Behavioural Research in Cancer

New Results

n Cancer Prevention Research Centre (CPRC), Qld

PLACE Project

Physical activity provides many health benefits, including reduced risk of colon and breast cancer. There is the need for and improved understanding of the modifiable determinants of physical activity, so that population health interventions can target the relevant factors to increase participation. Common suburban designs with low mixed use (few destinations to which one can walk), lower population density and poor connectedness (few intersections, more cul-de-sacs), may be fundamental limitations on the walking habits of adults. The CPRC team has just completed the second phase of the NHMRC-funded PLACE project (Physical Activity and Localities in Community Environments), collecting prospective data from around 2,200 of the 2,650 participants who took part in our initial survey. Participants were recruited from communities, comprising 156 census collection districts selected to represent low and high walkable, and high and low socio-economic neighbourhoods. Geographic Information System data and methods, as well as 2001 census data, were used to classify and select communities. Preliminary analyses have examined relationships between neighbourhood physical attributes and residents' body mass index (used as a marker for overweight and obesity). These show that residents in high walk, high SES neighbourhoods had significantly lower BMI, after controlling for socio-demographic variables. Age, sex, income and household size were found to be significant predictors of BMI in the expected directions. Analyses aimed at identifying links between walking behaviours and the physical and social environment continue. The PLACE study is one of two studies (in Australia and the USA), on which CPRC members are developing the International Physical Activity and the Environment Network: http://www.ipenproject.org/. PLACE is a collaboration with the Key Centre for Social Applications of Geographical Information Systems (GISCA), at the University of Adelaide, and is a key part of CPRC's participation in the new ARC Research Network on Spatially Integrated Social Sciences: http://www.uq.edu.au/cr-surf/arcsiss/.

n Centre for Behavioural Research in Cancer (CBRC), Vic

Televised state-sponsored anti-tobacco advertising and youth smoking beliefs and behaviour in the United States, 1999-2000

As part of her US National Cancer Institute grant, Melanie Wakefield, along with colleagues at the University of Illinois at Chicago, the University of Michigan and the National Bureau of Economic Research, has obtained commercial ratings data on average audience exposure to anti-tobacco advertising that appeared on network and cable television across the largest 75 media markets in the United States for 1999-2000. These data were combined with nationally representative US survey data from school-based samples of youth. Multivariate regression models were used to analyse associations between mean exposure to state anti-tobacco advertising and youth smoking-related beliefs and behaviours, controlling for individual and environmental factors usually associated with youth smoking, and other televised tobacco-related advertising. Mean exposure to at least one state-sponsored anti-tobacco advertisement in the past four months was associated with lower perceived rates of friends' smoking (OR=0.72, 95% Confidence Interval [CI] = 0.58-0.88), greater perceived harm of smoking (OR=1.25, 95% CI = 1.11-1.42), stronger intentions not to smoke in the future (OR=1.43, 95% CI = 1.17-1.74), and lower odds of being a smoker (OR=0.74, 95% CI =0.63-0.88). This study is the first to explore the potential impact of state-sponsored anti-tobacco media campaigns while controlling for other tobacco-related advertising and other tobacco control policies. State-sponsored anti-tobacco advertising is associated with desired outcomes of greater anti-tobacco sentiment and reduced smoking among youth. This study is now in press in the Archives of Adolescent and Paediatric Medicine.

The role of smoking restrictions in social venues in preventing smoking and reducing relapse: a qualitative study

Melanie Wakefield and Melissa Cameron conducted a study to explore the utility of smoking in nightclubs and pubs and investigated the perceptions of smokers as to the likely effect on their smoking behaviour of smoke-free policies in social venues. A qualitative approach using focus group methodology was used to investigate the role of smoking in bars/clubs, experiences and perceptions of smoking in social settings, opinions and perceptions about smoke-free policies and experiences of quitting. Four focus groups were conducted with a total of 22 younger social smokers (18-24 years), who attended nightclubs or bars at least monthly. This method also involved an initial telephone interview, attending a club venue and participating in follow-up focus groups discussions. Another four focus groups involved 31 older regular smokers (25-45 years), who attended pubs or bars at least monthly, were contemplating quitting smoking in the next 6 months and had made one serious quit attempt. For the young social smoker, smoking in a social setting contributed to a positive self-image, an opportunity to be part of the 'cool' group, involved a degree of rebellion and facilitated opportunities for social interaction outside their primary groups. Social smokers were quite positive about the potential of smoke free venues and felt they would ultimately smoke less. The older regular smokers felt that the pub was the last bastion, providing them with a relaxed indoor environment in which they could smoke with abandon. The pub or bar environment continuously provided triggers for smoking, and smoking was used as a tool in social interaction. Regular smokers also felt that they monitored their smoking less in these venues. Regular smokers were less accepting of the notion of smoking bans, although they generally perceived that such bans would have a range of benefits, such as reducing their own smoking and that they would adapt to them. In concluding, these smokers enjoyed smoking in social venues. Although there were some concerns about losing their 'right to smoke', most felt they would adapt and that such restrictions would serve to reduce the amount they smoked. A journal article has been submitted for consideration.

Developing and evaluating PapScreen Victoria's 2004 advertisement: Don't Just Sit There

In 2003 data from the Victorian Cervical Cytology Register identified that two-yearly cervical screening rates in Victoria had declined from 67% (1999/2000) to 63.9% (2002/3). Improvements in the data collection methods helped account for some of this, but it was believed that part of the decrease was genuine. Data indicated that 22% of women screened in February 2000 had not returned for another test within three years, suggesting that there was a need to encourage women who had had a least one Pap test to become regular screeners. Consequently, PapScreen Victoria decided to develop a mass media campaign focussed on encouraging under-screened women to attend for a test, with the secondary aim of maintaining appropriate screening practices among the regular screeners. Women over the age of 45 were the key target group, as they are most likely to die from cervical cancer. Robyn Mullins in CBRC coordinated three stages of qualitative research to develop the television advertisement. Initial interviews with 32 under-screened women established that most were aware of the appropriate screening interval but that they did not rate having a Pap test as a high health priority and disliked the process. These interviews were used to develop the agency brief for the concepts. Two rounds of focus groups (nine in all) were conducted until an appropriate advertisement concept was developed. The advertisement was screened in July/August 2004, and can be viewed on www.papscreen.org. A telephone survey of 1,000 women aged 25-65 was conducted to measure women's awareness of the advertisement and their intention to act as a result of it. The advertisement was recalled by 61.5% of women surveyed. Intention to have a Pap test was highest among women whose test was overdue by up to a year (49.1%) or more than a year (43.1%), and very low (3.2%) among those who had had a test in the past year. VCCR data indicated that there was an increase of 18.3% in the number of tests conducted daily during the campaign and that the increase was concentrated among women who needed to have a test. A journal article is currently being prepared for publication.

n Centre for Behavioural Research in Cancer Control (CBRCC), WA

Understanding of the UV Index

The ultraviolet (UV) index has been regularly reported in Australia for a decade but utilisation remains extremely low (~5%). Blunden et al., (2004) suggest that Australians' understanding of the UV Index is 'good' and education surrounding the Index is no longer warranted. To test this position, Dr Owen Carter asked various questions related to the UV Index to 44 participants in six focus groups, followed by intercept interviews with 404 residents of Perth, aged 16-44 years. Results suggested that far from being 'good', understanding of the UV Index is extremely poor. This was exemplified by: exaggerated estimations of average UV Index values (11.8 in winter and 19.8 in summer – actual averages are 3 and 12 respectively); 48.3% (CI 43.4-53.2) of the sample believing that the UV Index is dependent upon temperature; participants nominating solar noon as the time when UV conditions peak at no better than chance; and 15.3% (CI 11.8-18.8) confusing the Index with a 'burn-time' measure. It therefore remains highly likely that utilisation of the UV Index remains low because understanding is poor. Future efforts to improve utilisation of the UV Index, particularly those looking at new display formats, should therefore include strategies to facilitate understanding of the measure. Results have been submitted for peer review in the Journal of Health Communication.

Childhood Television Viewing Behaviours 1961-2003

Sedentary behaviour leading to being overweight is a serious risk factor for many cancers. Subcutaneous skin-fold thickness and BMI measures suggest Australian children have been getting progressively fatter since the 1970s; a worrying trend as childhood obesity is one of the best predictors of adult obesity. An extremely common, but uncorroborated assumption is that this trend is in large part caused by 'increased' childhood sedentary behaviours dedicated to modern media, such as television viewing and computer use. Dr Owen Carter dusted off a 1962 investigation of the impact of the introduction of television to Perth children, and compared the results to 2003 ABS data on children's use of televisions and computers. The comparison suggested that today's grandparents spent just as much time watching television as children (2.3 hrs per day) as their grandchildren spend watching television and using computers today (2.4 hrs per day). Furthermore, the introduction of television to Perth in 1959 appears to have had minimal impact on sedentary behaviours as it largely replaced other sedentary behaviours children had previously been engaged in, such as listening to the radio, going to cinemas, and reading comic books. The results suggest that blaming TV and computers for our fat kids is a poor explanation, and perhaps we should be attending more to their energy-dense diets. Results are available in the April edition of the Australian and New Zealand Journal of Public Health.

Member of Parliament Tobacco Control Position Survey

At the beginning of the year, the Centre surveyed State Members of Parliament on their stance on tobacco control issues. Of the 103 State Members of Parliament, 44% were surveyed, 26% declined to participate and 30% were contacted but an appointment to conduct the interview could not be arranged prior to the announcing of the 2005 State election. There was strong support against sales to minors and stricter enforcement of such legislation, prohibiting all advertising and promotion of tobacco products, reducing the visibility of these products in retail outlets, and making various public places smokefree (except the international room at Burswood Casino). Overall, although there was a high level of support for many of these tobacco control issues, only 10 out of the 19 statements received more than 50% nominating 'strongly' in favour. There are clear opportunities for The Cancer Council Western Australia to increase the 'strength' of support for a number of these issues among State Members of Parliament.

Evaluation of the 'Make Smoking History' Campaign: Wave 9

In July 2004, The Cancer Council Western Australia launched the ninth wave of its Make Smoking History Campaign As in wave 8, wave 9 of the campaign targeted older smokers aged 45 to 64 years who smoke on a regular or occasional basis. The message promoted was that smokers may have many years ahead and continuing to smoke could lead to disability and diminished quality of life as a result of smoking-related illness, therefore, a positive commitment to a better quality of life in the future would be to quit smoking. The campaign featured a television advertisement and three press advertisements. Random digit dialling telephone surveys were conducted within the Perth metropolitan area of 201 current smokers or recent quitters aged 45-64 years. Overall, the older mmokers advertisement was far more salient for women than men, reflecting the relative media reach and frequency for the two groups. The advertisement appears to impact the 45-54 years age group more than the older age group on several measures. The overall results suggest

that smokers over 55 years are more difficult to impact with mass media campaigns than younger smokers. Nevertheless, this advertisement targeted at older smokers was perceived as more convincing and achieved greater personal relevance amongst this older age group than previous campaigns.

n Centre for Cancer Control Research (CCCR) and the Tobacco Control Research and Evaluation Program (TCRE), SA

Community perceptions of cancer risk

Community perceptions of the importance of various cancer-related risk factors was assessed via a series of questions in the 2004 South Australian Health Omnibus Survey, a face-to-face survey of 3,000 South Australians aged 15 years or older, conducted in October of that year. Cigarette smoking and having a family history of cancer were rated as the most important cancer risk factors among respondents. Greater emphasis was placed on factors such as pollution, pesticides in food and stress than on dietary factors, such as a lack of vegetables or fruit. Despite the growing evidence of cancer risk associated with a lack of exercise, being overweight and consuming alcohol, these factors were not considered very important by the South Australian community. The results suggest that the community perception of cancer risk is somewhat distorted. Continued effort is required to increase public awareness of the link between cancer and diet, alcohol consumption, physical activity and body weight.

Progress in tobacco control in South Australia, 2004

TCRE reported on the latest findings from the 2004 Health Omnibus Survey. Importantly, it was shown that in 2004, South Australia observed the lowest ever adult smoking rate. In regards to passive smoking, the majority of South Australians were supportive of smoking bans within children's playgrounds. Strong support was also recorded for smoking bans or restrictions for outdoor dining areas (alfresco). Additionally, almost all South Australians prefer some smoking restrictions at work.

Public awareness of smoke-free legislation and the smoke-free licensed venues campaign

Amendments to the Tobacco Products Regulation Act 1997 took effect in December 2004, and the Department of Health conducted a concurrent public education campaign. TCRE surveyed smokers and non-smokers to evaluate the campaign and a majority were aware of it. Importantly, support for the new laws (especially smoke-free workplaces) was sound and was higher among non-smokers.

Gay Men and Tobacco Project (Phase Two) impact evaluation report 2005

The final phase of this project was evaluated by TCRE recently. Key findings were: the campaign posters were positively appraised; specifically targeted cessation courses for gay men were supported and shown to have generated quitting behaviour; respondents highlighted the importance of staff working with gay men to model non-smoking behaviour; and a need to address staff smoking within workplaces such as Gay Men's Health.

n Centre for Health Research & Psycho-oncology (CHeRP), NSW

It's not all doom and gloom: well being of cancer survivors five years after diagnosis

It is estimated that about 267,000 Australians are currently living with cancer. Due to improving cancer survival rates, this population of cancer survivors is growing. Although there is considerable evidence describing the psychosocial effects of cancer and its treatment on recent survivors, little is known about the later physical, emotional and social effects of cancer or the issues faced by long-term survivors. During 2002-2003 we undertook a state-wide cross-sectional survey to identify the prevalence and predictors of cancer survivors' anxiety, depression, quality of life and perceived needs five to six years after diagnosis. A random sample of 1,008 cancer survivors was recruited from the NSW Central Cancer Registry. Of these, a total of 863 participants completed a 142 item self-administered scannable survey comprised of the Hospital Anxiety and Depression Scale, EORTC Quality of Life Questionnaire-Core 30, Supportive Care Needs Survey-short form 31, MOS Social Support Survey, Mini-Mental Adjustment to Cancer Scale, and standardised questions about patient demographic, disease and treatment characteristics. Information about participant primary cancer type, spread of disease at diagnosis, sex and age was obtained from cancer notification to the Cancer Registry. The prevalence of clinically significant levels of anxiety (9%) and depression (4%) for long term survivors was similar to that found in the general population. Survivors' quality of life on both symptom and functional scales was good; their global quality of life was not statistically or clinically different to general population normative values. Overall, survivors' levels of perceived needs was low; reported need for help was greatest in the areas of physical and daily living needs, sexuality needs and psychological needs. Multivariate analyses were conducted to identify the factors associated with 'poor' cancer survivorship. Cancer survivor characteristics associated with poor psychosocial outcomes included a history of psychiatric illness; younger age; being single, separated, divorced, widowed; not born in Australia; being an invalid pensioner; perceived low social support and maladaptive coping style. Disease and treatment characteristics associated with poor psychosocial outcomes included receiving treatment within the last two years; ever receiving hormone treatment or chemotherapy; not in remission and being diagnosed with prostate cancer. Although a sub-group of long-term cancer survivors experience adverse outcomes and are in need of assistance, generally, five years after a cancer diagnosis, the psychosocial well-being of cancer survivors is similar to that of the general population. We are currently undertaking longitudinal research following cancer survivors for five years from diagnosis to identify at what point in the cancer journey survivors' well-being returns to general population levels.

n The Viertel Centre for Research in Cancer Control (VCRCC), Qld

Pathways to diagnosis of melanoma

Survival of melanoma varies dramatically with the depth of invasion at diagnosis. Skin screening is a method that has the potential to achieve earlier diagnosis. However, there is currently no conclusive evidence as to whether skin screening actually leads to earlier diagnosis. One of the aims of this study, conducted with collaborators at the National Cancer Control Initiative and The Cancer Council Victoria, was to describe the diagnosis process for melanoma including who first notices the melanoma, and the skin screening history of those with thick and thin melanomas. 3,772 patients with melanoma (78% of those eligible) completed an interview. In accordance with our sampling scheme, about half (54.3%) of the sample was diagnosed with a thin melanoma (<0.75 mm). Percentages in the results have been weighted to reflect the actual thickness distribution of melanomas in the Queensland population. Almost half (44.0%) of the melanomas were detected by the patient themselves, with doctors detecting a quarter (25.3%) and partners a fifth (18.6%). Melanomas detected by doctors were more likely to be thin (<0.75mm) than those detected by the patient or other lay person. Melanomas detected during a deliberate skin examination were thinner than those detected incidentally. There are clear differences in the depth distribution of melanoma in terms of method of detection and who detects the lesions which are consistent with, but do not automatically lead to the conclusion that, promoting active methods of detection may be beneficial. Further results from this study will follow over the next 12 months.

Brain Tumour Supportive Care Needs Study

This study aims to identify the supportive care needs of Queensland brain tumour patients and their carers. Qualitative interviews and focus groups with 36 patients with a brain tumour or their carers have been undertaken, and all interviews and focus groups have been recorded, transcribed and analysed. Participants were recruited from among the adult members of the Queensland Cancer Fund's Brain Tumour Support Service, which comprised 302 patients, carers and family members in 2004. For the focus groups, 15 out of 56 randomly selected households within a one and a half hour drive of the study centres were contactable and agreed to participate (response rate 27%), resulting in 12 patients and 10 carers recruited for group participation. Three groups for patients and three groups for carers (mean length 80 minutes) were facilitated by one or two trained researchers or cancer nurses. Fourteen telephone interviews, 6 with patients and 8 with carers, were also completed (56% response rate) by a study-trained researcher and the mean length of the interviews was 20 minutes. The questions discussed during focus groups and interviews followed a predefined structure to establish supportive care needs at present and at each stage of the disease process (diagnosis, treatment, post-treatment and, where appropriate, bereavement). This allowed the collection of core common data across groups and interviews. Results revealed that patients and carers had a high need for support but were frequently unable to define exactly the type of services that could help them at any given time, often due to lack of awareness of available services. Participants suggested several strategies to overcome this problem: 1) the assignment of a dedicated member of the care team or case manager to each patient, who could provide information and emotional support; 2) proactive dissemination of information, education and psychosocial support to patients and carers; 3) access to objective assessment of neuropsychological functioning and dissemination about the impact of deficits among patients, carers, healthcare professionals, welfare agencies and employers; 4) for patients who cannot return to previous roles and activities, easy access to welfare payments, home care and home visiting services as well as respite care for their carers; and 5) where highly malignant tumours may reduce the patient's life-expectancy, services facilitating communication about treatment decisions, life prolonging procedures, death and dying and legal implications early in the treatment process. The focus group and interview data will inform the development of an instrument to measure the supportive care needs of patients with brain tumours and their carers. During the next phase of the research the survey's psychometric properties will be evaluated. It is the aim of this research to inform support services for patients with a brain tumour and their carers.

Research in the Pipeline

n CBRC

Framing dietary and physical activity messages to promote healthy body weight

Obesity increases people's risk of a range of chronic diseases, including certain cancers. Whilst it is widely recognised that healthy eating and regular physical activity are important in achieving and maintaining a healthy body weight, more information is needed about how to best frame health communications on these issues in order to persuade people to adopt healthier dietary and physical activity patterns. Although the promotion of healthy eating is crucial in the fight against obesity, greater public attention needs to be placed on the role energy balance plays in controlling body weight. Increased weight occurs when the amount of physical activity completed is insufficient to burn the kilojoules being consumed in the diet. As such, enjoying an active lifestyle and eating according to one's energy needs is a message that should also be highlighted. Given the high levels of sedentary behaviour in the Australian population, encouraging people to make small lifestyle changes that can be incorporated into their daily routines appears to be a sensible approach. Communicating concrete information about the energy expended by various sedentary and vigorous activities, and similarly, the energy content of various healthy and unhealthy foods has potential to raise awareness of the important links between diet and physical activity and energy balance, and provide examples of gradual dietary and lifestyle changes that can help people achieve energy balance. Helen Dixon and Maree Scully are investigating how adults respond to portion size and energy balance information, both separately and as a combined message. This research will help inform how best to proceed with promoting healthy body weight in the community. This 2X2 study design will explore whether focusing on: (a) only portion size information; (b) only energy balance information, or; (c) a combination of the two, enhances people's knowledge of dietary recommendations, the energy content of foods and energy burnt by activities, promotes more positive attitudes and intentions towards healthy eating and physical activity, and provokes short-term behaviour changes. This study is funded as part of an NHMRC Program grant for which Melanie Wakefield and David Hill are chief investigators.

Comparing GPS and accelerometer counts

Dr Ester Cerin (Cancer Prevention Research Centre, UQ), Anthony Barnett (Queensland Academy of Sport) and Dr David Jenkins (School of Human Movement Studies, UQ) are currently conducting a study whose aim is to improve the estimation of walking, the most common physical activity of adults. Accelerometers, which act as movement sensors, appear to be the best currently available means of estimating the intensity of free-living walking. Higher accelerometer counts are indicative of higher intensity levels (speed) of walking. There are individual differences in the relationship between accelerometer counts and walking speed, which can be mathematically described by regression equations. The determination of these equations requires the participants to walk at pre-determined, controlled walking speeds. To date, this had been done using treadmills. As it has been shown that the 'treadmill' method does not yield very accurate measures of free-living walking speed, this project investigates the novel use of a Global Positioning System monitor (GPS) to control speed in the field (that is, in a more natural, non-restrictive environment). This project will compare the validity and reliability of the GPS and 'treadmill' methods to estimate free-living walking speed and energy expenditure. The end result of the project will be a more accurate method for the measurement of free-living walking in physical activity studies.

n CBRCC

National Audit of Unpublished Quit Research 1997-2004

In a joint initiative of the National Quit Coordinators group, CBRCC has been appointed to conduct an audit of unpublished research on anti-smoking mass media campaigns and smoking in Australia from 1997 to 2004. The project aims to update knowledge of effective communications strategies on smoking cessation, assess whether there is a need to revise the communications model developed as an outcome of the National Tobacco Campaign review and identify possible themes, issues and approaches that might inform future campaigns (be they state or national collaborations).

Children and Energy-dense Food Advertising

Childhood obesity, which has been increasing since the 1970s, is an excellent predictor of adult obesity, which has been linked to a full range of cancers. Evidence suggests that the energy-dense food intake of Australian children has increased correspondingly. Previous literature suggests that the advertising of energy-dense foods is ubiquitous during children's television time-slots. Other literature suggests that children's desires are heightened for advertised products from an early age, but they do not have the faculties to appreciate the persuasive intent of such advertising until quite old, leaving them particularly vulnerable. Prof Rob Donovan, Dr Owen Carter and Geoffrey Jalleh, in partnership with Prof Mike Ewing from Monash University, are currently conducting an audit of energy-dense food advertising on children's television to identify potential breeches of advertising regulations and codes. In addition, 600 children aged 5-12 years from 10 primary schools are currently being tested for: the effect of energy-dense food advertising, embedded in 10 minutes of cartoons along with other advertisements, on their food preferences; and their verbal and non-verbal ability to articulate appreciation of the persuasive intent of energy-dense advertising.

n CHeRP

Doctors' perceptions of specialist palliative care and the referral of advanced cancer patients

Medical practitioners have been identified as the main gatekeepers to specialist palliative care services (SPCS). Doctors are pivotal to the process of informing patients of the need and availability of SPCS, and facilitating timely access. There is significant evidence to suggest that in the US and Europe, a large per cent of cancer sufferers are not referred to palliative care services or are referred late in the trajectory of the disease. There is also a growing body of evidence to suggest that the needs of advanced cancer patients may not be adequately met by later referral to palliative care. Preliminary investigation indicates that referral patterns may be similar in Australia. However, before measures to increase the profile and utilisation of palliative care services can be adopted in Australia, a deeper understanding is required of current referral patterns, perceptions of palliative care and barriers to referral to palliative care. A qualitative approach was initially used to investigate how Australian doctors perceive palliative care, what factors precipitate the referral process, what the perceived barriers to referral are and how these influence referral practices. This information was used to develop a quantitative research instrument to explore how extensively these particular issues influenced the referral patterns nationally. Early findings from a national survey of approximately 1,000 specialists and general practitioners suggest that whilst SPCS are viewed very positively by doctors, they are largely perceived to be for the care of the physical aspects of terminally ill patients. Physical symptoms and disease process and trajectory dominated the reasons for both referral and non-referral of advanced cancer patients in the preceding 12 months. Psychosocial, spiritual, cultural and family issues were cited less frequently as reasons for referral to SPCS. This research is being undertaken as part of Claire Johnson's PhD, under the supervision of Afaf Girgis, Chris Paul and David Currow.

n VCRCC

ProsCan: Prostate Cancer Supportive Care and Patient Outcomes Study

What are the pathways to diagnosis and treatment patterns for prostate cancer in Queensland? What are the clinical and quality of life outcomes associated with various treatments? What is the best way to provide support to the growing number of men diagnosed with prostate cancer in Queensland? These are all questions that are being answered by the ProsCan trial, currently being conducted by the Queensland Cancer Fund in collaboration with the Northern Section of Urological Society of Australasia and Queensland University of Technology. ProsCan is recruiting 800 men with prostate cancer from all the major treatment centres and the majority of urologists' private practices across Queensland. The study is documenting the pathways to diagnosis and treatment patterns of participants, along with related clinical and psychosocial outcomes. In addition, about 600 men being treated with curative intent are being recruited to take part in a randomised controlled (2x2 factorial) trial evaluating the outcomes of a telephone + print-delivered psycho-education/decision support and lifestyle intervention. The psychoeducational component includes stress management and problem solving skills training, and treatment education integrated with decision support. The lifestyle intervention targets improvements in physical activity and healthy eating. Primary outcomes, assessed at baseline, two, six, 12 and 24 months post-treatment for prostate cancer, include general and disease-specific quality of life, decisional distress, psychosocial well-being, physical activity, dietary behaviour, health care utilisation and an evaluation of cost-effectiveness. ProsCan is one of the first large scale trials to recruit men with prostate cancer at the point of diagnosis and will play an important role in informing the delivery of clinical and psychosocial support services to men with prostate cancer.

The Logan Healthy Living Program

Getting regular physical activity and eating a healthy diet are key to the management of our most common chronic conditions, and recent research suggests that physical activity and diet are also important in improving the quality of life of cancer survivors. We need to know more about how best to deliver lifestyle interventions to the growing number of cancer survivors. The Logan Healthy Living Program is a randomised controlled trial that is evaluating a telephone + print-delivered lifestyle intervention targeting physical activity and diet for cancer survivors as well as patients with other chronic conditions. Five hundred patients with a previous diagnosis of cancer, type 2 diabetes or high blood pressure are being recruited from general practices in the Logan area, south of Brisbane. Half of the patients will receive telephone counselling and mailed print materials on diet and physical activity over a 12-month period. The remainder will receive standard print materials. The health behaviour and quality of life changes and cost effectiveness of the telephone and print-delivered intervention will be compared to those observed in the print only intervention. A pilot of the program commenced at the end of 2004 and the larger project is now underway. Lifestyle changes to improve diet and physical activity may assist cancer survivors to improve their quality of life as well as to reduce the risk of recurrence and of developing other chronic illnesses. The Logan Healthy Living study will have important implications for the delivery of community-based lifestyle intervention programs to cancer survivors in Queensland.

News

n CPRC

Dr Karin Proper, a Postdoctoral Fellow from the Netherlands has just completed a three-month visit at CPRC (Feb-April 2005). Karin worked as a Research Fellow in the NHMRC 'Physical Activity and Population Health' research program. She used the PLACE study database to investigate the contributions of occupational physical activity to overall health-related physical activity and inactivity at work in relation to overweight. In Amsterdam, Karin is employed by Toegepast Natuurweienschappeiyh Onclerzoeh (TNO) which roughly translates to 'Applied Scientific Research', where she has worked since 1997. Her research areas are epidemiology, behavioural interventions, physical activity and occupational health. Her recent work has been on studies of the (cost) effectiveness of worksite physical activity interventions and investigating the determinants of physical activity (in order to develop more effective behaviour-change programs).

The Centre would like to introduce Ms Genevieve Healy, PhD candidate, who started March 2005. Genevieve's research topic is How does physical activity act to attenuate the risk of type 2 diabetes in overweight men and women? Genevieve also completed her MPH with CPRC in 2004. Also, Dr Corneel Vandelanotte from Ghent University in Belgium has accepted the position of Research Fellow, Physical Activity, with the Centre and joined us at the end of June.

Three representatives from the Centre attended the International Society of Behavioural Nutrition and Physical Activity annual conference, held in June 2005 in Amsterdam. Professor Neville Owen presented a poster titled Associations of Perceived Local Environment Factors with Walking for Transport. Ms Lorinne du Toit presented a poster titled Walkable Neighbourhoods and Community Engagement: Is there a Relationship? Dr Ester Cerin attended the pre-conference workshop titled 'Multi-level modelling in research on physical activity and nutrition'. She also took part in the IPEN meeting (see below). Professor Neville Owen also chaired a meeting of the International Physical Activity and Environment Network (IPEN) at the conference. The IPEN is co-ordinated by James Sallis (San Diego, USA), Ilse DeBourdeaudhuij (Ghent, Belgium) and Neville Owen (Australia). It aims to promote the collection and synthesis of new research findings on how different environmental 'exposures' (for example, cities in the USA, small towns and older cities in Europe, rapidly-expanding cities in Asia) influence residents' habitual physical activity.

n CBRC

The Centre has welcomed Dr Matt Spittal as our Data Analyst. Matt has a doctorate in psychology from Victoria University of Wellington. He has a background in social policy research and a strong interest in population-based sample research. CBRC also welcomes Dr Louisa Hoey as our Patient Research and Evaluation Officer. Louisa has been working with CBRC as a casual research assistant while completing her Doctorate of Psychology. Her position at CBRC involves research and evaluation of various support programs aimed at assisting people with cancer and their families.

n CBRCC

CBRCC has received over $2 million dollars in grants to implement a mental health promotion campaign in seven rural communities in Western Australia. The Western Australian Health Promotion Foundation (Healthway), Lotterywest and WA Country Health Services have contributed funding to support a two year intervention to improve mental health in two farming, three coastal and two mining towns in WA. While the role of psychosocial factors in prevention, treatment and cure of cancer has not been established, it is known that people living in rural communities smoke more, drink more and eat more than their city cousins. It is also known that country people have less health and medical services and are less likely to seek help for psychological distress. This innovative program will implement a combination of community-based social marketing strategies to encourage individuals to take positive steps to improve their mental health. The Act-Belong-Commit campaign will also enhance community cohesion by encouraging local service clubs, agencies and community groups to work together to improve individual resilience. The project will be formally launched in October 2005.

n CCCR and TCRE

The Cancer Statistics Unit of the CCCR has been providing technical support to the Epidemiology Branch of the South Australian Department of Health to facilitate relevant data analyses and feedback on trends and outcomes of the clinical management of myelomas, lymphomas, leukaemia and colorectal and breast cancers. This work is undertaken by the Health Department every four years. It involves combining hospital cancer registry data from the State's teaching hospitals to assist clinicians to monitor patterns of care by stage and other indicators and to compare these patterns with guideline recommendations. Survivals and other outcome data also are presented by stage and related clinical indicators to assist clinicians to make comparisons with expectations based on the scientific literature and other international evidence. This descriptive research of clinical practice outcomes has an important role to play in quality appraisal. Aggregated data is used by individual hospitals to obtain benchmarks for evaluation of their own experience.

The CCCR is also extending its research into preferred place of cancer death by assisting palliative care researchers to investigate concerns about dying at home. It is anticipated that results of this research will assist planners to address key concerns.

Sophie Kriven (Evaluation Officer) has left TCRE to pursue new employment opportunities. We are currently recruiting for her replacement.

n CHeRP

The following research grants have been secured by CHeRP:

1. Paul C, Mee K, Walsh R, Girgis A. Research into tobacco retailing: exploring the relationships between retail access to tobacco, socio-economic status and tobacco consumption. The Cancer Council NSW 2005-2006, $50,598.
2. Girgis A, Boyes A, Ackland S, Berry M, Harnett P. Proactive routine monitoring and intervention to reduce the psychosocial impact of cancer therapy. Cancer Institute NSW Infrastructure Grants, 2005, $117,000.
3. Butow P, Dunn S, Girgis A, Kelly B, King M, Mason C, Meiser B, Solomon M, Stockler M, Tattersall M, White K. NSW Psycho-oncology Cooperative Research Group. Cancer Institute NSW Infrastructure Grants, 2005-2006, $180,000.
4. Dunn S, Heinrich P, Boyle F, Butow P, Girgis A, Massellos P. Communication skills training for cancer nurse care

coordinators. Cancer Institute NSW, 2005, $39,606.

n VCRCC

Two staff in the VCRCC have recently received recognition for their outstanding contributions to their fields. In early April, Kirsty Pickering was awarded the Australian Health Promotion Association (Qld Branch) President's Award for commitment and service to the organisation. Kirsty has been a member of the association since she was an undergraduate and has served on their executive board for the past 3 years. On 16 April, Dr. Marina Reeves was awarded the Queensland Young Achiever of the Year Award (Science & Technology Category) for her years of high academic achievement, coupled with her more recent work in the area of cancer control. The award was

17th Lorne Cancer Conference, 10 – 13 February 2005

ABSTRACT

The 17th Lorne Cancer Conference, underwent a change of venue this year and was held on Phillip Island at Cowes. A variety of themes were covered by a talented array of invited speakers, giving attendees a broad overview of cancer research. Topics included among others the epithelial-mesenchymal transition, angiogenesis, oncogenesis and tumour-stroma interactions. The first plenary lecture was delivered by Professor Walter Birchmeier, Director of the Max-Delbrück-Center and Professor at the Charité/Humboldt University of Berlin. The second plenary lecture, The Ashley Dunn Oration, was given by Dr Nancy Jenkins, head of the Molecular Genetics of Development Section in the Mouse Cancer Genetics Program at NCI~Frederick in Maryland, USA.

EPITHELIAL-MESENCHYMAL TRANSITION

The epithelial-mesenchymal transition (EMT) whereby non-proliferative, non-migratory and non-invasive epithelial cells transform into proliferative, migratory and invasive mesenchymal cells was theme of the initial session and that of the first plenary lecture. A number of aspects were covered. Dr Carmen Birchmeier of the Max-Delbrück-Center for Molecular Medicine, Berlin, showed that signalling implicated in tumourigenesis, like the c-Met tyrosine kinase receptor or the $CXCR_4$ chemokine receptor turn also control decisive steps in muscle progenitor cell migration during normal development.

Dr Donald Newgreen of the Murdoch Childrens Research Institute, Melbourne, spoke about how epithelial cells may be more mobile and mesenchymal cells more stationary than is conventionally stated. Associate Professor Rik Thompson of St Vincent's Institute of Medical Research, Melbourne, presented upon the PMC42 cell line for EMT in breast cancer and identifying better indicators of this transition with the aim of improving assessment at diagnosis. That Pez may be a novel regulator of EMT was the topic of Dr Yeesim Khew-Goodall of the Hanson Institute, Adelaide.

CLINICAL DEVELOPMENTS

The clinical development session has an innate capacity to engage the entire audience, and the three speakers, Professor Nancy Davidson from John Hopkins, USA, Dr Glenn Begley, vice president of research at Amgen, USA, and Dr Jonathan Cebon from the Ludwig Institute, Melbourne, gave talks that captured pertinent issues. Nancy Davidson spoke about DNA methylation and histone acetylation in the context of estrogen receptor gene regulation and its role in breast cancer. Jonathan Cebon spoke about strategies for optimising cancer vaccines and presented preliminary data showing that melanoma vaccine recipients had longer disease free survival, with the most promising vaccine being NY-ESO-1, an antigen known to contain many CD4 and CD8 epitopes.

Glenn Begley presented a fascinating talk juxtaposing the rising cost of drug development, and the reducing number of agents gaining approval against the background that a large number of significant pharmaceutical patents are shortly to expire. In the US market over the next two years patents with approximately US$15 billion in revenue, including Combivir®, commonly prescribed in first-line antiretroviral therapy regimens in HIV medicine from GSK, Zocor®, a cholesterol medication from Merck, and Zoloft®, a selective serotonin reuptake inhibitor type of anti-depressant from Pfizer, will expire. Contrast this with the number of drugs gaining approval. In the four year period 1996 – 1999, the FDA approved 34 drugs for cancer use, in the subsequent four year period 2000 – 2003, 14 drugs were approved for cancer use. Temper this with the costs associated with a new drug gaining FDA approval which have increased far greater than the rate of inflation; current estimation approximately US$800 million. This situation has major implications for all, from researchers to patients. The thought left hanging was if income is being reduced, and costs are rising, then from where will improved treatments be sourced.

Glenn Begley then went on to outline some of the potential products that Amgen currently have in the development pipeline for cancer patients undergoing phase II and III trial, including Panitumumab, a fully humanised antibody against the EGF receptor, and AMG706 a small molecule inhibitor of the VEGF receptor.

WHAT'S HOT IN BREAST CANCER RESEARCH?

Prior to the Ashley Dunn Oration, an invigorating talk was given by Professor Joe Sambrook from the Peter MacCallum Cancer Centre, Melbourne. He focussed on breast cancer, and that whilst much research progress has been made, how do we proceed from what is currently known to a cure. Historically there is often poor cohesion and mobilisation of all interested and required parties, an approach that would benefit most diseases. He said that the best example we have to date of this is perhaps the gay community and the response to HIV/AIDS, and then went on to speak about kConFab, a research collaborative bringing together all those from molecular biologists to psychologists. An example of just one issue they are undertaking to tackle is how to more accurately predict the consequences for a person carrying a mutation in BRCA1 or BRCA2, a gene known to predispose for breast cancer.

THE ASHLEY DUNN ORATION

Nancy Jenkins delivered a fascinating talk focussing on how insertional mutagenesis can provide a road map to navigate the cancer genome. It is known that retroviruses can induce haematopoietic cancer in mice by integrating into the genome and insertionally mutating cancer genes and she discussed that this process provides powerful molecular tags for identifying cancer genes, especially in the post genomic-sequence era. She then went on to describe the unfortunate case where two human severe combined immunodeficiency (SCID) patients undergoing retroviral gene therapy acquired insertional mutagenesis induced T cell leukaemia.

The final part of the lecture focussed on the discovery of a new and powerful insertional mutagenesis system that relies on the Sleeping Beauty (SB) family of transposons. SB transposons, or jumping genes, insert between or into genes and in doing so can activate or inactivate the normal function of a gene. In the late 1990s researchers took defunct, non-functioning jumping genes from fish, that over millions of years of evolution had become inactive and reactivated them, hence the term SB. While transposons have been important genetic tools in lower eukaryotic functional genomic screens, their low transposition frequency in higher eukaryotes rendered them less useful. However research using SB transposons, designed with transposition frequencies higher than previously thought obtainable, were introduced into mouse DNA, inducing developmental defects and cancer in mice. By isolating and studying the genes from tumours containing SB, researchers were able to efficiently detect genes linked to cancer by examining whether SB turned them on or turned them off. In conclusion Nancy Jenkins highlighted that SB transposons integrate randomly into the mouse genome and in both dividing and non-dividing cells, in contrast to retroviruses, which tend to preferentially integrate into the 5′ end of genes and only into dividing cells. Therefore while this discovery was made in mice, the SB transposon mutagenesis approach should reveal new insights into human cancer which can be translated for clinical use.

OTHERS SESSIONS

The sessions from the rest of the conference were also of high calibre. Specifically the others sessions were on angiogenesis, cytokines and blood cells, oncogenesis, normal and malignant haematopoiesis, cell motility/cytoskeleton, tumour-stroma interactions, and immune regulation and tumour surveillance.

Dr Peter Murray from St Jude Children's Research Hospital, Memphis, USA, spoke about regulation of the innate immune system. He focussed on the role of IL-10, a cytokine that attenuates inflammatory responses by regulating cytokine, chemokine, and cell surface molecule levels produced by activated macrophages. Evidence that IL-10 regulates the anti-inflammatory response through a STAT-3 dependent mechanism was shown.

Dr Neal Copeland, director of the Mouse Cancer Genetics Program at NCI~Frederick, USA, gave an interesting presentation upon the identification of cancer stem cell immortalisation genes. Emerging studies suggest that many cancers may arise from small populations of immortalised cancer stem cells that give rise to phenotypically diverse cells with reduced proliferative capacity, but which represent the bulk of tumour cells. Genes involved in the immortalisation of cancer stem cells are potentially appealing drug targets. To date their group has produced more than 80 such cell lines that have properties attributed to cancer stem cells. Furthermore their production has resulted from insertional mutagenesis of a known human leukaemia gene or a gene that regulates one, indicating potential drug targets.

There were two speakers from John Hopkins in Baltimore, USA, who had to come all the way to Australia to meet one another! Dr Neil Watkins spoke about Hedgehog (Hh) signalling in cancer and cancer stem cells. While Dr Denise Montell gave a talk based upon her Drosophila research. In particular, a forward genetic analysis of cell motility, which is a process known to contribute to tumour invasion and metastasis. She presented results showing Myosin VI, an unconventional myosin protein, is required for border cell migration. This work had been extended to show that Myosin VI contributes to the motility of ES2 ovarian carcinoma cells in vitro and depletion of Myosin VI expression inhibits their ability to spread in nude mice.

Dr Andrea McClatchey from Harvard Medical School, USA, spoke upon membrane organisation in tissue morphogenesis and tumourigenesis. Merlin, the NF2 tumour suppressor, and the related ERM proteins, Ezrin, Radixin, and Moesin, connect membrane proteins to the actin cytoskeleton and are thought to coordinate cortical membrane domains in many cell types. Studying NF2-deficiency over a number of cell types enabled identification of a key role for Merlin in mediating contact dependent growth arrest through stabilisation of cadherin containing cell-cell junctions. Additionally recent generation of conditional Ezrin mutant mice found that Ezrin is necessary for villus morphogenesis in the developing mouse intestine. The combined studies of Ezrin and Merlin suggest they both function in organising membranes involved in cell-cell communication.

Professor Jacqueline Lees, MIT Center for Cancer Research, USA, talked about the role of E2F3 in the control of cellular proliferation. She focussed on retinoblastoma protein (pRB) tumour suppressive activity and it being partially dependent on its ability to regulate E2F transcription factors. The work identified E2F3 as a key proliferation regulator, null E2F3 mouse embryonic fibroblasts have a major defect in both cellular proliferation and in mitogen induced activation of E2F responsive genes. Additionally E2F3 also played a role in regulation of the p53 tumour suppressor pathway, loss of E2F3 causing de-repression of Arf, activation of p53, and induction of p21Cip1, the cdk inhibitor.

Professor Alpha Yap, Institute for Molecular Biosciences, Queensland, presented on cadherin signalling to the actin cytoskeleton. It is known that loss of E-cadherin activity promotes tumour invasion and metastasis. However determining how cadherins exert their morphogenetic effects will aid elucidation of the molecular mechanisms that drive tumour progression. One current avenue of thought is that cadhedrins act as adhesion activated cell signalling receptors and affect morphogenetic effects in this fashion.

AWARDS

Six poster presentation awards were presented. The Applied Biosystems award went to Kirsteen Campbell of the University of Dundee, UK. The Cure Cancer Foundation award, which includes a registration to the 2006 Lorne Cancer Conference, went to Leila Wyatt of the Hanson Institute, Adelaide. The Cancer Council Australia award went to Sandy Hung of the Peter MacCallum Cancer Centre, Melbourne. The Lorne Cancer Conference award went to Kevin Spring of the Queensland Institute of Medical Research. Finally two Agilent Technologies awards were made, one to Louise Winteringham of the Western Australian Institute for Medical Research, Perth and the other to Julia Ellyard of the John Curtin School of Medical Research, Canberra.

ACKNOWLEDGMENTS

Thanks must go to the organising committee for putting together a stellar cast of speakers and sessions. Thanks must go to the speakers for the quality of their research and presentations. Also very important to thank all of our sponsors for their continued support, which is fundamental to the ongoing success of the Lorne Cancer Conference. We look forward to the 18th Lorne Cancer Conference, February 9th – 12th 2006. Put it in your diaries now!

Karen Murphy
Division of Cancer & Haematology

NEWS & ANNOUNCEMENTS

Senate inquiry into cancer services backs Cancer Australia

A Senate report into cancer services has recommended Cancer Australia implement measures to improve patient outcomes that are largely consistent with The Cancer Council Australia and Clinical Oncological Society of Australia (COSA) policy priorities.

The Cancer Council and COSA, who with the National Cancer Control Initiative and the National Aboriginal Community Controlled Health Organisation lodged a detailed submission to the Senate inquiry, publicly commended the report's potential to effect measurable improvements in service development and delivery.

The Federal Government announced a commitment to establish Cancer Australia during last year's federal election and backed it with budget commitments in May this year, moves welcomed by The Cancer Council and COSA, who had jointly advocated for the agency's creation.

The Senate has since added impetus to Cancer Australia's introduction, by recommending the agency take on a number of the functions also put forward by The Cancer Council and COSA.

The Cancer Council's Chief Executive Officer, Professor Alan Coates, said the recommendation that Cancer Australia work with The Cancer Council and COSA to develop accreditation and credentialing systems would ensure wider availability of services focused on patient need.

COSA President, Dr Stephen Ackland, welcomed recommendations to improve referral pathways and promote multidisciplinary cancer care, particularly through expanding the Medicare Benefits Schedule.

Professor Coates and Dr Ackland said the Senate Community Affairs References Committee should be commended for its painstaking work in converting hundreds of complex written and oral submissions into a set of recommendations that sought to put the needs of patients first.

A copy of the committee's report is available at www.aph.gov.au/Senate/committee/clac_ctte/cancer/index.htm.

New Cancer Council subcommittees

The Cancer Council Australia is seeking to boost its capacity to work with general practitioners and to play a stakeholder role in the national implementation of bowel cancer screening, with the establishment of two new subcommittees.

Both subcommittees are extensions of the Public Health Committee and will assist in the development of national policy and advocacy advice.

The General Practice Subcommittee is focusing on cancer prevention and primary health issues relevant to GPs and will aim to improve networks, contribute to general practice resources and provide information through fact sheets and the National Cancer Prevention Policy.

The Bowel Screening Subcommittee will be a central point of information for all state and territory Cancer Councils, provide high-level advice on bowel screening issues and look at developing initiatives to help ensure effective screening is introduced Australia-wide.

The General Practice Subcommittee is chaired by Rebecca Russell and co-chaired by Professor Brian McAvoy from the National Cancer Control Institute. The Bowel Screening Subcommittee is chaired by Alison Peipers. Rebecca and Alison are both are based at The Cancer Council Victoria.

There's a new treatment for bowel cancer – prevention

Around 25%, or more than 3000 of the 13,000 bowel cancers diagnosed in Australia every year could be prevented if men and women maintained a healthy body weight, ate a healthy diet and engaged in daily physical activity.

In an Australian first, The Cancer Council Australia has developed a public health campaign which links the three elements of good nutrition, physical activity and healthy body weight with bowel cancer prevention.

The centrepiece of the new campaign is a television commercial which promotes a healthy lifestyle as the best way to reduce the risk of developing bowel cancer. The campaign is called "Avoid the Cure".

At the launch of the new advertisement, nutritionist Dr Rosemary Stanton said it was an excellent campaign as there was little understanding in the community of the preventative benefits of a healthy diet and healthy body weight.

"I don't think people have any idea there is a link between nutrition and bowel cancer. I think they have a vague idea that fibre is important but don't realise that weight or exercise have anything to do with it.

"The ad provides a simple and direct message. It's not talking about getting skinny – it's about being a healthy weight. This will be very refreshing for people who may be very confused about all the diet messages out there."

Terry Slevin, Chair of The Cancer Council Australia Nutrition and Physical Activity Committee, the group which developed the campaign, said bowel cancer had been a 'silent' killer in Australia.

"It is socially frowned upon to talk about bowels so people have never been keen to talk openly about it. The result is a disease which has been overlooked in terms of public awareness. This campaign is about redressing the balance."

To view the radio and television advertisements for the new campaign, visit www.cancer.org.au/avoidthecure.

Cancer Council welcomes budget commitments

The Federal Government's $189.4 million cancer program announced as part of the 2005-06 budget in May built on the commitments made during last year's federal election and were applauded by The Cancer Council Australia.

It was the most comprehensive cancer control package ever announced in a federal budget, funding a number of measures over five years which largely reflected The Cancer Council Australia's national policy initiatives.

Highlights included $21.7m to support independent cancer clinical trials, $35.6m to commence rolling out a national bowel cancer screening program and $13.7m to establish a new national cancer agency, Cancer Australia (see below).

The government also announced $25m for a new anti-smoking campaign targeting youth, which was not an election commitment and which the Minister, Tony Abbott, told a Parliament House function was aimed at getting "a better report card" from The Cancer Council Australia CEO, Professor Alan Coates.

The Cancer Council Australia publicly welcomed the budget commitments and will seek opportunities to represent its stakeholders in the development of implementation plans.

A breakdown of the budget commitments is available on the Department of Health and Ageing website at www.health.gov.au.

Government urged to help Pacific nations enforce first world tobacco control treaty

Australia has a "moral obligation" to help its Pacific neighbours combat the rising prevalence of smoking and tobacco related disease by helping them enforce the world's first treaty on tobacco control, which came into effect in February, according to The Cancer Council Australia.

The Cancer Council's Chief Executive Officer, Professor Alan Coates, said the Framework Convention on Tobacco Control (FCTC), ratified by Australia and 56 other countries, was the world's first global health treaty and offered a unique opportunity for Australia to help less resourced Pacific island and south-east Asian nations boost their tobacco control efforts.

"There are almost five million tobacco related deaths worldwide each year, 70% of which occur in developing countries where legislative regimes and education campaigns are weak or non-existent," Professor Coates said. "The tobacco industry, including Australian companies, preys on vulnerable countries, profiting from activities that have been prohibited in Australia for 20 years."

Chair of The Cancer Council Australia's Tobacco Issues Committee, Dr Andrew Ellerman, said Australia was well along the path to meeting the requirements of the FCTC and was ideally placed to provide technical expertise and financial support to help our neighbours meet their obligations under the FCTC, such as developing effective legislation and implementing public education programs.

Requirements under the FCTC include: elimination of tobacco advertising, promotion and sponsorship; requirements for warning labels; prohibition of misleading descriptors such as "light" and "mild"; protection of non-smokers from tobacco smoke in public places; regulation of tobacco product contents; and calls for higher tobacco taxes, global coordination to fight tobacco smuggling and promotion of tobacco prevention, cessation and research programs.

Further information can be found on the following websites:

Federal Government announcement: www.health.gov.au/internet/wcms/publishing.nsf/Content/health-mediarel-yr2004-cp-pyn001.htm

Framework convention alliance: www.fctc.org

World Health Organisation: www.who.int/tobacco/framework/en/

Position statements

The Cancer Council Australia has recently published three new position statements: Risks and benefits of sun exposure; Advertising and display of tobacco products in retail outlets; and Prostate cancer screening. The statements cover topics that have generated significant interest in both the health and mainstream media.

Risks and benefits of sun exposure

While skin cancer continues to impose the greatest financial burden on the health system, there was concern that media reports about people being at risk of vitamin D deficiency through sun avoidance could compromise the sun protection message. In response to the debate about the risks and benefits of sun exposure, The Cancer Council Australia has developed and published a comprehensive position statement with the endorsement of the Australian and New Zealand Bone and Mineral Society, Osteoporosis Australia and the Australasian College of Dermatologists.

The position statement continues to reinforce the SunSmart message to all Australians, with particularly strong warnings for people at higher risk of skin cancer and advice for individuals at risk of vitamin D deficiency.

Advertising and display of tobacco products in retail outlets

Meanwhile, as health promotion groups call on state and territory governments to remove tobacco marketing at point-of-sale, The Cancer Council Australia has published a position statement, Advertising and display of tobacco products in retail outlets, which provides evidence to support the proposed restrictions.

The statement is particularly powerful, as it references tobacco industry documents released by US courts that clearly indicate the industry's use of point-of-sale display as the major vehicle for reaching buyers and the desire to recruit young customers who are yet to commit to a favoured brand.

The statement is being widely released at the national and state/territory level, in the hope that it will add to the weight of evidence being put to state and territory governments showing how the elimination of retail displays can save thousands of lives, by preventing the recruitment of new smokers and helping ex-smokers avoid a relapse.

Prostate cancer screening

The benefits of population screening for prostate cancer is a much debated issue. The Cancer Council Australia does not support population screening of asymptomatic men for prostate cancer, as there is currently no direct evidence indicating a reduction in mortality rates.

The Cancer Council Australia recommends men speak with their doctors and make an informed, personal decision based on an understanding of the risks, benefits and uncertainties of testing, treatment options and side effects. Discussions between doctor and patient should include age and other individual risk factors such as family history of the disease.

It is important the research into prostate cancer diagnosis and treatment continue to be a high priority, particularly the development of an accurate test to detect prostate cancer.

A practice resource recently launched for GPs aims to assist patients make an informed choice about prostate cancer testing.

Developed by the Australian Prostate Cancer Collaboration, the Queensland Cancer Fund, Northern Section of the Urological Society of Australasia, RACGP (Qld faculty), The Cancer

Council Australia and the National Cancer Control Initiative, the resource comprises a GP/Patient show card, Six Decision Steps and referral guide.

Workshops addressing prostate cancer testing and patient informed choice are running in Queensland and Victoria and are being planned for other states.

Copies of the practice resource or information on the workshops can be obtained by phoning 13 11 20.

Updated position statements

The Sun protection and infants (0-12 months) and Use of SPF30+ sunscreen position statements have recently been updated.

Australia's Biggest Morning Tea

What a successful event!

For Australia's Biggest Morning Tea, it has been our biggest year yet. Thousands of Australians hosted morning teas, raising over $6.4 million to date. We are well on the way to reaching our fundraising target of $7 million.

And our Guinness World Record attempt? We are still adding up the numbers, but it looks as though we are going to smash the record!

The success of Australia's Biggest Morning Tea relies on the people who host the event. We would like to thank all of our hosts for their support and for helping us to raise the funds that will be used in the fight against cancer.

All Cancer Council Australia position statements can be viewed at: www.cancer.org.au/positionstatements.

Daffodil Day looking for believers

The Cancer Council Australia is gearing up for another successful Daffodil Day on Friday 19 August, with hopes of raising $7.8 million.

Fresh Daffodils and a range of merchandise will line stalls at train stations and shopping centres to raise funds for cancer research, control programs, advocacy, education and support services.

However Daffodil Day is more than just one day of activity. It is a month of high profile promotions and publicity. Daffodil Day merchandise is also available at the following national supporting outlets during the month of August: Amcal, ANZ, Cartridge World, Coles, HIC Medicare, Miller's Retail Group, Plants Plus, Quix and Rockmans.

Inspiring belief that cancer can be beaten is the motivation behind this year's Daffodil Day creative campaign which taps into the optimism that Australians maintain as they continue to strive for a cancer-free future.

National Cancer Prevention Policy 2004-06

For ease of use, the National Cancer Prevention Policy 2004-06, has been updated on The Cancer Council Australia's website to include bookmarked PDF files. The bookmarked version of the policy allows readers to link to directly to the chapters and subject headings of interest.

Pink Ribbon Day

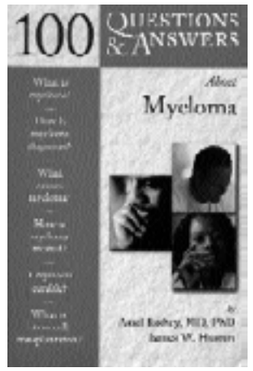
Don't miss out on your chance to 'think pink' this October. You can do your part in making an impact on breast cancer by raising funds for The Cancer Council Australia – to find out more, visit www.pinkribbonday.com.au or call 1300 65 65 85.

PINK RIBBON DAY™

BOOK REVIEWS

100 QUESTIONS AND ANSWERS ABOUT MYELOMA

A Bashey, JW Huston
Jones and Bartlett Publishers, Inc (2005)
ISBN: 0-7637-4553-7 133 pages plus index
RRP: $A22.95



This is a 130 page booklet for people diagnosed and living with myeloma and has been written by an American haematologist and a very enthusiastic author and lawyer who was diagnosed with myeloma. Whilst it is clearly written from a health professional perspective, the patient's personal contributions and informed reflections add valuable insights. It is a new addition to a series of booklets about specific cancers and other diseases, including the most common cancers, and now less common cancers where good information for people with the diseases is rare such as for brain, ovarian and pancreatic cancers. Myeloma is a rare form of blood and bone marrow cancer. In Australia, myeloma constitutes less than 3 percent of all malignancies.

It literally is 100 questions and detailed answers – a format designed to mirror perhaps the anxiety and worried states people find themselves in when first diagnosed, when thinking logically starts to overcome and settle the panic. The terminology used for and around myeloma (such as light chains, electrophoresis, etc) can be particularly challenging to newcomers (health professionals and patients and family), yet this booklet covers them sensibly and inclusively.

The questions are ordered into 8 parts:

- The Basics covers what it is, what it isn't (differential diseases such as Waldenstrom's Macroglobulinaemia and Amyloid need to be correctly excluded), and the basics of blood and bone marrow.
- Diagnosis and Staging covers questions and answers about the different and unique tests associated with diagnosing myeloma (examining immunoglobulins in serum and urine, cytogenetics on bone marrow tissue and skeletal surveys, for example), symptoms, and the staging and classification systems used. It includes a balanced discussion around seeking second opinion – reasonable given the disease's rarity, often vague symptoms and grumbling history in some patients.
- Treatment Options is the substantive component of the booklet and allows focus on questions around the now broader multiple options available, clinical trials, prognostic issues. It glosses briefly over the old stalwarts, and moves quickly to bisphosphonates to prevent/address bony erosion, thalidomide and other immunomodulatory drugs, proteasome inhibitors, radiation therapy and ortho-surgical techniques for pathological fractures. Other questions address bone pain, renal failure, central venous access devices and the role of complimentary therapies.
- A weaker section of the booklet, Side Effects and Complications of Treatment, skims over neutropenia, anaemia, fatigue, decreased libido and neuropathy.
- A valuable section explores the complex notions of Stem Cell Transplantation, emerging as being important treatment options for many myeloma patients.
- Important questions are asked in the If Treatment Fails section – the language of good palliative care is rarely used in the curative culture of haematology.
- Various life questions are asked in the Advocacy and Support section, mainly around exercising, risks of myeloma running in families, getting flu shots and working.

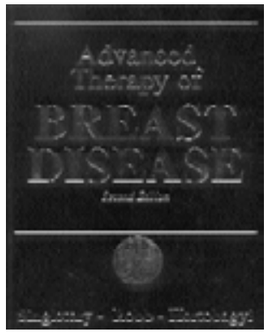
The resources at the end run out of puff – the glossary is limited and so is the list of organisations and websites. For example, given the discussion of similarity with amyloid, there are no amyloid resources.

Essentially, this is a great resource for people living with myeloma – they are now a group of people living with a chronic disease and they want to know more. Improvements in treatments have ensured their options are more positive than ever before. They deserve good quality information to give them understanding, to ensure good decision making with their treatment team.

Gabrielle Prest
Leukaemia Foundation NSW

ADVANCED THERAPY OF BREAST DISEASE 2ND EDITION

Singletary, Robb and Hartobagyi
BC Decker (2004)
ISBN: 1-550-09262-6 868 pages plus index
RRP: $203.50 (incl GST)



This volume joins a group of textbooks of breast diseases. The three editors are all from the MD Anderson Cancer Centre in Houston, Texas and review of the contributors to this multi-author work indicates they are mostly on the faculty of or have been associated with that institution.

This work is an encyclopaedia of breast diseases and covers all the main topics with succinct and freestanding reviews. This feature makes it easy to obtain a well-rounded discussion of a particular area of interest without being directed to multiple pages from the index. This volume does not seem to suffer from the problem as many multi author textbooks of Breast Diseases such as primary prevention, risk assessment and the emerging role of ductal lavage amongst others are examples of the wide ranging extent of this volume. Benign disease is not forgotten

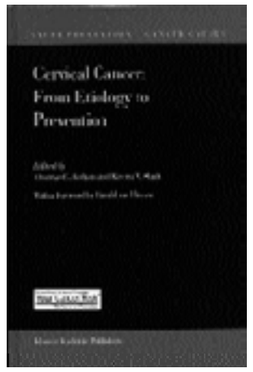
and reconstruction is prominent no doubt due the special interest of one of the authors. Minor omissions and conflicts of opinion do occur but on the whole they are limited. For example whilst there is a whole chapter dedicated to neoadjuvant chemotherapy, the role of neoadjuvant hormonal therapy which is not widely practiced in the United States does not figure prominently.

The level of the discussion is certainly appropriate for breast specialists who require a greater or in depth understanding of a specific topic. This is consistent with the title of Advanced Therapy of Breast Disease. This volume would not be an easy read for a reader with no previous interest or knowledge of breast diseases. This book is strongly recommended for its timeliness in a rapidly developing field. The editorial style is crisp and clear and the chapters are well written and easy to understand. Some of the pictures are of a lower standard than might be expected. Never the less the student of breast diseases from any discipline would benefit from a more than casual acquaintance with this work. The volume is enhanced by a CD, which reproduces the text.

Michael Henderson
Peter MacCallum Cancer Centre, VIC

Cervical cancer: from etiology to prevention

TE Rohan and KV Shah (Eds)
Springer-Verlag Netherlands (2004)
ISBN: 1-4020-1410-4 402 pages plus index
RRP: $US127.00



Cervical Cancer: From Etiology to Prevention is a well-presented collection of chapters on the science behind the current understanding of the development of cervical cancer. Whilst it briefly covers diagnostic methods for detection of preinvasive disease, the focus of the book is an analysis of the available data on the epidemiology, causative factors, and strategies for preventing cervical cancer.

The text is divided into four broad sections – pathology and natural history, the molecular biology of human papilloma virus (HPV) infection, the epidemiology of squamous and adenocarcinomas of the cervix and finally, potential strategies for prevention.

The pathophysiology involved in the acquisition of HPV infection, the phenotypic expression of infection and histological types of cervical neoplasia are succinctly described. The text is supported with good quality black and white photomicrographs. A brief chapter on the current understanding of the natural history of cervical dysplasia and carcinoma highlights the long natural history of cervical cancer in most women and the difficulties in identifying factors important in progression of preinvasive lesions.

The following section provides a description of the structure, classification and oncoprotein expression of HPV. The currently known roles of E6 and E7 proteins are well described, together with the assays available to measure HPV exposure and expression. Epidemiological evidence for HPV and other co-factors in development of squamous cell cancers and adenocarcinomas is discussed, together with limitations of the evidence.

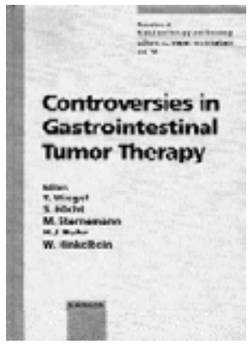
Preventative measures discussed in the final chapters cover a broad area from behavioural interventions, through screening strategies and medical treatment of cervical neoplasia, to the development of vaccines directed against high risk HPV subtypes. The lack of a brief review of surgical treatment of cervical neoplasia is a notable omission. Social issues are included in the discussion of the design, assessment and implementation of preventative HPV vaccines. A well-considered exploration of the available strategies in constructing and administering therapeutic bacterial, viral, peptide/protein and cell-based HPV vaccines follows. Finally, a chapter on the issues confronting developed and developing countries highlights the need for policies tailored to the population and resources of each region.

This book will be a very useful guide for scientists working in the area of cervical cancer. It provides a summary of the evidence available on the epidemiology, molecular events and potential points of intervention in the development of cervical cancer. The breadth of topics covered require succinctness which will not satisfy an expert working in the area but the book provides a very good introduction to the subject.

Russell Hogg
Westmead Hospital, NSW

Controversies in gastrointestinal tumor therapy

T Wiegal, S Hocht, M Sternemann, HJ Buhr, W Kinkelbein (Eds)
Karger (2004)
ISBN: 3-8055-7690-0 121 pages plus index
RRP: $US112.75



Controversies in Gastrointestinal Tumor Therapy is part of a series of books Frontiers of Radiation Therapy and Oncology. As the title suggests it covers controversies in the diagnosis and treatment of rectal cancer, pancreatic cancer and liver metastases.

The authors of the chapters are predominantly from German institutions as the book is based on the proceedings of the 6th International Symposium on Special Aspects of Radiotherapy held in Berlin in 2002. Notable amongst these is Rolf Sauer who co-authors a chapter on neoadjuvant radiochemotherapy in rectal cancer and chairs the German Rectal Cancer Study Group that recently published the results of the randomised trial of preoperative versus postoperative chemoradiotherapy in rectal cancer in the New England Journal of Medicine. Heald from Basingstoke co-authors a chapter on whether total mesorectal excision alone is sufficient for rectal cancer.

Two other surgical chapters include one on predicting resectability of recurrent rectal cancer and the other on resection of liver metastases. Imaging is covered in two chapters – one on MRI in rectal cancer and the other is on PET scanning pancreatic cancer. Both of these chapters are good in that they cover in detail the limitations and pitfalls of the respective modalities in the clinical situations.

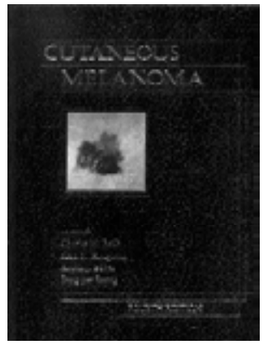
There is very much a focus on the radiation aspects of management in this book with other chapters on preoperative radiotherapy to increase sphincter preservation, intraoperative radiotherapy, radiation therapy for rectal cancer recurrence, stereotactic radiotherapy for liver metastases, adjuvant chemoradiation for pancreatic cancer and chemoradiotherapy for unresectable pancreatic cancer. There is also an interesting chapter on laser thermal ablation for hepatic metastases.

This 125 page text is rather pricey at the recommended retail of $US112.75 but does provide a reasonable brief overview from a European perspective of the controversies in rectal and pancreatic cancer and liver metastases. It would be suitable to help guide reading for oncology trainees and also for specialists wanting to update their knowledge in these areas.

Desmond Yip
The Canberra Hospital, ACT

Cutaneous melanoma (4th Edition)

CM Balch, AV Houghton, AJ Sober, SJ Soong
Quality Medical Publishing (2003)
ISBN: 1-57626-159-X Pages: 750
RRP: $US195



Cutaneous Melanoma is an ideal reference text for anyone with an interest in melanoma management and an essential library addition for melanoma specialists of all persuasions, or for anyone who manages skin cancer and melanoma on a less frequent basis in their clinical practice. Given its detailed nature, it is primarily a postgraduate text. Although it is principally aimed at a surgical audience it is full of practical, useful information for epidemiologists, dermatologists, nurses, medical oncologists, nuclear medicine physicians, radiation oncologists or basic science researchers with an interest in melanoma or skin cancer. It particularly forms an ideal resource outside of one's own specialty, and is also a useful study reference text for general and plastic surgeons, or dermatologists in training.

Now in its 4th edition, it is a well-written and comprehensive single volume text containing practical information concerning virtually all aspects of melanoma epidemiology, diagnosis and management, in a particularly well-reasoned manner. New sections have been included on Epidemiology, Prevention and New Diagnostic methods, together with several chapters on lymphatic mapping and sentinel node dissection.

The chapters are easy to follow and are usefully organised in such a way so access to the desired information a simple task. This is testimony to the collective experience of the editors. The referencing is very comprehensive and especially useful when writing papers or verifying original data for presentations. The reliable and accurate index and contents sections aids rapid accessibility to practical facts and figures for busy clinicians and researchers. This takes a lot of the effort out of locating useful information expediently. Virtually the only "down-side" was the weight of the book due to the high quality denser-weight paper used, which makes carrying less easy, although good exercise.

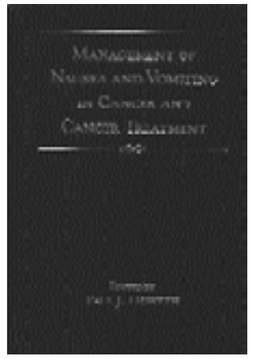
This book was a pleasure to read and characterised by careful editing which has created a consistent style and a uniform standard throughout the text.

At a recommended cost of US$195 it is therefore a highly recommended reference text for the busy clinician or researcher.

Brendon Coventry
Royal Adelaide Hospital, SA

Management of nausea and vomiting in cancer and cancer treatment

PJ Hesketh (Ed)
Jones and Bartlett Publishers, Inc (2005)
ISBN: 0-7637-3139-0 245 pages plus index
RRP: $A136.50



Nausea and vomiting remain two of the most distressing symptoms for patients with cancer receiving treatment. Paul Hesketh has published extensively on the topic of nausea and vomiting in cancer treatment and as editor has put together this timely monograph.

Recent advances in understanding the patho-physiology of the emetic process and recognition of delayed emesis as a major issue in chemotherapy induced nausea and vomiting (CINV) has lead to development of new antiemetics such as the selective neurokinin 1 (NK1) antagonists and the introduction of palonosetron a serotonin antagonist with a long half life, although this agent is not yet available in Australia.

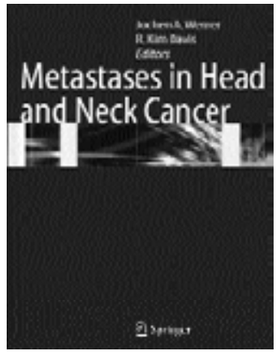
The book predominantly covers issues related to chemotherapy induced nausea and vomiting, however one chapter does cover the issues related to radiation-induced emesis. The table of contents is structured clearly and logically. The mechanisms of acute, delayed and anticipatory emesis induced by cancer treatment is covered. Also the role of serotonin antagonist in emesis control particularly acute emesis and nausea is reviewed. Attention is also given to the persistent problems faced in emesis control particularly that of delayed emesis. Finally the role of substance P antagonists as one of the newer antiemetics agents available is also reviewed.

The book is well written and each chapter objectively covers the topic. The target audience for the book is physicians and nurses interested in cancer symptom management. This monograph would be a valuable resource to support the education of nurses and doctors on oncology units in managing CINV and ensuring the use of the best treatment approaches currently available.

Diana Moore
Mater Private Hospital, Qld

Metastases in head and neck cancer

J A Werner, R K Davis (Eds)
Springer-Verlag (2004)
ISBN: 3-540-20507-1 230 pages plus index
RRP: $US149.00



Audience: Clinicians with a specific interest in head and neck cancer.

Purpose: To discuss metastases from head and neck cancer focussing almost completely on lymph node metastases in the neck, and to discuss therapeutic approaches.

Content: The introductory chapter covers basics of lymphology. The subsequent two chapters discuss pathology of lymphogenic spread and the 'what goes where' of head and neck nodal spread. There is a chapter on diagnostic techniques, and then four chapters on treatment: principles of surgery and radiation therapy, a 'detailed discussion' of neck dissection, and complications following surgery and radiotherapy. There is a chapter discussing malignancy of unknown primary presenting in the neck nodes, a three-page chapter on distant metastatic disease, and finally a chapter on post treatment follow-up.

Highlights: I found the strongest chapter to be the first, integrating lymphatic embryology physiology and anatomy. It provides a different approach to investigations and follow-up from our usual one. Judging by scattered exhortations to American surgeons to familiarise themselves with sonography it seems the majority of the book comes from the German authors. For the practising surgeon the central surgical chapters are very much 'the authors approach', which may be of value.

Limitations: This book is neither fish nor flesh. It claims to cover 'neck dissection in great detail' but I doubt 13 pages are enough to guide fellows in head and neck surgery and the discussion does not appear to highlight finer nuances for the practising specialist. Coverage of radiotherapy is superficial, with much time spent on discussing IMRT, which again seemed too much for the head and neck surgeon/fellow and not enough for the radiation oncologist. Although local metastatic disease is the major problem in head and neck cancer the title flatters to deceive.

Comment: The title clearly mislead the editors to send me the book, for which I thank them – having almost no 'medical oncology' in it this was a nice look at how the surgical side views life. In the usual tradition of Springer books they are well presented and pricey: at US$149 I do not think my surgical colleagues would find it of great value, and I would suggest to a new head and neck fellow that Stell and Maran on amazon.com for the same price is a better bet.

Brian Stein
Ashford Cancer Centre, SA

Molecular genetics and colorectal neoplasia (2nd ed)

JM Church, G Casey
Kluwer Academic Publishers (2003)
ISBN: 1-4020-7611-8 168 pages plus index
RRP: $US135.00

This is a very simple book aimed at clinicians with scant or no knowledge of genetics or molecular biology. Although it is subtitled A Primer for the Clinician, it is probably valuable only to a restricted audience – perhaps junior oncology registrars, allied health practitioners, medical practitioners with no lab experience embarking on basic research and medical students.

Written in partnership by a consultant surgeon and a molecular biologist, the style is conversational but sometimes patronising and unsubtle ("… lack of family history does not exclude an inherited syndrome of (CRC). Every family has to start somewhere...").

The book suffers from cheap production, with too few diagrams and photographs where needed, eg: Chapter 3: Molecular genetics methods simplified. Yet elsewhere bizarre inclusions such as photos of "The registry coordinators" and "The Registry Team" (unidentified individuals, but presumably the author's colleagues at The Cleveland Clinic). The quality of the diagrams and reproductions is generally poor. In particular, the histology and clinical photographs are unclear and should have been produced as coloured plates to be of any use. In several diagrams the text and labels are illegible. The punctuation and layout is also fairly amateur.

References are limited and there are many sections in which more up-to-date data could have been included. For example, the sole reference in the section discussing the effects of COX-2 inhibitors on polyposis is from 1995. Given the rapid progress in knowledge in this field, references from 2003 are fairly scarce.

There are some good points: clear, albeit very basic explanations and step-by-step guides in some sections, for example, how to construct a family tree.

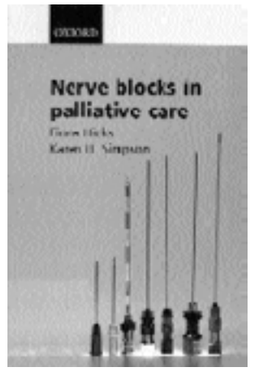
Worth reading if you are a complete novice to the world of molecular genetics, but I'd borrow rather than buy.

Eva Segelov
St Vincent's Clinical School, NSW

Nerve blocks in palliative care

F Hicks, K H Simpson
Oxford University Press (2004)
ISBN: 0-19-852703-9 130 pages plus index
RRP: $A67.50

With the development of the speciality of palliative medicine, the wide availability of controlled release morphine together with an understanding of neuropathic pain and it's treatment, the control of most cancer-related pain is now possible. There are however a small group of patients who may benefit from nerve blocks and it is to them and their health care providers that this small but ambitious book is directed.



There is a good description of coeliac plexus block and a chapter on spinal drug delivery. However a considerable amount of the rest of the book is spent discussing nerve blocks more commonly associated with the non-cancer pain population, the relevance of which is not entirely clear to this reviewer. I have no doubt that patients with cancer can have pain from spinal degenerative and other chronic conditions, however the number of patients found suitable for spinal cord stimulation – even if one includes refractory angina pectoris as an end of life condition – must be very small.

This is not a 'How to do it' book but a 'Could this procedure be good for my patient book?' The photographs and line diagrams are of quite variable quality and some of the radiographic images have reproduced very poorly.

To maximise the readership my suggestion would be to rename the book to something like An Introduction to Nerve Blocks for Non-anaesthetists, as I found very little specific to palliative care.

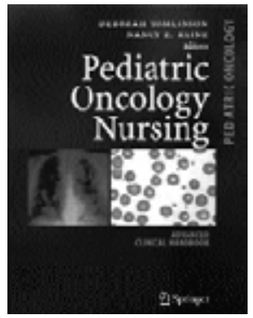
That said this book covers a very wide spectrum of interventional pain medicine and would be of value to most general medical and nursing libraries. There is appropriate emphasis on safety and monitoring and a focus on adequate patient information and consent. The importance of a team approach to decision making is also acknowledged.

Roger Goucke
Sir Charles Gairdner Hospital, WA

Pediatric oncology nursing

D Tomlinson, NE Kline (Eds)
Springer Berlin Heidelberg New York
ISBN: 3-540-40851-7 442 pages plus index
RRP: $US99.00

An unusual but welcome transatlantic collaboration, Pediatric Oncology Nursing provides a refreshing perspective on nursing children with cancer from UK and North American contributors. It is indeed, as it claims, an advanced clinical handbook pitched at advanced clinical paediatric oncology nurses. Its easy readability ensures that those reasonably new to paediatric oncology will also find it useful. Its application for advanced practitioners may be limited by the lack of evidence based nursing practice and research.



The text consists of 30 chapters that are organised into five sections. Part one deals with epidemiological, diagnostic and genetic aspects as well as staging, treatment and prognostic issues of paediatric cancers, including leukaemias and solid tumours. Part two addresses non-malignant haematological disorders in children. In part three cancer treatment issues are organised according to modality. Part four employs a systems approach to discussing side effects of treatment. Part five comprises supportive and palliative care considerations both during active treatment and terminal phases of the cancer trajectory. The familiar, well organised format and comprehensive list of contents facilitates easy navigation to the area of interest necessary for busy clinical practitioners.

The contributors represent a range of expertise in paediatric oncology from ward based staff nurse to academic professors. Whilst the North American contribution predominates, (as does the spelling!) the content is reasonably internationally applicable with globally appropriate relevance. It is a shame that chapters were written either by UK or North American authors rather than co-authorship to enhance the international perspective. As a result some of the data is not as generalisable as it could be.

The strong empirical focus, detailed pathophysiology and future perspectives are welcomed in an advanced nursing reference. The extensive inclusion of non-malignant haematological disorders accurately acknowledges the place of these patients and conditions in practice in paediatric oncology settings. Such is their significance that they warrant a complete section comprising four chapters – Anaemias, Neutropenia, Thrombocytopenia and bleeding disorders. The title should possibly read Paediatric Oncology and Haematology Nursing to reflect this.

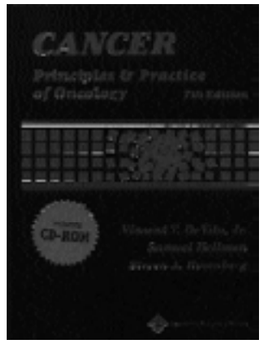
Some omissions of note include discussion about the importance and implications of clinical trials to paediatric oncology. Cursory mention only is made in the context of chemotherapy and drug approvals. The inclusion of morphological slides and diagnostic images is welcome in an advanced practice handbook, however the reproduction of some images significantly compromised their quality and would benefit from some explanation for the radiologically and morphologically naive. There were many useful tables and algorithms for clinical application. There was also a notable failure to identify adolescents as a separate entity. This was surprising and disappointing in a text originating from regions where much work has been done emphasising the very unique issues facing this population. A greater emphasis on nursing research would also be appropriate and welcomed in the advanced practice context.

Of most appeal is this book's collaborative perspective and the wide ranging experience of the authors. Colleagues who have also perused the book agree that this represents a unique and welcome contribution to the paediatric oncology clinical setting. The comprehensive focus on up-to-date pathophysiological science will ensure that this will be a well used reference for advanced paediatric oncology and haematology nurses.

Meg Plaster
Princess Margaret Hospital for Children, WA

CANCER – PRINCIPLES & PRACTICE OF ONCOLOGY (7TH ED)

VT DeVita Jr, S Hellman, SA Rosenberg (Eds)
Lippincott Williams & Wilkins (2005)
ISBN: 0-781-74450-4 2898 pages plus index
RRP: $A440.00



Yet again this book provides a comprehensive overview of cancer from the basic science and molecular biology through to recent changes in clinical practice. The information included for most common malignancies is quite up-to-date, often including trials published only last year, eg: Phase III trials of Docetaxel in prostate cancer, although obviously very recent publications are not included.

As in previous editions it remains an excellent referral point for the more unusual tumours. Some printing errors are seen through the book but these are fairly obvious if reading through the chapter, eg: table on adjuvant breast cancer recommending tamoxifen for ER –ve tumours. There are new sections examining molecular techniques such proteomics and tissue array, and new information on anti-angiogenesis agents and targeted therapies. These latter topics are covered well, with simple explanations and enough detail to provide understanding to enable clinical usage of these newer medications.

The included CD-ROM not only provides a more mobile and user friendly option than the book itself, but has excellent included features such as links to the PubMed abstracts for all references and colour slides. Unlike other CD-ROM's included with other textbooks, this one includes all the text of the book without having to access the internet.

This text continues to be an ideal reference for all aspects of oncology, including radiation and surgical management.

Karen Briscoe
Cancer Services, Coffs Harbour Health Campus, NSW

Prostate cancer: New horizons in research and treatment

ML Cher et al (Eds)
Kluwer (2002)
ISBN: 1-4020-7352-6. 386 pages plus index
RRP: US$165.00

This is a really good book. It brings together new areas of prostate cancer research, the pace of which has increased dramatically over the past few years, despite the fact that prostate cancer remains a major source of treatment-related morbidity amongst men in Western society and their families.

In particular, there are reviews by leaders in the field, with special emphasis on the relationship between tumour cells and the surrounding microenvironment, that have increase our understanding of the process of angiogenesis, apoptosis, androgen insensitivity, tumour cell dissemination and growth at distant sites. Such studies are identifying new targets for therapy for patients who have hormone refractory prostate cancer. The research ranges from genetic (including identification of a cancer susceptibility gene on chromosome 17 [ELACs/HPC2]), molecular (especially a discussion of tumour and metastasis suppressor genes, recognised not only be conventional loss of heterozygosity and comparative genomic hybridisation, but also by the production of knockout mice that develop prostate cancer [NKX3.1, PTEN and p27/Kip1]) and cellular analyses (including studies of endogenous lectins that may play a role in establishing an innate or adaptive immune response, and of the androgen receptor and its mutations that cause altered signalling pathways, such as kinase-mediated pathways and altered expression of co-regulatory proteins that may contribute to disease progression) through to epidemiological studies, refinements in local treatment strategies and new biologically based non-hormonal therapies for systematic disease. One of the basic changes in prostate cancer is the inability of prostatic epithelial cells to undergo apoptosis. The relevant genes are discussed with respect to their potential therapeutic potential. The role of serine and cysteine proteases, in particular, urokinase plasminogen activator, and expression of integrins, which have emerged as modulators of cellular functions, in metastases are also major topics. There is an excellent chapter on the cross-talk between prostate and bone, in terms of growth factor production by each, that may explain the predeliction of these cancer cells for bone.

The first part of the book relates to the pathology of prostate cancer showing photomicrographs not just of adenocarcinoma and precursor lesions, but of more rare forms, such as signet ring cell carcinoma, endometrioid variants, small cell carcinoma, sarcomatoid carcinoma and high-grade intraepithelial neoplasia and research topics, whilst the latter part if clinically based, concentrating on diagnosis, surgery techniques and outcomes, brachytherapy and fast neutron irradiation, the future of cancer imaging, novel therapeutic strategies, including anti-sense Bcl-2 and clusterin, Vitamin D and gene therapies and antiangiogenic strategies in clinical trials.

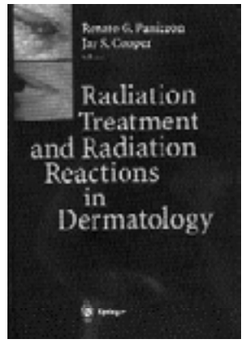
The chapters are well written and well referenced, and there is a good index. The book is suitable for researchers and clinicians alike, and would be excellent for students of this complex subject.

Pamela Russell
Prince of Wales Hospital, NSW

RADIATION TREATMENT AND RADIATION REACTIONS IN DERMATOLOGY

RG Panizzon, JS Cooper (Eds)
Springer-Verlag 2004
ISBN: 3-540-00345-2 164 pages plus index
RRP: $US99.00

This book follows on from Modern Dermatological Radiation Therapy which was first published more than 10 years ago by H Goldschmidt and RG Panizzon. In this new book, the editors suggested that they aimed to provide "an easy to use, affordable introduction to the wonders of dermatology radiation therapy and radiation reactions". In most aspects, they have achieved this.



The book opens with an excellent chapter describing the physics of dermatological radiation therapy with concise description of the physical processes and should have appeal to those with minimal prior knowledge of radiation physics. The chapter is followed by a brief chapter on radiobiology of the skin where basic radiobiology principles are explained.

The use of radiation therapy for benign diseases and the applications of Grenz Ray therapy for benign disease were discussed but the evidence quoted did not emphasise the poor quality of data in this area. There was insufficient emphasis on the caution required in the use of radiation for benign disease based on the current evidence, or lack of, particularly for late effects.

A chapter is devoted to use of superficial radiotherapy in an "office setting" for non-melanomatous skin cancers. This is accompanied by photographs of techniques used for different skin cancer locations. This chapter was the only one authored by an Australian, and includes a discussion about licensing of superficial units in Australia, as well as in the United States.

The chapter on the treatment of skin carcinomas was excellent with balanced commentary on different dose prescriptions, techniques, fractionation, evidence and results for different lesions and tumour sites, as well as, the areas of controversy.

There are chapters on use of electrons in dermatological radiotherapy and two chapters on the management of cutaneous lymphomas with one of those describing the Indian experience. All these chapters discuss total skin electron beam therapy with significant repetition (all describing the Stanford technique), although one of the chapters gives a very clear and well illustrated description of the technique.

There are well presented chapters on management of Kaposi's sarcoma, Merkel cell carcinoma and melanoma.

This book should have appeal to those involved in treatment of skin malignancy and also benign conditions, including dermatologists, radiation oncologists and radiation therapists and trainees in these fields. It provides a good summary of the scientific basis, techniques and results of dermatological radiotherapy.

I was pleased to see a whole chapter devoted to the late effects of radiation to the skin. The standardised scoring of toxicities with an explanation of the LENT-SOMA system, the molecular basis of late reactions, radiation induced cutaneous malignancies and the management of skin injury from radiation was presented.

This book helps in informing us of the available evidence for the treatment we administer, the radiobiological background for such treatments, the techniques available and the late effects. It is a welcome and important up to date addition to the small body of evidence based literature in this area.

CALENDAR OF MEETINGS

CALENDAR Of MEETINGS – AUSTRALIA AND NEW ZEALAND

Date	Name of Meeting	Place	Secretariat
2005			
July			
7-9	Royal College of Nursing Australia National Conference	Glenelg SA	Royal College of Nursing Australia PO Box 219 Deakin West ACT 2600 Tel: +61 2 6282 5633 Fax: +61 2 6282 3565 Email: Nicole@rcna.org.au Web: www.rcna.org.au
21 -23	Cancer Nurses Society Of Australia	Hobart TAS	Pharma Events Ph: +61 2 9280 0577 Fax: +6 1 2 9280 0533 Email: conferences@pharmaevents.com.au
August			
10-13	Medical Oncology Group Australia Annual Scientific Meeting	Hobart TAS	Pharma Events Ph: +61 2 9280 0577 Fax: +61 2 9280 0533 Email: conferences@pharmaevents.com.au
21-26	11th World Congress on Pain	Sydney NSW	International Association for the Study of Pain (IASP) 909 NE 43rd Street Suite 306 Seattle USA Tel: +1 206 547 6409 Fax: +1 206 547 1703 Email: iaspdesk@juno.com Web: www.iasp-pain.org
30 – 2 Sept	8th Australian Palliative Care Conference – "New Horizons"	Sydney NSW	Secretariat: Conference Managers GPO Box 128 Sydney NSW 2001 Tel: +61 2 9265 0700 Fax: +61 2 9267 5443 Email: pallcare2005@tourhosts.com Web: www.pallcare.org.au
October			
6-9	Royal Australian and New Zealand College of Radiologists, Faculty of Radiation Oncology Annual Scientific Meeting	Sydney NSW	RANZCR Level 9, 51 Druitt Street Sydney NSW 2000 Tel: +61 2 9268 9777 Fax: +61 2 9268 9799 Email: ranzcr@ranzcr.edu.au Web: www.ranzcr.edu.au
7-8	28th Annual Oncology Nurses Group Conference	Cairns QLD	Oncology Nurses Group Conference Secretary Queensland Cancer Fund PO Box 201 Spring Hill QLD 4004 Tel: +61 7 3258 2263 Fax: +61 7 3257 1306 Email: ADewar@qldcancer.com.au Web: www.qldcancer.com.au
November			
15-18	32nd Clinical Oncological Society of Australia Annual Scientific Meeting	Brisbane QLD	Pharma Events Ph: +61 2 9280 0577 Fax: +61 2 9280 0533 Email: conferences@pharmaevents.com.au

CALENDAR Of MEETINGS – International

Date	Name of Meeting	Place	Secretariat
2005			
July			
3-6	11th World Conference on Lung Cancer	Barcelona Spain	Heather Drew Imedex 70 Technology Drive Alpharetta - 30005 - Georgia Tel: +1 770 751 7332 Fax: +1 770 751 7334 Web: www.2005worldlungcancer.com/2005WLC/
14-16	2005 Gastrointestinal Oncology Conference	Arlington USA	International Society of Gastrointestinal Oncology (ISGIO) 200 Broadhollow Rd Melville New York 11747 USA Tel: +631 390 8390 Fax: +63 13 935091 Email: email@isgio.org Web: www.isgio.org
September			
13-16	9th International Nottingham Breast Cancer Conference	Nottingham UK	Nottingham Breast Cancer Conference City Hospital Nottingham, UK Tel: +44 11 596 257 07 Fax: +44 11 596 277 65
25-28	109th Annual Meeting of the American Foundation Academy of Otolaryngology – Head and Neck Surgery Foundation	Los Angeles USA	American Otolaryngology – Head and Neck Surgery c/o The AAO-HNS Foundation Inc. 1 Prince Street Alexandria VA 22314-3357 USA Tel: +1 703 836 4444 Fax: +1 703 519 1546 Email: aaomeet@entnet.org
29 – Oct 1	10th International Conference on Geriatric Oncology & 6th Meeting of the International Society of Geriatric Oncology (SIOG)	Genolier Switzerland	IMO – Clinique de Genolier Genolier 1271 Switzerland Tel: +41 22 366 9106 Fax: +41 22 366 9131 Email: siog@genolier.net
October			
2-5	31st European Congress on Cytology	Paris France	MCI France 11, rue de Solferino Paris France Tel: +33 1 53 858252 Fax: +33 1 53 858283 Email: Cytology2005@mci-group.com Web: www.cytologyparis2005.com
9-12	34th Congresso Brasileiro de Radiologia	Brazil	Congresso Brasileiro de Radiologia Av, Paulista 491 130 Andar Cj. 132-CEP 01311-909 Brazil Tel: +55 11 285 4022 Fax: +55 11 285 4022 Email: cbradiol@cbr.org.be
16-20	ASTRO: 47th Annual Meeting	Denver Colorado USA	American Society for Therapeutic Radiology and Oncology (ASTRO) 12500 Fair Lakes Circle Suite 375 Fairfax Virginia 22033 USA Tel: +1 70 3227 0170 Email: meetings@astro.org
30 – Nov 3	ECCO 13 The European Cancer Conference	Paris France	Federation of European Cancer Societies Avenue E. Mounier 83 Brussels 1200 Belgium Tel: +32 2 775 0205 Fax: +32 2 775 0200 Email: ECCO13@fecs.be Web: www.fecs.be

Date	Name of Meeting	Place	Secretariat
November			
5-9	53rd Annual Scientific Meeting of the American Society of Cytopathology	San Diego USA	American Society of Cytopathology 400 West 9th Street Suite 201 Wilmongton DE 19801-1555 USA Tel: +1 302 429 8807 Email: asc@cytopathology.org Web: www.cytopathology.org/meetings/index.php
7-9	CNIO Cancer Conference: Cancer and Aging	Madrid Spain	CNIO – Spanish National Cancer Centre C/ Melchor Fernandez Almargo 3 Madrid 28029 Spain Tel: +34 91 2246900 Fax: +34 91 2246980 Email: ccc@cnio.es Web: www.cnio.es/ccc
11-13	Oncology Nurses Society Institutes of Learning	Phoenix USA	Oncology Nursing Society 125 Enterprise Drive Pittsburgh Pennsylvannia 15275-1214 USA Tel: +1 866 257 4667 Fax: +1 877 369 5497 Email: meetings@ons.org Web: www.ons.org
27 – Dec 2	91st Meeting of the Radiological Society of North America (RSNA)	Chicago USA	Radiological Society of North America (RSNA) 829 Jorie Blvd, Oak Brook IL 60523-2251 USA Tel: +1 630 571 7879 Fax: +1 603 571 7837 Email: sdrew@rsna.org
December			
2-6	47th Annual Meeting of the American Society of Hematology	San Diego California USA	American Society of Haematology 1900 M street NW Suite 200 Washington DC 20036 USA Tel: +1 20 2776 0544 Email: meetings@hematology.org Web: www.hematology.org
6-10	28th Annual San Antonio Breast Cancer Symposium	San Antonio USA	San Antonio Breast Cancer Symposium c/o San Antonio Cancer Institute 7979 Wurzbach Rd Suite U-531 San Antonio Texas 78229 USA Tel: +1 210 616 5912 Fax: +1 210 949 5009 Email: RMarkow@ctrc.net Web: www.sabcs.org
8-10	12th Hong Kong International Cancer and Congress & 2nd Annual Meeting of Research Centre of Cancer	Pokfulam Hong Kong	Congress Secretariat, Department of Surgery University of Hong Kong Medical Centre, Queen Mary Hospital Tel: +852 2818 0232 Fax: +852 2818 1186 Email: hkicc@khu.hk Web: www.hkicc.org
10-14	American Society for Cell Biology (ASCD): 45th Annual Meeting	San Francisco USA	American Society for Cell Biology (ASCB) 8120 Woodmont Avenue Suite 750 Bethesda MD 20814-2755 USA Tel: +1 301 347 9300 Fax: +1 301 347 9310 Email: ascbinfo@ascb.org

THE CANCER COUNCIL AUSTRALIA

The Cancer Council Australia is the peak national 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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CLINICAL ONCOLOGICAL SOCIETY OF AUSTRALIA INC

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

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

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

Membership fees for 2005

Ordinary Members: $140
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(includes GST)

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