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The last 50 years have seen major changes in cancer management. There have been great advances in prevention, early diagnosis and cost effective management with much emphasis on “holistic” care involving multidisciplinary teams with a commitment to the best possible care for all phases of cancer management including terminal care. Underpinning these developments has been a major emphasis on understanding community and social causes of cancer, based on epidemiology and psycho-sociology. These advances have led to the current mantra that the best possible cancer care is evidence-based medicine, built on sound clinical trials and good quality statistical evaluation. Many talented and dedicated clinicians have had major roles in these developments. High on this list is Alan Coates. Medical oncologist, statistician and clinical researcher, Alan has played leading roles in clinical management, clinical trials and administrative excellence in two major cancer fields, melanoma and breast cancer. In 2002, Alan was awarded membership to the Order of Australia for “services to medicine in the field of oncology, and particularly through breast cancer research”.

In 1978 Alan came to the Sydney Melanoma Unit (SMU) from the Ludwig Institute for Cancer Research and the Walter and Eliza Hall Institute, at age 36, already with an enviable reputation for diligence, competence and commitment, both as a clinician and a clinical researcher. He immediately impressed his colleagues, especially Gerry Milton and myself, with his emphasis on properly designed clinical trials, rather than the more ‘ad hoc’ approach current in those days. There is no doubt that Alan, who subsequently became research director of the SMU, played a major role in the worldwide reputation gained by the SMU research program during his years with the unit. Woe betide the clinician or researcher who made a ‘seat of the pants’ assessment of a clinical or research problem in Alan’s presence.

During his years with SMU, Alan found time to make major contributions to cancer research and clinical care generally as president of Clinical Oncological Society of Australia, director and deputy chairman of the Australia New Zealand Breast Cancer Trials Group and internationally, as the first elected non-US oncologist member of the American Society of Clinical Oncology. Of course, there were numerous memberships of Health Department committees, oncology groups and the National Health and Medical Research Council. More than 200 papers published in peer-reviewed journals attest to Alan’s research and clinical trial productivity.

No record of Alan’s contributions would be complete without acknowledgment of his excellence as a cancer clinician. His patients and nurses are effusive about his clinical care and commitment to management of the difficult problems facing oncologists dealing with advanced cancer. “Calm”, “reasoned”, “unflappable” with a fine sense of humour are some of the comments of his patients.

Alan’s retirement from The Cancer Council Australia marks the end of yet another chapter in a brilliant career. His achievements in furthering the cause of cancer control as head of the nation’s peak independent cancer organisation are too extensive to list here. I have no doubt Alan will continue to make a significant impact on cancer control through his ongoing contribution to research and academia.
Upon Alan Coates’ retirement after eight years as Chief Executive Officer (CEO) of The Cancer Council Australia we have the honor to dedicate this issue of Cancer Forum to an acknowledgement of the achievements and contributions of one of Australia’s foremost figures in cancer research, management and advocacy.

In this Forum, a number of Australia’s leading oncologists and researchers discuss the work and impact of a man who has not only contributed greatly to cancer care in Australia, but has also inspired others pursuing similar goals, an ability Alan has demonstrated throughout his career with The Cancer Council Australia and internationally with the International Union Against Cancer, a consistent interest in improving cancer control for Australian Indigenous communities and has helped over the last few years to develop strategies whereby The Cancer Council can assist with cancer control policies for those countries within the region who seek assistance.

Alan’s emphasis on properly designed clinical trials is renowned. In his article describing the Australia New Zealand Breast Cancer Trials Group’s (ANZ BCTG) contributions to reducing breast cancer mortality John Forbes acknowledges Alan’s leadership in the ANZ BCTG and in the development of “evidence-based medicine” for management of breast cancer. Alan was a member of the group of researchers who formed the Ludwig Breast Cancer Study Group, based in Melbourne. This group evolved into the ANZ BCTG, heralding what Forbes describes as a “new era of clinical trials”. Alan was then, and has remained, one of the profession’s most vocal advocates for clinical trials.

While CEO of The Cancer Council, Alan and former President Ray Lowenthal initiated efforts to increase clinical trial participation (by professionals and patients) and lobbied for increased government funding for infrastructure support for independent trial groups. He has been instrumental in bringing all of the existing cancer cooperative groups together, through the Clinical Oncological Society of Australia (COSA) and The Cancer Council, in response to the Federal Government’s commitment to supporting clinical trials and the successful COSA enabling grant.

Sue Pendlebury discusses Alan’s career in the context of the resurgence of adjuvant radiotherapy for breast cancer. Pendlebury notes that Alan’s emphasis on properly designed clinical trials is a “challenge for all oncologists. In a tribute to his father’s “cross-disciplinary vision”, Andrew Coates illustrates the potential benefits to be gained from this collaboration of disciplines – in this case, the combination of radiography and geography to challenge commonly held perceptions about draining node fields and consequently improve the information available to surgeons. As Coates notes, the primary lesson is to “step back from the minutiae and look about for others pursuing similar goals”, an ability Alan has demonstrated in his dedication to multidisciplinary care (before the term had entered common parlance) and to increasing alliances and collaboration while at the helm of The Cancer Council.

Ian Tannock questions whether the increasing commonness of PSA testing is in fact “progress” in cancer management, apart from effectively curing prostate cancer. Toronto-based Tannock argues for the need to develop and promote research that more accurately reflects patient preferences and public values. Tannock questions the current use of PSA screening and states that solving the problem of prostate cancer burden requires new research into the effects of screening.
When in 1998 Professor Alan Coates accepted appointment as the first full-time CEO of the Australian Cancer Society (ACS) – soon to be renamed The Cancer Council Australia – it was a gamble on both parts. The appointment followed a strategic review carried out by the ACS which desired to strengthen the role of the national organisation. Alan came from a background as a respected scientist; but he understood scientific knowledge clearly was going to be only one requirement of a job that would demand skills of many orders. He was untested, for example, in high politics and financial management. Although he had an impressive track record of publication in peer-reviewed technical journals, his on-the-job experience was largely on the topic of cancer management rather than prevention, whereas the role of The Cancer Council would be a major act of a national cancer organisation. And from Alan’s perspective, there must have been concern that the demands of the position would stifle, if not suppress completely, the opportunity to continue to contribute to oncological knowledge through scientific publication.

Fortunately any reservations the appointments committee may have had were quickly quelled. Under Alan, the ACS swiftly almost at once became recognised as Australia’s peak non-government cancer control organisation. What had been an efficient and well-run secretariat soon became noticed by the Federal Government. The ACS became a primary cancer control organisation, influencing and guiding national cancer control policy and action. His rare combination of intellectual, clinical knowledge, leadership, skillful advocacy and diplomacy has greatly contributed to reducing the burden of cancer.

The defined mission of the ACS/The Cancer Council was and is “to lead in the development and promotion of national cancer control policy”. This was to be achieved through advocacy, alliances and member services, and these were headings Alan used to report his activities to The Cancer Council Board. (In this context ‘members’ are the state and territory cancer organisations, that was only known as The Cancer Council of each jurisdiction.) Let us see how his achievements stack up against these yardsticks.

Development of national cancer control policy

There is an ‘alphabet soup’ of organisations involved in cancer policy in Australia: government, non-government and mixed. A short list included ACN (Australian Cancer Network), COSA (Cancer Oncological Society of Australia), NCCI (National Cancer Control Initiative), NHPPAC (National Health Priorities Action Council), CSS (Cancer Strategies Group) and NBCC (National Breast Cancer Centre). One of Alan’s regular party tricks was to produce a slide purporting to demonstrate the relationship between these organisations. Even after having seen the presentation several times I cannot say that I am much the wiser. That Alan was able effectively to steer his way through this maze and use this knowledge to further the cancer control cause is a triumph of his intellect.

Illustrative of the way in which policy development within The Cancer Council has had a major influence on government has been the area of tobacco control. Australia now leads the OECD in tobacco control, in part through Federal Government reforms over the past eight years initiated through liaison with The Cancer Council. The introduction in March 2006 of stark pictures on tobacco packs illustrating the adverse medical consequences of tobacco use, albeit not as potentially effective as a plain pack model, The Cancer Council of Australia proposed, came about through representations over many years. Of course Alan and The Cancer Council Australia did not achieve this alone, however he spearheaded a grand coalition and was unrelenting in his efforts. As in everything he does, his advocacy was backed by an all-inclusive knowledge of the facts. Constantly he repeated to politicians the unequivocal evidence that if one aims to reduce the impact of cancer, the biggest ‘bang for the buck’ comes from tobacco control. These advocacy efforts are now well and truly bearing fruit.

Arguably the single most influential policy document produced by The Cancer Council and allies is the 2003 publication Optimising Cancer Care in Australia.1 This is a carefully crafted, evidence-based work that has had and will have an impact on cancer policy in Australia. Its publication over the development of government policies at both state and federal levels. There is no other work like it and it provides an independent source of information that is immediately available to the public and government. The Cancer Council had to convince governments of the need for reform to enhance the treatment and care of people affected by cancer in this country. Another publication that has greatly influenced public policy for the better is Cancer in Australia: A National Cancer Control Report. That was held at The Cancer Council Australia’s initiative. It highlighted the inequalities suffered by cancer patients residing in Australia’s rural and remote communities and their need for specialised care was made pointedly self-evident. The specific cancer control needs of Australia’s Indigenous populations got the spotlight too, following a 2004 workshop convened by The Cancer Council.

Publication of two revisions (2001-2003 and 2004-2006) of The Cancer Council of Australia’s National Cancer Prevention Policy, the only comprehensive guide to effective measures for preventing cancer in Australia, also occurred during Alan’s term. The Australian Cancer Network, an organisation supported by The Cancer Council Australia – which was and is to continue to be superbly steered by Emeritus Professor Tom Reeve AC CBE – has produced a number of highly influential Clinical Practice Guidelines.2 The aim is to guide clinical behaviour to minimise unjustified variability, between recommendation arising from different specialists or different geographical locations. Although initially some clinicians were fearful that these guidelines would stifle their decision-making, they have now found that these guidelines give the evidence base that underlies what is best for their patients, in fact the opposite has proved to be the case. Guideline development has been shown to enhance cancer control policy-making. Overall there is little doubt they have contributed significantly to improving the survival state of cancer patients, which are among the best in the world. Alan, through his work in this sphere, has shown how a clinician can influence more widespread treatment procedures in oneself and one’s immediate colleagues, to the benefit of thousands of cancer patients.

During his term Alan met a succession of federal Ministers for Health and their opposition counterparts, as well as the health spokespersons for the minor parties, most of them on several occasions. Through Alan’s efforts, this direct interface was and is maintained by representation on many government forums and by influential submissions made to numerous government inquiries. Alan is a prime example of an independent authoritative voice in the Health Priority Area. Alan proved to have a high degree of political astuteness which had not been apparent in his previous employment, but which met the hopes of those who appointed him. From a clinician’s perspective, the recent decision of the Federal Government to follow persistent lobbying – to actively support the independent cancer clinical trials organisations was an enormous step forward. To illustrate Alan’s overall success, one can, perhaps unfairly, congregate eight years of effort into a single set of figures from 1998 to 2005, in which the Federal Government invested its four-year cancer-specific funding from $8 million to $189 million. Although The Cancer Council did not act alone in bringing about the Federal Government’s role, the link was evident. The specific cancer control needs of Australia’s Indigenous populations got the spotlight too, following a 2004 workshop convened by The Cancer Council. The Australian Cancer Network, an organisation supported by The Cancer Council Australia – which was and is to continue to be superbly steered by Emeritus Professor Tom Reeve AC CBE – has produced a number of highly influential Clinical Practice Guidelines. The aim is to guide clinical behaviour to minimise unjustified variability, between recommendation arising from different specialists or different geographical locations. Although initially some clinicians were fearful that these guidelines would stifle their decision-making, they have now found that these guidelines give the evidence base that underlies what is best for their patients, in fact the opposite has proved to be the case. Guideline development has been shown to enhance cancer control policy-making. Overall there is little doubt they have contributed significantly to improving the survival state of cancer patients, which are among the best in the world. Alan, through his work in this sphere, has shown how a clinician can influence more widespread treatment procedures in oneself and one’s immediate colleagues, to the benefit of thousands of cancer patients.
Pharmaceutical Benefits Advisory Committee to add a special category of Pharmaceutical Benefits Service listing to palliative care medications that enabled people with cancer to remain at home.

Alliances
Any advocacy organisation is more effective if it is able to forge alliances with bodies of like mind. Internal contradictions must be avoided at all costs. Thus the first hurdle faced by the new CEO was to gain the confidence of the ACS’s members, the state and territory Cancer Councils, and that of the Clinical Oncological Society of Australia (COSA). With COSA there was never any serious disagreement. As a new place to have a seat at the table was certainly initial challenge, as is the case of position in the relationship with some of the state and territory bodies, but ultimately unity of purpose was achieved within the organisation.

Collaboration with government occurred at many levels. Probably the most significant was that which resulted in the National Cancer Control Initiative, ably headed by Professor Mark Elwood. Alan was an advisor for its establishment and management. He has also chaired the National Cancer Strategies Group, Australia’s only multi-jurisdictional government cancer advisory body, and has contributed significantly to its work. In influencing government policy, alliances with other non-government bodies are vital. Among many, one could perhaps single out the setting up of the Australian Chronic Disease Alliance as a particularly important step.

Alan has strongly fostered The Cancer Council Australia’s international collaborations including support for the International Union Against Cancer (UICC). He was invited to be among the first signatories to the Charter of Paris Against Cancer, an international charter of cancer control. His leadership role with the American Society of Clinical Oncology, the world’s premier clinical cancer organisation, was strengthened when Alan was elected as the American member of its Board of Directors, a tribute to his international reputation.

All this was done in a way that enhanced rather than submerged the standing and independence of The Cancer Council. Indeed, the leadership role of The Cancer Council was greatly reinforced by these activities.

Member services
In Australia, community cancer organisations commenced separately in each state and federal collaboration came later. This history resulted in each state initially having its own identity. Some organisations with long-established local recognition had understandable reservations about change, but ultimately the greater value of a single Australia-wide outer shell became apparent. Along with this came the evolution of the national organisation from a secretariat to an umbrella body through which interchange of staff and ideas encouraged best national practice. Cohesive, national coordination of The Cancer Council continued to provide worthwhile worth with more than the sum of its parts. Among other benefits is an enhanced capacity to engage national corporate partners, due to a preference to deal with a single national agency, resulting in much increased sponsorship revenue.

Summary
In a short article one can select only a few of Alan’s many activities and successes from a very long list. Those who have worked closely with him, as I have, are in awe of his intellect, stamina, perspicacity, determination and resilience (both mental and physical). As the inaugural CEO, he has set a very high bar. His contribution to reducing the burden and impact of cancer in this country will be felt for many years to come.

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“Know Your PSA”: Not Always Good Advice

Ian F Tannock: Princess Margaret Hospital and University of Toronto, Canada
Email: ian.tannock@uhn.on.ca

Abstract
Men over the age of 50 are often advised to “know their PSA”, with the implicit assumption that screening for prostate cancer is effective in reducing morbidity and/or mortality. Likewise men who have received local therapy for prostate cancer routinely undergo repeated evaluation of their serum prostate specific antigen (PSA) in order to detect recurrence of disease. Indeed, there is strong evidence that PSA improves the ability to detect recurrent cancer when used in screening of older men or to detect recurrence of disease. In contrast, there is substantial evidence that knowledge of a raised serum PSA causes substantial anxiety and distress in men that not only may be harmful for them, but also in their families who have to cope with the emotional distress.

"Know your PSA” is a slogan used by prostate cancer advocates whose laudable goal is to decrease the mortality and morbidity due to prostate cancer. The statement implies benefit from PSA screening and the American Cancer Society, recommend that all men older than 50 with reasonable life expectancy, should have their serum PSA examined. Many urologists have advocated for this approach, and have been supported by evidence that the use of PSA screening has improved survival for those with clinically-detected early prostate cancer in the pre-PSA era.1,2 A Scandinavian randomised trial has shown an improvement in prostate cancer specific and overall survival at 10 years for those with clinically-detected early prostate cancer treated by prostatectomy compared to a conservative approach, but the effect is small and confined to men <65 years old.3 Even if similar benefit applied to those with screen-detected cancer, which is unlikely, the number of prostatectomies needed to save one life at 10 years would be about 20. That is a large number of men undergoing the substantial side-effects of local treatment, to ‘save’ one life, and ‘save’ is a relative term because curing prostate cancer does not buy immortality. While many men may function well after local treatment, comparison of reported side-effects of patients with those of urologists and radiotherapists tell somewhat different stories. Self-reporting by patients indicates that some degree of urinary leakage is prevalent after prostatectomy, of bowel dysfunction after radiotherapy, and that many men become functionally impotent within two years after either treatment – nerve-sparing or not.4 As Talcott has stated: “two things are certain: when screening produces a diagnosis of prostate cancer, the result is permanent sexual, urinary or bowel dysfunction much more often than a cancer death averted; and extending screening to younger patients or lowering the threshold for biopsy will tilt the balance ever more steeply toward harm.”

Large trials of PSA screening are underway, although they are threatened by contamination whereby men in the control arm obtain screening outside of the study. However, even if these very expensive studies can be completed, I don’t think we will have convincing information about the value or not of PSA screening. This is because for practical limits on sample size, their primary endpoint is death due to prostate cancer – whereas what is more important is death due to any cause. Screening is not a totally benign procedure. While an ultrasonic-directed needle biopsy of the prostate has a low chance of complications, if you biopsy a large number of men, and those who are diagnosed and treated have only a small gain in long-term survival, those complications can easily outweigh the benefit. Black et al.5 have reported no trends to improve all-cause mortality in cancer screening trials, although the power of studies to detect significant changes in all-cause mortality is limited. They defined some biases that might account for this – including ‘slippery-linkage bias, where the cause of death is reported as unrelated to screening. However, if you stick enough needles into people then there has to be bleeds or infection and a consequent death a few months later from pulmonary embolism is likely to be reported as unrelated.”

I am equally unconvinced of the value of PSA testing in men who have completed local treatment for...
prostate cancer. Certainly men who have undergone prostatectomy or radiotherapy show a substantial rate of relapse of prostate cancer and PSA testing can announce the failure of that prior treatment long before such men develop symptoms due to the disease. Most series the mean interval from rise in PSA to first symptom of disease (other than anxiety due to the PSA itself) is in the range of 5-10 years and in one large series median survival had not been reached at 15 years following the first detectable PSA after radical prostatectomy. Serum PSA is measured routinely after local treatment but the problem is what to do if it is rising. There is no randomised evidence to indicate that treatment of such men improves their survival – and long-term hormonal treatment conveys substantial morbidity including loss of bone and muscle, anaemia and perhaps cognitive change. There is a reason that athletes are tempted to take androgens! It has been argued that radiotherapy given to men with detectable PSA after prostatectomy represents the only chance of cure. While that may be true, retrospective studies have shown that most those likely to benefit had a low Gleason score and a long PSA doubling time – properties which also identify those who may never develop symptoms due to disease.

Then there are the asymptomatic men whose prostate cancer was treated conservatively, with observation or hormones, as well as those with metastatic disease that was either silent or became so after androgen ablation therapy. If these men are well and without symptoms, are we really helped by knowing that their PSA is rising? While a British Medical Research Council trial that compared early with later hormonal therapy did suggest a benefit for those with disease that was evident, most series the trial had substantial flaws. I know of no reliable evidence that early treatment will improve their survival, and it is wrong to wait until symptoms start to occur, and certainly you cannot improve the quality of life of an asymptomatic man by treating him. You can however, make it worse by telling him that his PSA is rising – PSA dysia or PSAitis – anxiety about PSA, is a major problem for patients who are otherwise without symptoms.

There are occasions when knowledge of serum PSA might be a useful guide to therapy, such as for those with symptomatic metastatic disease who are receiving chemotherapy, or other treatment – although even here improvement in pain or other symptoms may be an equal and more relevant guide to continuing or stopping therapy. For those involved in developing new treatments, including biological agents, PSA response or PSA progression are useful endpoints in clinical trials, but they are probably helping the investigator more than the individual patient.

The first studies of the relationship between presence of prostate cancer and the serum level of PSA appeared in 1983.3 PSA is the only symptom that is caused by their prostate cancer. Others who have been screened and treated, or who are given hormonal therapy or radiotherapy after “biochemical recurrence” following radical prostatectomy, have symptoms from treatment that was given as a direct result of measurement of their serum PSA. Asymptomatic prostate cancer used to be a very common (non)-disease. Now it has become rare – replaced by a huge increase in symptomatic prostate cancer. A large number of men who 20 years ago would have had asymptomatic prostate cancer now have impaired quality of life because they are consumed by anxiety about their PSA. Such is progress.

References


Abstraction

In the early 20th Century, excision of all primary melanomas with <1cm clearance margins was recommended, with amputation in selected cases – recommendations based on experience of a few patients with locally advanced disease. More recently, randomised trials showed that even thick (>4mm) primary melanomas require no more than 2-3cm clearance and thin (<1mmm) and intermediate thickness (1-4mm) melanomas no more than 1-2cm margins to achieve good local control with no adverse effect on survival. The management of regional lymph nodes has also changed on the basis of clinical trial results. Elective node dissection, formerly regarded as necessary, has been abandoned. Today, most patients with intermediate thickness melanomas are offered a “sentinel” node biopsy procedure, with node dissection only if the sentinel node is positive. Sentinel node biopsy provides the most accurate and staging information currently available and achieves good local control of regional node disease. It may also confer a survival benefit in patients who are node positive but long-term results of clinical trials are awaited to confirm this.

In the great majority of patients who present with thin primary melanomas, even sentinel node biopsy is generally not appropriate.

Surgical management of melanoma: have we made any progress in 100 years?

John F Thompson and Helen M Shaw
Sydney Medical School Cancer Centre, Royal Prince Alfred Hospital and The University of Sydney, NSW
Email: thompson@smu.org.au

Abstract

In the early 20th Century, excision of all primary melanomas with <1cm clearance margins was recommended, with amputation in selected cases – recommendations based on experience of a few patients with locally advanced disease. More recently, randomised trials showed that even thick (>4mm) primary melanomas require no more than 2-3cm clearance and thin (<1mmm) and intermediate thickness (1-4mm) melanomas no more than 1-2cm margins to achieve good local control with no adverse effect on survival. The management of regional lymph nodes has also changed on the basis of clinical trial results. Elective node dissection, formerly regarded as necessary, has been abandoned. Today, most patients with intermediate thickness melanomas are offered a “sentinel” node biopsy procedure, with node dissection only if the sentinel node is positive. Sentinel node biopsy provides the most accurate and staging information currently available and achieves good local control of regional node disease. It may also confer a survival benefit in patients who are node positive but long-term results of clinical trials are awaited to confirm this.

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Treatment of the primary melanoma

In 1907, William Sampson Handley 1 reported pathways along lymphatics and demonstrated centrifugal lymphatic permeation – all based on a single autopsy examination of a patient with very advanced melanoma. On the basis of this slender evidence, he recommended excision of lymph nodes to the local oncologist. 2 This proposal however, was replaced by a better defined, evidence-based policy of more limited local treatment. This change occurred primarily in response to a changing pattern of disease presentation, when it became apparent that these deforming operations did not enhance survival. In most countries the great majority of patients now present with tumours <1mm thick, rendering irrelevant the radical historical approaches for locally advanced melanoma. Two of the most recent prospective randomised trials, from France 3 and Sweden, 4 have provided further conclusive evidence that margins >2cm are generally unnecessary, even for tumours >2cm in thickness. It is currently accepted that a margin of 5mm for in situ tumours, 1 cm for all tumours ≤1mm thick and 1-2cm for all melanomas is appropriate.

Treatment of regional lymph nodes

In his 1908 report, Pringle also emphasised that, where feasible, wide excision should be performed in continuity with regional lymph node dissection. 5 This proposal established the basis of regional lymph node treatment for 60 years. The policy was founded on the earlier premise by Snow 6 that metastatic melanoma progressed sequentially from primary site to regional lymph nodes. Eventually, however, the results of a number of major studies cast doubt on the value of elective lymph node dissection.
node dissection (ELND) for all patients with higher-risk tumours. Some earlier randomised but poorly stratified trials undertaken by the World Health Organization (WHO) Melanoma Program10 and North American groups11 failed to demonstrate an overall survival benefit for all patients with higher-risk tumours. These and several early non-randomised studies were widely criticised, mainly because of the failure to stratify by thickness, disproportions in gender and primary tumour site and failure to accurately identify the correct regional node field for dissection. Sappey in 187412 had categorically stated that lymphatic drainage never crossed the midline. He later modified this to exclude sites within 5 cm of the trunk, drainage was quite diverse and unpredictable. It was shown that up to 30 % of patients may have had inappropriate node field dissections when clinical prediction of the path of lymphatic spread was used to select the dissection field. Later, more carefully stratified randomised trials, the Intergroup Melanoma Surgical Trial13 and the WHO Melanoma Program Trial14 in which either blue dye or radio-colloid tracers were used to map the draining fields, found by multivariate analysis that routine ELND had no impact on overall survival. However, in the intergroup trial, a small survival benefit emerged for patients 60 years of age or under. In the WHO trial, patients whose regional nodes became clinically and histologically positive during follow-up had the poorest prognosis. The principal criticism of this latter trial was that the sample size did not allow stratification by thickness, mainly because of the failure to stratify thickness, disproportions in gender and primary tumour site and failure to accurately identify the correct regional node field for dissection. The results were remarkably similar to those that had been obtained by Morton and his colleagues. Although there had initially been great scepticism, the technique was soon taken up by major melanoma treatment centres internationally. The unanswered question however, has been whether SN-positive and those who are SN-negative. A recent update of an earlier SMU experience28 has shown that in 1815 patients who were SN-negative the five-year survival rate was 89 %, while in 356 patients who were SN-positive the five-year survival rate was 58 % (Figure 2).

Lymphatic mapping and selective "sentinel" lymph node biopsy

At a meeting of the Society of Surgical Oncology in 1990, Dr Donald Morton of the John Wayne Cancer Institute in Santa Monica suggested that it was possible to determine the status of regional lymph nodes in patients with melanoma by performing a minimally invasive procedure that has subsequently become known as SN biopsy.15 Morton proposed that lymph draining from a primary tumour site, and potentially containing melanoma cells, drains first to a "sentinel" node before passing on to other nodes in the regional node field. He stated that it was possible to identify a SN with confidence by injecting vital blue dye at the primary melanoma site and tracing blue-stained lymphatics to the regional node field. Here, the SN (or SNs) would be blue-stained and therefore able to be identified. According to this proposal, the SN is the node most likely to contain tumour cells. If no tumour cells are present in this node, none should be present in other nodes in the node field. The publication outlining this proposal by Morton, his pathology colleague Dr Alistair Cochran and others was eventually published in 1992.17 The paper is now a citation classic, having previously been rejected by several major surgical journals. In this report it was emphasised that the minimally invasive SN biopsy procedure would allow full regional node dissection to be avoided in approximately 80% of patients with intermediate thickness melanomas because they had negative SNs. Confirmation of the accuracy of SN biopsy in identifying patients with metastatic disease in regional lymph nodes was quickly provided by studies undertaken in the United States4 and Australia.18 Both these studies involved SN biopsy with immediate complete lymph node dissection, so that all the remaining nodes in the node field could be examined. The results were remarkably similar to those that had been obtained by Morton and his colleagues. Although there had initially been great scepticism, the technique was soon taken up around the world and is now a routine procedure in most major melanoma treatment centres internationally. As already indicated, the initial studies reported by Morton's group involved only intradermal vital blue dye injection at the primary melanoma site. It was soon found however, that preoperative lymphoscintigraphy, involving injection of a radio-labelled colloid at the primary melanoma site, provided valuable information preoperatively. It also made the SN biopsy procedure easier, quicker and more accurate when a hand-held gamma probe was used intraoperatively to assist in location of the SNs. It has since become clear that SN identification is most accurate if all three methods are used – a preoperative lymphoscintigrarn, blue dye mapping and the use of a hand-held gamma probe intraoperatively. The Sydney Melanoma Unit (SMU) has made important contributions in improving our understanding of cutaneous lymphatic drainage pathways. This has been based on preoperative lymphoscintigraphy performed in large numbers of patients.20, 21 Several major studies have now shown that SN status provides the most accurate prognostic information currently available.22-26 There is a large difference in five year disease-specific survival for patients who are SN-positive and those who are SN-negative. A recent update of an earlier SMU experience28 has shown that in 1815 patients who were SN-negative the five-year survival rate was 89 %, while in 356 patients who are SN-positive the five-year survival rate was 58 % (Figure 2). The unanswered question however, has been whether early complete regional lymphadenectomy, performed in patients who are SN-positive, improves survival outcome. Results of a large international study, the first Multicenter Selective Lymphadenectomy Trial (MSTL-I),26, 27 have recently been reported at an international meeting and a paper documenting the outcome of this trial was submitted for publication in mid-February 2006. The MSTL-I results indicate

**Figure 1**

**Figure 2**

SN-negative patients (n=1815)

SN-positive patients (n=356)
that there is no significant overall survival advantage benefit for nodes with intermediate thickness melanomas randomized to receive wide excision of their primary melanoma together with SN biopsy and those having wide excision alone. However, patients who were SN-positive had a significantly better survival outcome if they have an immediate complete lymphadenectomy, than patients who are observed and who have a full regional lymphadenectomy when metastatic disease becomes clinically apparent. This result is consistent with the previous WHO Melanoma Program elective node dissection study mentioned earlier (see Figure 1). The publication of the full MSLT-I results is awaited with great interest. The morbidity of the SN biopsy is low and the suggestion that performing an SN biopsy may increase the rate of intranodal metastasis has been convincingly disproved by four large retrospective studies from the MD Anderson Cancer Center, the John Wayne Cancer Institute and the SMU,11,12 and most recently by the MSLT-I results.13

The next important question to be answered is whether all patients who are found to be SN-positive require a complete regional node field clearance. It is likely that only 15-20% of patients could possibly benefit, since this is the proportion who have additional (i.e., non-SN) metastases in their regional nodes. A second international multicentre trial (MSLT-II), designed to answer this question, commenced patient accrual in late 2001. In this trial patients who are found to be SN-positive are randomised to have an immediate complete node dissection (currently the standard treatment recommendation), or to be observed with regular ultrasound examination of the remaining nodes in the event that metastasis in the first dissection occurs at a late date if metastatic disease becomes apparent.

**Present role of sentinel node assessment**

At the third planned interim analysis of the first MSLT-I, no overall survival benefit was demonstrated for patients with intermediate thickness melanomas who had a SN biopsy procedure. When the results in SN-negative and SN-positive patients were analysed and compared with patients who did not have a SN biopsy procedure, it was found that patients who remained node negative did not benefit from having a SN biopsy, but those who were node positive benefited from early node dissection. There is a statistical difficulty with the MSLT-I results, since it was clearly not possible to pre-randomise SN-negative and SN-positive patients. However, after a median follow-up of almost five years, the proportion of patients found to be SN-positive was almost identical to the proportion of patients in the wide excision only group who subsequently developed clinically apparent disease in their regional node field. This strongly suggests that most if not all patients with a positive SN will ultimately develop clinically apparent nodal disease if early nodal intervention is not undertaken.

**Minimal invasive and non-invasive SN assessment**

Although the morbidity of SN biopsy is low, it involves a surgical procedure with an associated inconvenience and cost. Efforts are therefore being made to assess SNs in minimally invasive or non-invasive ways. It has already been shown that examination of fine needle aspirates from SNs using magnetic resonance spectroscopy (MRS) can provide a reliable indication of SN status.13,30 SNs containing metastatic melanoma produce spectra with characteristic peaks of taurine, cholino and other metabolites that are not present in nodes not containing melanoma. The ultimate objective is to perform completely non-invasive in vivo assessment of SNs using MRS with surface coils.40

**The role of surgery for apparently isolated regional lymph nodes**

It has been known for many decades that local melanoma recurrences and intranodal metastases are best treated by surgical excision. Some patients treated in this way are apparently cured by the procedure. It is also believed that surgery is the most effective form of treatment for macroscopic disease in lymph nodes. Long-term survival in excess of 50% can be achieved in some such patients. More controversial is the role of surgery in the treatment of patients with metastases in internal organs. Five-year survival rates of up to 40% have been reported after complete resection of gastrointestinal metastases13,34 and five-year survival rates exceeding 20% after complete resection of lung metastases.35 The difficulty with these studies is that they report the results obtained in highly selected groups of patients and it would be very difficult to undertake large scale randomised trials. Nevertheless, there does appear to be the possibility of cure for some patients with systemic melanoma metastasis when complete surgical resection of those metastases can be achieved.

**Summary and conclusions**

Substantial progress has been made over the last 100 years in defining appropriate surgical management protocols for patients with melanoma. Desirable excision margins have been determined on the basis of randomised clinical trials and progress is being made towards defining rational management of regional lymph nodes, also on the basis of well-designed clinical trials. In the absence of reliably effective non-surgical therapies for melanoma however, continuing efforts to find ways of further improving surgical outcomes are required.

**References**


Mapping has been part of the discipline of epidemiology for some time now. The genesis of the modern discipline of Geographic Information Systems (GIS) can be traced back to the work done in London in 1854 by John Snow, where the location of cholera cases was plotted on a map with pins and the proximity to various drinking water wells calculated. This led to the identification of one of the wells as being contaminated and the removal of the handle of that pump so that the epidemic was contained. More recently, the spread of diseases has been modelled using sophisticated mathematical algorithms and visualised with advanced computational and graphical techniques. Both of these examples of work on a scale beyond that of the single human. Applications of the numerical techniques used by geographers to the human body have been limited.

### Geographic information systems

Rhind (2005) defines Geographic information systems as follows:

> "Geographic information systems (GIS) are a means of storing, integrating, analysing and presenting geographic data. A typical GIS consists of a combination of computers, databases and software capable of processing and presenting different thematic data with reference to a single geographic framework. Each thematic data layer is a data layer that is linked geographically to other data layers through geographical relationships. GIS can be used to project combinations of geographical interrelationships of the various data layers onto a single map. Conversely, input from the map can be used to create the overall matrix and considered individually. GIS can provide insights into complex relationships not easily studied or observed by other means."

The key point here is that the data are geographic, that is where a location is related to some coordinate system and can be compared with other data located in the same coordinate system. The term geographic can sometimes be confusing in that it implies that the coordinate system is terrestrial (or, occasionally, extraterrestrial, such as the GIS showing the surface of the moon and data about the various missions there). This is not the case. The data merely need to have some coordinate system in common. This system can be a common system, for example latitude and longitude or a local coordinate system like Universal Transverse Mercator. But it may also be an arbitrary system for locating data that only makes sense in the context of that data. A generalised schematic representation of the body is an example of this and as long as the same schematic representation of the body is used for all layers of data, relationships between the data can be studied, analysed and presented.

### Lymphoscintigraphy

Lymphoscintigraphy is a technique whereby the path from the site of the primary lesion of a melanoma through the lymphatic system to the draining node field can be recorded. This is achieved by injection of the radiopharmaceutical Tc-99m-sulphur colloid around the biopsy excision site or primary lesion. Images of the tracer moving through the lymphatic system are captured using a digital gamma camera and enhanced to ensure that even the faintest channels are detected. Once the channels have been defined, they are marked on the skin of the patient by the physician for use by the surgeon. In addition to the lymph node fields (nodes along the channel but not in the lymph node fields) and sentinel nodes (the nodes to which the lesion directly drains) are also detected and marked.

This technique allows draining node fields to be accurately sampled for the presence of metastases with the minimum of surgery. It also ensures that all relevant material is removed, even if the paths taken through the system or the draining node fields themselves are different from those predicted by traditional methods.

Traditional medical concepts of lymph node drainage paths date back to 1843 when Sappey injected cadavers with mercury to trace the paths taken through the lymphatic system from various points on the body (Sappey 1843 cited in Uren et al. (1993)). Lymphoscintigraphy has shown these concepts to be incorrect in a large proportion of patients.

### Mapping the primary lesions and their draining nodes

The primary lesions and their draining node fields allows the researcher to quantify the divergence of paths actually taken compared to those predicted by Sappey and analysis of the factors influencing such divergence. Plots of all primary lesions draining to a particular node field can be used to establish the general pattern of distribution. With the addition of colour, it can be shown that the rather arbitrary lines traditionally used to delineate watershed boundaries in the lymphatic system are much less precise than was formerly thought.

### Mapping the human body – an example of cross-disciplinary science

The results of this technique, which was performed on over 1000 patients, were recorded in a spreadsheet and then transferred on to schematic maps of the body using a GIS (ArcView®). The images were used to examine some of the commonly held perceptions about the node fields to which lesions on various parts of the body drain. We have found using lymphoscintigraphy that the traditional concepts of lymphatic drainage in the skin proved to be incorrect in a large proportion of the patients. Displaying the information using the images produced by the GIS was a simple and effective way of illustrating this.

As a by-product of this research, a software application was developed which allows the physician performing the lymphoscintigraphy to enter the data for a particular patient and produce a formatted schematic for subsequent use by the surgeon. The schematic displays the primary lesion site and depth and number of sentinel nodes in each node field. This schematic diagram can be kept as a permanent record of the lymphatic drainage pattern for each patient.

### Day-to-day application – schematic visualisation

An application was developed which allows the physician carrying out lymphoscintigraphy to record the details of the patient and the results of the investigation. The location of the primary lesion is recorded as a map number and x and y coordinates on that map. The draining node fields are recorded as codes showing the depth and number of sentinel nodes. For example 1.5la2 indicates that the left axilla field contains two sentinel nodes at a depth of 1.5cm. The name and sex of the patient, as well as the number of draining channels and the maximum separation between the channels are also recorded. There is provision for noting details of surgery performed immediately or as follow-up.

The primary storage of the data is currently in an Excel spreadsheet. This communicates with the GIS via DDE (in Windows) or AppleTalk (on the final target system) and passes a script a list of the data for display in a report. The script processes the data and prints out a report based on it. This report can be sent to the surgeon and is also stored on the patient’s file.

### Research – challenging Sappey’s lines

Over 1000 patients have undergone lymphoscintigraphy in this study. In each case, the draining node fields and the number and location of the sentinel enhanced and interval nodes were recorded in an Excel spreadsheet. The challenge inherent in using a GIS to map the data was that the locations were descriptive. Only a small sketch of the location had been recorded and the images produced by the lymphoscintigraphy did not have any common reference points marked to allow normalisation and automatic geocoding of locations.

Six schematic diagrams representing the surface of the body were drawn and a grid marked on them. Each case was manually reviewed and a map number, X and Y coordinate recorded for each primary lesion site. These coordinates were then randomised within the level of precision of the grid used to avoid clustering at grid points. The consequence of having both the site of the primary lesion and the location(s) of the sentinel nodes was that a picture of the lymphatic drainage system was able to be produced with points at the locations of the lesion colour-coded based on their draining node fields. It was evident from the data that the sharp watershed lines predicted by Sappey were, in fact, merely fuzzy approximations and that patients would be much better served by advanced imaging techniques prior to surgery than by guesses based on Sappey’s predictions.

### Crossing disciplinary boundaries

While this is an apparently simple and perhaps unsophisticated example of inter-disciplinary science, it serves to illustrate some important principles in the identification of opportunities for collaboration and cross-pollination. The primary principle is to be able to step back from the minutiae and look for others pursuing similar goals. In this case, there were common words used in both fields. Geographic words such as “drainage”, “watershed” and “channel”, when used in a medical context, are an excellent indication that there is potential for some intersection between the disciplines. Similarly, both fields have a heavy emphasis on “imaging” and while they often use different techniques for collection and formats for storage of the data (medical imaging being heavily based on proprietary formats and geographic imaging being largely standards-based), these are merely technologically differences rather than conceptual.

Moving outside an established field of expertise and engaging with specialists from disparate fields is often seen as potentially uneconomical in terms of the limited amount of time available to researchers. It is important however, for at least some of a scientist’s time to be focused on expanding the boundaries of a speciality in a non-linear fashion. Attending seminars in fields that appear to be completely unrelated, perhaps as a part of a university’s post-graduate seminar program, is one technique as is an activity such as skydiving. In this case, much of the key words from one’s own field into a web-based search engine to see what other fields may also use similar terminology.

Once a piece of cross-disciplinary collaboration is underway, it is important to publicise the work in fora frequented by practitioners of both (or all) of the disciplines involved. Often this will mean presenting papers at disparate conferences, or publishing in multiple journals. The emphasis may change for each audience, but the essential value of the cross-disciplinary approach should encourage additional work between the fields.

Finally, it is incumbent on all scientists to remain open to the possibility of cross-disciplinary opportunities. No field of science is an island and while each seems to become more specialised and more insular, history has shown that evolutionary breakthroughs made have very often come with the introduction of ideas from outside the field.

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Melanoma: Narrowing the Sights on an Evasive Enemy

Richard F Kefford
Westmead Institute for Cancer Research
University of Sydney at Westmead Millennium Institute
Email: rick.kefford@wmi.usyd.edu.au

Abstract
Much of the resistance of melanoma to immunotherapy, radiotherapy 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. The exploration of melanoma susceptibility genes like CDKN2A, CDK4 and MC1R has highlighted a number of key pathways in melanomagenesis. Others have been revealed by a constitutive activating mutations in Nras and BRAF are the most common somatic oncogene mutations in melanoma, indicating the importance of the Ras-Raf pathway in the deregulation of melanocyte growth. Downstream targets of the signalling pathway include the cell cycle regulator cyclin D1 and the melanocyte-specific transcription factor, Mif. Newly tested inhibitors of the RAF pathways, like sorafenib, may sensitise melanoma cells to cytotoxic attack.

Inhibitors of apoptosis, like Bcl-2 and Mcl-1 are frequently over-expressed in established melanomas. Antagonists of the Bcl-2 family of proteins offer exciting potential for synergism with cytotoxic drugs. Other pathways highly relevant to melanoma tumour progression and its targeted therapy include the PI3K-PTEN-Akt-mTOR pathway and pathways of angiogenesis, which may be inhibited by molecules like bevacizumab and bosutinib. Considerable hope is also provided by recent Phase II trials with monoclonal antibodies such as tremelimumab and ipilimumab, which inhibit immunosuppressive cell signalling.

Metastatic melanoma
Melanoma is remarkable for variability in its pattern of spread. In selected patients the disease remains confined to loco-regional lymphatics for extended periods and some such patients have achieved long-term remissions even after long-duration treatment. In others, haematogenous dissemination occurs early and widely. Certain patients may have many years between the primary presentation and the development of metastases. Others may have serial presentations, each with relatively isolated metastases, remaining in clinical remission for many years between serial metastasectomy. Some patients present with fulminant illness in many organs simultaneously with a very rapid demise. The disease may have particular affinity for a specific 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.1 Approximately 4% of patients present with widespread metastases as the initial manifestation of metastatic disease.2 About 15% of patients presenting with metastatic melanoma in Australia have no identifiable primary site (occult primary melanoma). These patients show no discernible differences in pattern or prognosis from those with known primary sites.3 Psycho-social factors that show independent correlation with longer survival from metastatic melanoma include a positive perceived outcome from treatment, minimisation of perceived threat, anger and presence of a stable partner.4

In a recent revision of the American Joint Committee on Cancer (AJCC) Staging System for Melanoma, 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 and/or 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 serum lactate dehydrogenase (LDH). Although non-specific, the LDH is an independent prognostic factor for patients with metastatic disease and is frequently used in stratifying patients in clinical trials. M3 patients have a median survival of four to six months and a two-year survival of 5%.

Current status of drug treatment for metastatic melanoma
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 or DTIC), discovered in 1961, has been standard best systemic therapy for metastatic melanoma since the early 1970s and its use in Australia was pioneered by Gerald Milton and William McCarthy at Sydney Melanoma Unit.5 Partial responses to dacarbazine and two other commonly used single-agent cytotoxic drugs, temozolomide and fotemustine, occur in less than 25% of treated patients and complete responses in less than 5%.5,6 However, in recent Phase III prospective randomised trials, in which dacarbazine was the standard therapy, response rates were 6.8-13%.5,6 The use of combinations of cytotoxic drugs, such as the widely used ‘Dartmouth’ regimen – consisting of cisplatin, dacarbazine, carbustine and tamoxifen, shows no advantage over dacarbazine alone.7 The addition of potent cytotoxics like interlukin-2 and interferon-alpha to cytotoxic drugs (“biochemotherapy”) produces slightly higher transient response rates, but at considerable cost in toxicity and with no overall survival benefit.8 Predictors of response to dacarbazine include good performance status and disease confined to the skin, subcutis, lymph nodes and lungs.7,9 The median duration of response is five to six months.8 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.10 A major advantage of dacarbazine is that it is simple, ambulatory treatment, being administered intravenously on a three week schedule. It is associated with minimal toxicity when given with serotonin receptor antagonist anti-emetics. Alopecia does not occur with dacarbazine therapy and the drug is minimally myelosuppressive. Acute photosensitization reactions may occur.

Both temozolomide and dacarbazine are prodrugs of the active alkylating agent 5-(1-methyl-1-triazenoimidazole-4-carboxamide (MITIC). Unlike dacarbazine, which requires metabolic activation, temozolomide spontaneously converts to MITIC under physiological conditions. It has the advantage over dacarbazine of being orally administered. However, it is expensive and there is little difference from dacarbazine in toxicity and no difference in activity against metastatic melanoma.11 Temozolomide is not available under the Australian Pharmaceutical Benefits Scheme (PBS) for metastatic melanoma. The fact that temozolomide penetrates the central nervous system12 is widely used to justify its preferential use over dacarbazine in patients with brain metastases. However, the blood-brain barrier is nearly always disrupted in cerebral metastases from melanoma, demonstrated by the fact that they are nearly always strongly contrast-enhancing.

Fotemustine was superior to dacarbazine in inducing tumour responses in a Phase III trial, but its use is limited by severe and occasionally unpredictably protracted myelosuppression.13 Fotemustine, which is lipid soluble, also reaches high concentrations in the cerebrospinal fluid. It is PBS listed for metastatic melanoma.

Refining existing chemotherapy
The cytotoxic activity of the active metabolite of dacarbazine and temozolomide is probably mainly mediated through methylation of DNA at the O6 position of guanine bases. DNA O6-alkylguanine-DNA alkyltransferase (AGT) is thought to be the main determinate of resistance to dacarbazine.

Figure 1. Molecular targets in melanoma: the Ras/Raf pathway

Legend: RAS: retrovirus associated sequence oncogene; BRAF: v-raf murine sarcoma viral oncogene homolog B1; MEK, mitogen-activated protein kinase kinase (MAP2K); ERK, extracellular signal-regulated kinase, also known as mitogen-activated protein kinase (MAPK); Mif, microphthalmia transcription factor; PTEN, phosphatase and tensin homolog; PI3K, phosphatidylinositol-3 kinase, Akt, murine-v-akt oncogene homologue, also known as protein kinase B; mTOR, mammalian target of rapamycin.
and temozolomide. AGT detects and specifically removes alkylated base damage, effectively reversing cytotoxicity. Phase II trials are currently underway with lenoguanim, an agent that inhibits AGT and therefore may sensitize melanoma cells to these cytotoxic drugs. There is no rationale however, for this approach to be tumour specific and improved therapeutic ratios may therefore not be achieved.

Targeted drug treatment

The molecular pathways so far identified as being central to the regulation of melanoma cellular proliferation and apoptosis are the subjects of intense investigation for their potential as therapeutic targets.

The Ras/RAF pathway

Growth factors, such as stem cell factor (SCF), fibroblast growth factor (FGF) and transforming growth factor-alpha (TGF-alpha) are produced by the action of solar radiation on melanocytes and surrounding keratinocytes and fibroblasts (Figure 1). Resulting signals are transduced and amplified via the kinase signalling pathways NRas, then the RAF kinases BRAF and c-RAF and subsequently BRAF activates MEK-ERK-Mitf, or PI3K-Akt-mTOR. Mitf triggers the transcription of a suite of genes involved in regulation of melanocytes (TGF-alpha) are produced by the action of solar radiation on melanocytes and surrounding keratinocytes and fibroblasts (Figure 1). Resulting signals are transduced and amplified via the kinase signalling pathways NRas, then the RAF kinases BRAF and c-RAF and subsequently BRAF activates MEK-ERK-Mitf, or PI3K-Akt-mTOR. Mitf triggers the transcription of a suite of genes involved in regulation of melanocytes and surrounding keratinocytes and fibroblasts. Resulting signals are transduced and amplified via the kinase signalling pathways NRas, then the RAF kinases BRAF and c-RAF and subsequently BRAF activates MEK-ERK-Mitf, or PI3K-Akt-mTOR. Mitf triggers the transcription of a suite of genes involved in regulation of melanomas.

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The molecule usually central to the DNA damage response, p53, is rarely altered in melanoma. However, alterations and gene deletions affecting ARF permit degradation of p53 by its binding partner hdm2. This probably contributes to the natural resistance of melanoma cells to apoptosis (programmed cell death) in response to cytotoxic, radiation and immunological attack. As a further defence, melanoma cells frequently express high levels of the anti-apoptotic Bcl-2 family of proteins which include Bcl-XL and Mcl-1. These are important molecular vulnerabilities in melanoma. Oblimersen is an antisense oligodeoxyribonucleotide specific to Bcl-2, which is over-expressed in many melanomas. It was the first of this class of drugs to enter clinical trial in melanoma. In the largest Phase III trial in metastatic melanoma (771 patients), incremental benefits in progression-free survival and response rate were demonstrated for the combination of dacarbazine plus oblimersen versus dacarbazine alone. Overall survival benefit was similar for the two arms, but a pre-stratified subgroup of 500 patients with normal LDH showed a statistically significant survival benefit in the combination arm and seven of 11 patients with complete remission on the combination arm remained disease free at >24 months. However, this study was marred by failure to select patients with Bcl-2 over-expressing tumours. Furthermore, much better inhibitors of the Bcl-2 family of proteins are now in advanced development. Many of these specifically target the BH3 domain of the Bcl-2 family of proteins, releasing bound pro-apoptotic proteins, like Bax, and thereby sensitising cells to cytotoxic attack. Native inhibitors of Bcl-2, like Bim and Noxa, may also be inducible with proteosome inhibitors like bortezomib. It is likely that a multi-pronged attack on the redundant anti-apoptotic pathways in melanoma cells will be necessary to achieve significant tumour remissions.

Thalidomide has a variety of anti-tumour effects, which include immuno-modulation and anti-angiogenesis. It has been tested in small cohorts of pre-treated patients with metastatic melanoma, but failed to show convincing evidence of activity.4 It has been suggested that thalidomide may synergize with higher doses of thalidomide.4 However, much better inhibitors of the Bcl-2 family of proteins are now in advanced development. Many of these specifically target the BH3 domain of the Bcl-2 family of proteins, releasing bound pro-apoptotic proteins, like Bax, and thereby sensitising cells to cytotoxic attack. Native inhibitors of Bcl-2, like Bim and Noxa, may also be inducible with proteosome inhibitors like bortezomib. It is likely that a multi-pronged attack on the redundant anti-apoptotic pathways in melanoma cells will be necessary to achieve significant tumour remissions.

Anti-angiogenic agents

Thalidomide has a variety of anti-tumour effects, which include immuno-modulation and anti-angiogenesis. It has been tested in small cohorts of pre-treated patients with metastatic melanoma, but failed to show convincing evidence of activity. A large Phase III trial of a potent thalidomide analogue, lenalidomide, showed no benefit over placebo. Thalidomide has been tested in combination with a number of agents, including interferon-alpha and dacarbazine. Only a small trial in combination with temozolomide showed some trend towards improved response rates and survival in a preliminary report. Bevacizumab is a monoclonal antibody against Vascular Endothelial Growth Factor (VEGF), a mediator of tumour angiogenesis. It has shown significant benefit when combined with chemotherapy in colorectal cancer. Phase II trials in metastatic melanoma showed good tolerability and some responses. The monoclonal antibody MEDI-522 targets integrin alphaVbeta3, which plays a critical role in angiogenesis, tumour growth and metastasis and is highly expressed in melanoma. Preliminary results of a randomised Phase II trial of MEDI-522 with or without dacarbazine in previously untreated patients suggested potential clinical activity of MEDI-522 in Bosentan, an endothelin receptor antagonist used in the treatment of primary pulmonary hypertension, may modulate anti-proliferative and anti-angiogenic activities in melanoma. A Phase II trial of bosentan in patients with metastatic melanoma suggested some clinical activity and Phase III trials are now underway testing the combination of dacarbazine with or without bosentan.

Immunomodulators

Immunotherapy continues to be investigated intensively in metastatic melanoma and attempts are being made to target the major defences that melanoma mounts against an effective immune response. These defences include development of host tolerance to melanoma antigens, production of immunosuppressive factors by melanoma cells and clonal selection of melanoma cells that are resistant to apoptosis. Despite the presence of detectable immune responses in 30–60% of patients, tumours regress in only a few vaccine-treated patients.

Panel A: T cell activation involves presentation of melanoma-associated antigens by antigen presenting cells (APCs) such as dendritic cells, in the context of molecules of the major histocompatibility complex (MHC). Co-stimulatory signalling occurs via B7 on APCs which binds to CD28 cell surface molecules on T cells. Activation of T cells is normally dampened by a feedback route involving B7 interaction with an inhibitory molecule, CTLA4.

Panel B: Monoclonal antibodies ticilimumab and ipilimumab bind CTLA4 and inhibit its interaction with B7. T cell activation is thereby sustained and the threshold for T cell activation is also lowered.
with metastatic disease. The cytokine interleukin 2 has FDA approval for high-dose intravenous use in treating metastatic melanoma, on the basis of durable responses in some patients. However, the overall response rate is low (16%) and systemic toxicity is high and includes hypotension, capillary leak syndrome, sepsis and renal failure. Innovative immunotherapy approaches include the use of monoclonal antibodies such as ticilimubab (CP-675206) and ipilimumab (MDX-010) to inhibit immunosuppressive cell signalling (Figure 3). Both these monoclonal antibodies have been associated with durable remissions in patients with metastatic melanoma and are in Phase II and III Trials in many Australian centres. The major toxicity involves autoimmune-type reactions in skin, colon and endocrine organs.

**Conclusion**

The field of experimental therapies for melanoma has never been richer. Melanoma medical oncologists face increasingly difficult decisions about the choice of agents for clinical trials. The traditional endpoints of Phase II and Phase III trials (tumour response and survival) are stringent in the context of highly advanced tumours with an extensive repertoire of defences against cytotoxic attack. This is particularly so for biological agents, like anti-angiogenic drugs, that are likely to induce stable disease rather than the dramatic tumour regressions. New trial platforms are urgently required. One such design is ‘Treat, Rest, Analyse for Melanoma’ (TRAM), which proposes the use of relatively short-term biological response indicators in patients treated for short periods (several weeks) prior to surgical resection of in-transit or lymph node metastases. This type of clinical design would also permit the testing of multiple novel agents simultaneously, allowing selection of only the most promising for formal Phase II testing.

Advanced metastatic melanoma has attained its dramatic potential as a site for cutting-edge therapy. The acquisition of a bewildering array of molecular advantages requires an understanding of the details of these specific molecular abnormalities and the means for targeting them is finally enabling the sights to be narrowed on an elusive enemy.

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HARNESSING THE IMMUNE SYSTEM TO PREVENT CERVICAL CANCER

Ian H Frazer Centre for Immunology and Cancer Research, The University of Queensland, Princess Alexandra Hospital, Queensland Email: frazier@cicr.uq.edu.au

Abstract

Cervical cancer can be attributed to infection with a subset of high risk human papillomaviruses. While genital human papillomaviruses infection is common, persistence of infection is rare and conveys a significant lifetime risk of anogenital cancer. Vaccines based on human papillomaviruses, like particles produced using recombinant DNA technology, are in late stage clinical trial and are designed to induce neutralising antibody. These vaccines have demonstrated >90% efficacy at preventing persisting high risk human papillomaviruses infection, cervical intraepithelial neoplasia and anogenital warts. They provide a significant addition to strategies to prevent cervical cancer.

The viral aetiology of cervical cancer

Cervical cancer kills about 250,000 women worldwide each year. Uniquely among human cancers, cancer of the cervix is entirely attributable to an infectious agent, human papillomavirus (HPV). Shope showed that papillomavirus was a causal agent in rabbits and papillomaviruses were subsequently associated with tumours in cattle and horses. The hypothesis that some human papillomaviruses might be responsible for cervical cancer was developed by Professor Harald zur Hausen and his colleagues in the 1980s and strengthened by the epidemiological studies of the International Agency for Research on Cancer (IARC) on the global association of HPVs with cervical cancer. Thus, observations of Rigoni-Stern in the 19th century and professors of cervical cancer among nuns and prostitutes, suggesting an infectious agent, were
Papillomaviruses and cervical cancer

Papillomaviruses come in at least 200 different varieties, in four broad groups.1 Two groups infect the genital tract of humans, one associated with genital warts and one associated with genital cancer. Detailed epidemiological evidence suggests that there is a causal relationship between the papillomaviruses (PVs) and cervical cancer. The molecular basis by which papillomaviruses promote cancer is still the subject of intense study; studies in mice transgenic for HPV transforming proteins (E6 and E7) and mutated in several other genes suggest that the E6 and E7 proteins together are sufficient to promote cervical malignancy in the presence of oestrogens.2 Such models also suggest that induction of epithelial proliferation by viral gene products to facilitate viral replication can be distinguished from initiation of carcinogenesis as an unexpected consequence of some other viral gene function unique to high risk HPV.

The natural history of infection with high risk human papillomavirus

Infection of the genital tract with high risk HPV is extremely common, with up to 50% of women becoming infected during the first five years after commencing sexual intercourse.3 Up to 98% of these infections, which are associated with cellular abnormalities in the cervix generally termed low grade squamous intraepithelial lesion (LSIL) or cervical intraepithelial neoplasia 1 (CIN1), regress without intervention in humans with a competent immune system, though humans immunocompromised by immunosuppressive drugs or viral infection are much less likely to clear infection. Persistent infection with a high risk HPV genotype conveys substantial risk of cervical cancer,4 which can develop as early as five years after infection but more commonly takes 15-30 years to develop.

Screening as a method to prevent cervical cancer

Prevention of cervical cancer at present relies on screening programs which are designed to detect premalignant changes in squamous epithelial cervical cells; such changes are generally associated with integration of the papillomavirus genome into host genetic material and overexpression of the viral non-structural proteins E6 and E7. These two viral proteins are the key to cervical malignancy and together with cervical abnormalities results in a greater than 95% reduction in lifetime risk of cervical cancer and is the current basis of prevention of cervical cancer through screening.

Vaccines to prevent cervical HPV infection and cervical cancer

Future programs to prevent cervical cancer will likely incorporate the use of vaccines designed to prevent infection with the papillomaviruses (PVs) that are responsible for cancer. Initial studies in cattle and dogs showed that PV vaccines based on inactivated wart derived PVs could protect against challenge with live bovine PVs.4 However, human PVs cannot be grown in the laboratory and vaccines for human PVs are therefore based on virus like particles (VLPs).5-7 The current vaccines are constructed using recombinant DNA technology from the L1 major capsid protein of the PVs. Human papillomavirus expressed in recombinant yeast, or in insect cells using baculovirus vectors. Such VLPs resemble the viral capsid physically and immunologically. Early animal studies showed that virus like particles could induce humoral immune responses cross reactive with the natural virus and that neutralising antibody raised by VLP based vaccines could protect animals against challenge with the corresponding animal papillomavirus.8,9

Clinical trials of HPV vaccines

Initial studies in humans demonstrated that VLPs purified from an AS04 adjuvant induce HPV type specific antibody10 and protect against infection with the corresponding HPV type.11,12 Two Phase III trials of quadrivalent vaccines based on HPV virus like particles are currently underway. Vaccine administered on three occasions over six months has proven in interim analysis to be 100% effective at preventing not only persistent infection with high risk HPV, also HSIL/CIN2, and anogenital warts in young sexually active women.

Vaccines to prevent HPV infection, genital warts and cervical cancer are about one year away from approval for general use in the US and Australasia. If administered prior to sexual activity, the two vaccines currently under development (Cervarona™ and Gardasil13) which both incorporate HPV16 and HPV18 VLPs, should prevent up to 70% of cervical cancer in an unscreened population and the majority of abnormal pap smears in screened populations. The quadrivalent vaccine (Gardasil14) which incorporates HPV6 and HPV11 VLPs will additionally prevent >90% of genital warts. Use of these vaccines should not impact on delivery of existing cervical screening programs because they protect against only two types of HPV and associated cancer most commonly with cervical cancer. All sexually active women can potentially benefit from vaccination, particularly if they are likely to change partners in the future. The best benefits will however, follow immunisation before sexual activity, as the vaccine can prevent infection but is unlikely to alter the natural history of existing infection. Duration of protection is varying and the majority of abnormal pap smears in screened populations. The quadrivalent vaccine (Gardasil) which incorporates HPV6 and HPV11 VLPs will additionally prevent >90% of genital warts. Use of these vaccines should not impact on delivery of existing cervical screening programs because they protect against only two types of HPV and associated cancer most commonly with cervical cancer. All sexually active women can potentially benefit from vaccination, particularly if they are likely to change partners in the future. The best benefits will however, follow immunisation before sexual activity, as the vaccine can prevent infection but is unlikely to

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**THE AUSTRALIA NEW ZEALAND BREAST CANCER TRIALS GROUP: SOME CONTRIBUTIONS TO BREAST CANCER TRIALS**

John F Forbes | Australian New Zealand Breast Cancer Trials Group, University of Newcastle · Newcastle Mater Hospital | Email: john.forbes@unsw.edu.au

**Abstract**

The Australian New Zealand Breast Cancer Trials Group was formed in 1978 after the first adjuvant therapy trials were published. This commenced a new era of clinical trials and the commencement of substantial global collaboration, particularly with the International Breast Cancer Study Group. The Australian New Zealand Group is currently conducting 46 trials encompassing prevention and early and advanced disease. In the Australian New Zealand Breast Cancer Trials Group model the elected Board of Directors is responsible for legal and financial affairs, the Scientific Advisory Committee sets the research agenda and the Operations Office is responsible for conduct of the research program. The Australian New Zealand Breast Cancer Trials Group Statistical Centre is contracted out to the National Health and Medical Research Centre Clinical Trials Centre. The Australian New Zealand Group has had peer reviewed research funding (National Health and Medical Research Council) since 1979 and has contributed to more than 400 peer reviewed publications. The research program has always been based on quality science and multidisciplinary collaboration. The Breast Cancer Institute of Australia was established to foster education and involvement of consumers in research.

**John**

**Contributions**

The Australian New Zealand Breast Cancer Trials Group (ANZ BCTG) was established in 1978. At that time new advanced breast cancer trials in Cardiff were comparing first line treatment with tamoxifen or chemotherapeutic and initiating quality of life measurements in the former patients. Results from the initial trials of adjuvant chemotherapy compared to no adjuvant chemotherapy were published, the L-PAM trial of the National Surgical Adjuvant Breast and Bowel Project (NSABP), and the Bernasek, Fisher and colleagues' and the CMF trial from the Istituto Nazionale Tumori, Milan, by Gianni Bonadonna and colleagues.1 The Cardif trials was 12 months of adjuvant CMF versus no adjuvant chemotherapy for women with positive nodes, showed that after 27 months follow-up, relapse rates were reduced by 78% (control 24%, CMF 5.3%). Twenty-seven months was a very short follow-up time for analysis by today's standards, 24%, CMF 5.3%). Twenty-seven months was a very short follow-up time for analysis by today's standards, and OS 47% and 24% for the CMF and control groups respectively. In contrast, in postmenopausal women, DFS was 26% and 24% for CMF and control and OS was 22% in both groups. We have subsequently relied on the Early Breast Cancer Trials’ Collaborative Group (EBCTG) Overviews for evidence that chemotherapy does indeed provide advantages for postmenopausal women.2

Concurrent with Jan Stjernsward's initiative, a group of oncologists at the Welsh National Medical School in Cardiff showed in randomised controlled trials (RCTs) that chemotherapy and endocrine therapy produced superior outcomes in women with advanced breast cancer.3 Pioneering studies of quality of life (QoL), using LAQA (Linear Analogue Self Assessment) scales for the first time in oncology, established that endocrine therapy was associated with a better QoL despite a smaller response rate.4

**Formation of the ANZ BCTG**

The ANZ Group was initially established in the Department of Surgery, University of Melbourne at the Royal Melbourne Hospital in 1978 (with one data manager, one computer, one National Health and Medical Research Council grant and 14 collaborating institutions) and relocated to the Department of Surgical Oncology, University of Newcastle, at the Newcastle Mater Hospital in 1987.

In 1977 a young and enthusiastic group of oncologists5 returned to New Zealand and from centres in North America and Europe and brought experience and ideas from Cardiff, the Eastern Co-operative Oncology Group and the MD Anderson Hospital in particular. A similar meeting to that held in Lausanne led to the establishment of the new ANZ Group. The first ANZ BCTG trial, ANZ 7801/2, commenced in 1978. It compared first line treatment of advanced breast cancer with cytotoxic therapy (AC), endocrine therapy (tamoxifen in postmenopausal women and oophorectomy in premenopausal women) and also combined therapy with both modalities.6 These trials were the logical extension of the Cardiff trials and a small premenopausal trial from the Mayo Clinic and were successful.

From the outset it was recognised that sufficient accrual in Australia and New Zealand to complete adjuvant trials in a reasonable timeframe was not possible, so adjuvant therapy trials were supported through collaboration with the new LBCSG. In 1975, there was no mammography screening and women with breast cancer presented because of clinical symptoms; patients were treated with a radical mastectomy (usually a Halsted mastectomy), lymph glands were not counted, steroid receptors were not measured, there was no adjuvant systemic therapy and breast cancer mortality had probably not changed. The large response to the first LBCSG adjuvant trials had just 491 patients. It soon became apparent that clinical trials introduced new standards of care – in LBCSG IV, lymph nodes had to be counted and examined, pathology protocols were standardised, follow-up was according to an accepted protocol and an international quality review facilitated reliable measurement of steroid receptors for the first time. This was the beginning of “evidence-based medicine” for management of breast cancer.

Lessons from the initial trials

After a median follow up of 20 years, women in LBCSG trials presented with a biological phenotype of advanced breast cancer, 3 patients with an OS of 54% and a DFS of 40%, clearly better than what might have been expected before adjuvant chemotherapy. LBCSG Trial II produced the first evidence that in premenopausal women with an endocrine sensitive tumour, the combination of endocrine therapy (oophorectomy) and chemotherapy might be superior to chemotherapy alone. This was followed by a series of current trials for premenopausal women investigating combinations of chemotherapy and endocrine therapy. In LBCSG III, the first evidence was obtained that, in postmenopausal women with endocrine sensitive tumours, there may be no difference in efficacy between chemotherapy and additional tamoxifen (even with just 12 months therapy - current tamoxifen five years), but in women with endocrine insensitive tumours, tamoxifen is no better than control and chemotherapy is indeed superior to both tamoxifen and control. These analyses by steroid receptors status were retrospective. They identified new questions and hypotheses which led to International Breast Cancer Study Group (IBCSG) trials 8 and 9, with prospective stratification by steroid receptor categories, and now in 2006, to new trials for chemotherapy and endocrine therapy for young premenopausal women with endocrine sensitive tumours. Progress may seem slow, however the importance of quality data, sufficient accrual, prospective stratification, prospectively planned sub-studies and broad collaboration is evident in the beginning and remain so today. And new hypotheses based on Trials I-IV have been largely proven. Today endocrine therapy is confined to endocrine sensitive tumours.

After LBCSG trial V accrual was completed in 1985 the LICR decided to focus on laboratory research and confined its LBCSG trials support to follow-up of trial V. The ANZ BCTG continued with a strong support for the new IBCSG, which has since built on the substantial contributions of the LBCSG. The ANZ BCTG continued its strong support for the new IBCSG, which has since built on the substantial contributions of the LBCSG. The ANZ BCTG continued its strong support for the new IBCSG, which has since built on the substantial contributions of the LBCSG. The ANZ BCTG continued its strong support for the new IBCSG, which has since built on the substantial contributions of the LBCSG. The ANZ BCTG continued its strong support for the new IBCSG, which has since built on the substantial contributions of the LBCSG. The ANZ BCTG continued its strong support for the new IBCSG, which has since built on the substantial contributions of the LBCSG. The ANZ BCTG continued its strong support for the new IBCSG, which has since built on the substantial contributions of the LBCSG. The ANZ BCTG continued its strong support for the new IBCSG, which has since built on the substantial contributions of the LBCSG. The ANZ BCTG continued its strong support for the new IBCSG, which has since built on the substantial contributions of the LBCSG. The ANZ BCTG continued its strong support for the new IBCSG, which has since built on the substantial contributions of the LBCSG. The ANZ BCTG continued its strong support for the new IBCSG, which has since built on the substantial contributions of the LBCSG. The ANZ BCTG continued its strong support for the new IBCSG, which has since built on the substantial contributions of the LBCSG. The ANZ BCTG continued its strong support for the new IBCSG, which has since built on the substantial contributions of the LBCSG. The ANZ BCTG continued its strong support for the new IBCSG, which has since built on the substantial contributions of the LBCSG. The ANZ BCTG continued its strong support for the new IBCSG, which has since built on the substantial contributions of the LBCSG.

In 1978 advanced breast cancer was increasingly being treated with cytotoxic chemotherapy, particularly in the US. ANZ BCTG 7801/7802 was the largest advanced breast cancer trial done at that time with accrual of 408 patients. First line treatment with chemotherapy or combined modality therapy produced no apparent advantage in terms of survival and QoL was compromised. There was almost no receptor data, as tissue biopsies were not often done for the relapsed patient and very few women had receptors measured at the time of their primary treatment. Despite this it was clear that patients treated with initial endocrine therapy had a similar survival and a superior initial QoL. Today the availability of tissue from women with advanced breast cancer is becoming very important due to reliably selected patients on biological assays; increasingly we are able to identify...
the many patients who do benefit from chemotherapy and targeted therapies. In 2000, we now have active targeted therapies to treat advanced breast cancer and can approach it as a potentially curable disease.

Wider international collaboration

The EBCTCG Overviews have been vitally important in answering major questions and consolidating evidence-based treatments. They have been strongly supported by the ANZ BCTG and the IBCSG. The overviews have added a dimension to RCTs and have provided the most reliable evidence to support the use of many current treatment strategies, including ovarian ablation, tamoxifen in premenopausal women and for longer durations for chemotherapy in smaller tumours. Combination chemotherapy, rather than single agent chemotherapy and anthracyclines containing chemotherapy regimens. The demonstration in the overview of reduced rates of contralateral breast cancer for women taking adjuvant tamoxifen, was a sound basis for IBIS I and other tamoxifen prevention trials.

However some adjuvant trials today test a specific treatment modality and involve defined patient subsets for “targeted” therapy evaluation. These trials are very large and future overviews may be simpler and more about the treatment instead of the study. The Current EBCTCG overview involves much larger patient groups. The first CMF trial involved 386 pre and post-menopausal women. The addition of cyclophosphamide, doxorubicin and cyclophosphamide plus tamoxifen to adjuvant chemotherapy for breast cancer patients with node-positive disease does not have a “National Cancer Institute” to provide infrastructure and operational funding for collaborative groups; however, the BCIA is vitally important to help the ANZ BCTG to coordinate and ensure prevention strategies, results, and data are reported in accordance with scientific priorities. The establishment of the ANZ Consumer Advisory Panel (CAP) and the IMPACT program (Improved Participation and Advocacy for Clinical Trials) have enhanced our research programs for Clinical Trials. IMPACT program (Improved Participation and Advocacy for Clinical Trials) have enhanced our research programs for Clinical Trials. The CAP members comment on all ANZ BCTG protocols, particularly on patient material and issues that will affect accrual to the trial. The IMPACT program now includes mentoring of individual patients at the groups’ Scientific Meeting and provides information about trial results for women who have been on ANZ BCTG trials.

Current research program

The ANZ Group has grown substantially since 1997 and now collaborates with more than 80 institutions, more than any other group. Australia and New Zealand and many more globally. It has had continuous NHMRC support since 1979 and has had more than 400 publications in peer-reviewed journals – many resulting from international collaboration. Currently 17 trials are being conducted, including: (i) two trials to confirm accrual and follow-up after completion of trials completed and published; (ii) trials with accrual completed and follow-up continuing whilst awaiting analyses, including the definitive taxane based adjuvant chemotherapy trial (BIG 2-98/IBCSG 18-98); (iii) trials open for accrual; and (iv) trials with endorsement from the SAC to be commenced. Since 1978 more than 10,600 women have been entered on breast cancer trials through the ANZ BCTG with total trials accrual of more than 70,000 women. The group continues to evolve and meet new research challenges and is well placed to translate future research discoveries into better outcomes for patients.

Conclusion

Through its commitment to clinical trials the ANZ BCTG has made important contributions to the falling mortality of breast cancer in developed countries. It has done this simply by focusing on the quality of the science and pursuing collaboration with good researchers. The Group has pioneered involvement of consumers in breast cancer research through its CAP and IMPACT Program. It has also helped establish QoL measurement as the key to breast cancer trials. We will see further improved outcomes for women and improved understanding of the biology of breast cancer.

Improved use of existing treatments, new biological targeted agents, gene expression based targeted therapies, unravelling the biology of stem cells and the science of prevention strategies can all produce better outcomes for patients with or at risk of early or advanced breast cancer. Each of these requires collaborative research and documented controlled outcome data. Our clinical trials agenda is even more important today than it was in 1978 and will remain so for some time.

A tribute

The standing and achievements of the ANZ BCTG and the IBCSG are a tribute to the contributions of my friend and colleague Alan Coates. His rigorous and robust scientific leadership of the SAC, his remarkable breadth of scientific knowledge, his humanity and his wise counsel have been of great benefit to his colleagues and many patients worldwide.

Local therapy in a systemic world: the evolution and incarcations of adjuvant radiotherapy for breast cancer

Sue Pendlebury - Department of Radiation Oncology, Royal Prince Alfrord Hospital, NSW Email: spendleb@email.cs.nsw.gov.au

Abstract

Alan Coates’ career has seen the evolution of radiotherapy in the adjuvant treatment of breast cancer move from the only modality available, through a period of little utilisation, to its current resurgence amid technology that can provide treatment to regions at risk with little dose delivery to sensitive normal tissues. The results of the early randomised trials reflected poor trial entry procedures, poor dose delivery of the radiotherapy and little accurate targeting of the regions at risk. The results were a failure in the era of evidence; if a treatment modality was to be used there must be evidence as to its efficacy. With the development over the last 15 years of high quality machinery and clinical practice...
Breast conservation
Meta-analysis of the 15 randomised breast conservation studies has shown a similar survival benefit of 8% relative reduction in all-cause death (hazard ratio = 0.92, 95% CI: 0.85 to 0.98).10 The decision to advocate for radiotherapy in the breast conservation setting however, has always been more compelling, as the risks of local relapse carry with them increased rates of mortality.11

Multidisciplinary care
Clearly the clinical challenge is to optimally integrate all modalities of treatment. This is the fundamental outcome of multidisciplinary care. The multidisciplinary clinic in which Alan Coats practised his clinical oncology was a great forum for that, producing guidelines for the delivery of systemic therapy for patients not on clinical trials as early as 1996. At the same time we had guidelines for the indications for radiotherapy and both were freely discussed, as were the patients being seen. The radiotherapy and chemotherapy clinics ran side by side in the environment of great intellectual flair. As national bodies and governments endeavor to establish criteria by which such clinics can be optimised,12 a clinic in which systemic and local therapy decisions are optimally integrated must remain an ideal.13

References

A study reported by Coates et al in 1983 is often quoted in the literature as providing the rationale for the research effort to prevent chemotherapy induced emesis.1 In this study, 99 patients who had received a range of cytotoxic drugs within the previous week were shown a set of 45 cards with physical side-effects and 28 cards with non-physical side-effects, from which they were asked to assess the side-effects they had experienced and subsequently to rank their severity. When all the results were combined for this group of patients, vomiting and nausea were ranked first and second.

Not only are nausea and vomiting distressing side-effects in their own right, but they also adversely impact on the health-related quality of life of patients. A group of 832 chemotherapy naïve patients who received chemotherapy of high or moderate emetogenic potential completed both the European Organization for Research and Cancer Care Quality of Life Questionnaire (QLQ-C30) before and after chemotherapy, as well as a self report nausea and vomiting diary. Those patients who reported both nausea and vomiting in comparison with a group who reported neither, had significantly worse physical, cognitive and social functioning, global quality of life, fatigue, anorexia, insomnia and dyspnoea. Those patients who experienced nausea only had less worsening of symptoms. The health related quality of life scores returned to baseline, or better, within two to four weeks.

Patient versus observer assessments

A strength of these studies is that patients are being asked to assess their own symptoms. In the design of many antiemetic studies both the patient and an observer record the nausea and vomiting. Intuitively one might expect objective criteria may be recorded by observers, particularly if the patients are feeling unwell or their drugs have sedative side-effects. In testing this, Kris and colleagues in a study of nausea and vomiting which may have been influenced by the timing of the collection, but highlight the hazards of comparing data between studies and suggest the limits to the accuracy of relying only on patient reporting.

The 5 hydroxytryptamine, antagonists

Emesis following chemotherapy became particularly problematic with the introduction of cisplatin in the mid 1970s. It was recognised that antineumetics should be given prophylactically to prevent emesis, but the available drugs were ineffective. The main antiemetics tried were the dopamine antidepressants, particularly metoclopramide which blocked the D2 receptor, thought to mediate emesis. Subsequently, based on animal studies, high doses of metoclopramide, up to 3mg/kg, were more effective for preventing cisplatin induced emesis, but caused more side-effects including spastic extrapyramidal reactions. It is interesting that patients rated nausea and vomiting so high in the list of worst side-effects of chemotherapy.

A breakdown in the control of acute chemotherapy induced emesis occurred with the recognition that the 5 hydroxytryptamine (SHT) receptors in the small intestine were involved in triggering the acute emetic response to cytostatics. The first of the SHT, receptor antagonists, ondansetron, dramatically reduced the acute phase of emesis in the first 24 hours after the administration of chemotherapy. Ondansetron was shown to be superior to high dose metoclopromide regimens for preventing chemotherapy-induced emesis with the mild reversible side-effects of headache, constipation and mild elevations in liver transaminases being the most common side-effects.2 A SHT, receptor antagonist combined with dexamethasone became the gold standard given prophylactically to prevent acute post chemotherapy induced emesis.3 This resulted in complete protection from cisplatin-induced acute emesis ranging from 70-90%.4

Patients' perceptions

Ten years after the initial study reported by Coates et al, and following the introduction of the SHT, receptor antagonists, the study on patient perceptions of the side-effects of chemotherapy was repeated.5 There was a change in the ranking of side-effects by severity, but nausea was still ranked first. Vomiting was now ranked fifth for related tiredness and hair loss, and there was a shift from concerns about physical to psychosocial issues. In exploring the predictors of whether nausea and vomiting were selected as one of the top five symptoms, nausea within 24 hours was the strongest predictor of the nausea ranking, followed by delayed nausea, that is nausea after 24 hours. Delayed vomiting was the most powerful predictor of the ranking of vomiting. These results were confirmed by other studies. A French study in 100 patients noted that the shift from physical to psychosocial concerns and ranked fatigue as the most severe physical symptom.6 A trial in the Netherlands reported a high correlation of Coates et al who had received antiemetica and his SHT, antagonists and found that nausea and vomiting were still ranked in the top three side-effects.7,8 These results are not surprising when the SHT, literature is analysed. Although very effective for preventing acute vomiting after chemotherapy, if a SHT, antagonist and dexamethasone were continued the control of the delayed phase of emesis, which commences after 24 hours and can last for a week, rarely exceeded 50%.9,10 Moreover nausea was not being controlled as well as vomiting. In a prospective study, despite prophylaxis with ondansetron, the majority of patients experienced nausea, with delayed nausea twice as frequent as acute nausea.11,12 Clinicians' predictions of emesis

With the advent of the SHT, receptor antagonists, how much nausea and vomiting did clinicians perceive that their patients would experience? Grunberg et al determined the incidence of acute and delayed chemotherapy-induced nausea and vomiting among patients receiving chemotherapy of high (HEC) or moderate (MEC) emetogenic potential.13 They also assessed whether doctors and nurses could accurately predict the incidence of acute and delayed nausea and vomiting in their own patients. Twenty-four physicians and nurses from 14 oncology practices in six countries recruited 298 patients. Physicians and nurses accurately predicted the incidence of acute nausea and vomiting, but underestimated the incidence of delayed nausea and vomiting by 26% and 28%, respectively. Moreover delayed symptoms could appear without acute symptoms after HEC (emesis, 38%; nausea, 33%) and MEC (emesis, 19%; nausea, 21%).13

Neurokinin, receptor antagonists

Somewhat fortuitously, the next major breakthrough in the control of acute chemotherapy-induced nausea and vomiting occurred with the recognition that their patients would experience? Grunberg et al determined the incidence of acute and delayed chemotherapy-induced nausea and vomiting among patients receiving chemotherapy of high (HEC) or moderate (MEC) emetogenic potential. They also assessed whether doctors and nurses could accurately predict the incidence of acute and delayed nausea and vomiting in their own patients. Twenty-four physicians and nurses from 14 oncology practices in six countries recruited 298 patients. Physicians and nurses accurately predicted the incidence of acute nausea and vomiting, but underestimated the incidence of delayed nausea and vomiting by 26% and 28%, respectively. Moreover delayed symptoms could appear without acute symptoms after HEC (emesis, 38%; nausea, 33%) and MEC (emesis, 19%; nausea, 21%).13

Neurokinin, receptor antagonists

Somewhat fortuitously, the next major breakthrough in the control of acute chemotherapy-induced nausea and vomiting occurred with the recognition that 1. Coates A, Abraham S, Kaye SB, et al. On the receiving end - patient perception of the side-effects of common chemotherapy. Curr Oncol Clin North America, Europe and Australia (Hesketh et al, 2001). These differences were seen in delayed emesis; 67.7% versus 46.8% (p<0.001) and 74.4% versus 55.8% (p<0.001) respectively. The efficacy of aprepitant was maintained over six courses. However, more patients receiving aprepitant reported no impact of antiemetic therapy induced nausea and vomiting on their daily lives.

Similar benefits were seen when aprepitant was used as part of the antemetic regimen to control the acute and delayed nausea and vomiting after combination chemotherapy with an anthracycline and cyclophosphamide. However, some patients have side-effects that are not adequately controlled by the standard antiemetics and additional therapy is then given. A lack of adequate pharmacological explanations for side-effect variation following chemotherapy suggests psychological factors may contribute to the experience of side-effects. Our understanding of how patients' expectations were associated with toxicities.14 Eighty-seven chemotherapy-naive patients rated their expectations of 20 common side-effects before treatment and then rated their expectations following their first chemotherapy dose. Subjective side-effects, including inability to concentrate, sleep problems, mood changes, tiredness and nausea, were all influenced by expectation.

Assessing the experience of chemotherapy from the patients' perspectives will focus research activity on the side-effects; most problematic are also perceived by patients. The assessment of whether therapeutic interventions have altered the patients' perceptions. In the antemetic literature such studies were used to justify the research effort to find new antemetics, then highlight the limitations of the impact of the SHT, antagonists. Ultimately the NK, receptor antagonists were developed, which proved useful for ameliorating delayed nausea and vomiting after chemotherapy. Now the assessment of the impact on the patients' perceptions of nausea and vomiting needs to be reassessed. Further information is required about the factors which explain differences in the patients' perceptions of the toxicities of chemotherapy.15

References


FORUM

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On the receiving end: Cancer patients' perceptions of the burden of chemotherapy

Martin HN Tattersall | University of Sydney and Royal Prince Alfred Hospital
Email: mhtt@med.usyd.edu.au

Abstract

During the 1970s cancer chemotherapy began to emerge from the research environment of leukaemia and paediatric cancer units to become a part of the management of common cancers occurring in adults. Expectations were high that the successes of chemotherapy in leukaemia and lymphoma would be mirrored in treatment of adult solid tumours. This paper provides a summary of work done at the University of Sydney, the Royal Prince Alfred Hospital in 1977, reported in 1980 that approximately half the chemotherapy given to adults was palliative in intent and that median life expectation of those patients was 44 weeks. At the time, most chemotherapy was prepared. On each card was the name of one potential side-effect of chemotherapy. Group A cards (45 cards) listed physical side-effects and Group B (28 cards) non-physical side-effects. Patients selected cards from each group which they described as a side-effect they attributed to their chemotherapy and then they ranked the top five cards in each group. The top five cards in each group were combined and the patient selected the five most severe symptoms regardless of group putting them in order from most to least severe. The median number of non-physical symptom cards selected was seven and of physical symptoms 12, giving a total number of symptom sets of 19. The relative severity of side-effects for the entire group ranked the top five side-effects as vomiting, nausea, loss of hair, thought, of coming for treatment and length of time treatment takes at clinic. The abstract concludes: “Evaluation of patient perception of the severity of side-effects is an aid to striking the cost-benefit balance when deciding whether to use cancer chemotherapy.”

The second paper describes the application of linear analogue self-assessment (LASA) scales to evaluate general well-being and the severity of certain specific problems (mood, pain, nausea and vomiting, appetite, breathlessness, physical activity) perceived by 110 patients receiving therapy for malignant melanoma, small cell lung cancer and ovarian cancer. A number of correlations were observed and it was concluded that LASA techniques provide a convenient method for the assessment of quality of life (QoL) in patients receiving cancer therapy and potentially allows comparison of patient perception of treatment-related morbidities.

The third paper extended the use of LASA scales for eight groups of symptom items as important in the earlier studies. These items formed a new instrument (QLQ) for measuring aspects of QoL. One hundred and sixty-six patients completed both the QLQ-8 and five previously validated LAA scales, together with the visual analogue version of the Spitzer QLQ Index. The new scales showed high reliability, with retest correlation coefficients exceeding 0.8 for most items. Correlations were in general higher for the QLQ-8 items than for the five older LAA items. It was concluded that the QLQ-8 and QLQ LAA scales were efficient and reliable instrument measuring aspects of patients’ QoL in patients receiving cancer chemotherapy. The fourth paper in the series extended cross validation of the QLQ-8 against three established measures of QoL, mood and psychological adjustment to cancer. Correlations were high and it was concluded that the regular inclusion of practical indicators (or predictors) of QoL in clinical trials would allow improved assessment of the cost-benefit ratio of treatment to outcome in cancer patients.

The fifth paper replicated the first paper in patients receiving chemotherapy at RPAH 10 years after the initial report. Patients reported experiencing on average 20 symptoms (13 physical and seven psychosocial). Nausea was the most severe symptom followed by tiredness and loss of hair. Vomiting was now ranked fifth compared to first in 1983. Differences were detected in the symptoms experienced and reported as most severe between chemotherapy regimens, between older and younger patients, and between males and females. It was concluded that there had been a reduction in the severity of some symptoms experienced while receiving chemotherapy and a shift from concerns about physical to psychosocial issues.

The final paper explored which dimensions of QoL scores carry prognostic information, a theme discussed further by others in this issue of Cancer Forum.

Conclusions

This sequence of papers under the title On the receiving end provides insight into Alan Coates’ attention to the needs of patients, the detailed and creative analysis of results and the need to compare new instruments to determine their worth over earlier measures.

References

Continuous chemotherapy also yielded superior survival in early breast cancer, but that it also had measurable adverse effects on QoL. These adverse effects on QoL were transient and seemed minor compared with patients' adaptation and coping after diagnosis and surgery. Investigators concluded that this finding should encourage patients and doctors to choose appropriate adjuvant therapy with less concern for initial toxicity.

These observations were taken further in the seminal study of patients' preferences for adjuvant chemotherapy in early breast cancer conducted by Alan Coates and John Simes.18,19 They interviewed 100 women who had adjuvant chemotherapy to determine the benefits they considered necessary to make the experience of adjuvant chemotherapy worthwhile. The majority of women considered small benefits (a few extra percentage points or months) sufficient to warrant the side-effects and inconvenience of adjuvant chemotherapy. Subsequent studies corroborated these findings for other countries, treatments and eras.6,20 Even more interesting were the subsequent findings that women considered larger benefits necessary to make adjuvant endocrine therapy worthwhile.17,18

Quality-adjusted survival analysis was another novel approach to incorporating patients' attitudes and opinions into judgements about adjuvant chemotherapy. This method for formally integrating the effects of adjuvant chemotherapy on length and QoL also supported the conclusion that adjuvant chemotherapy was worth considering for most women with early breast cancer.21

Alan Coates has made a substantial, enduring contribution to thinking and practice in oncology. These studies have shown that patients have a strong desire to participate in the decision-making and treatment for people affected by cancer. They also provide a shining example of how to combine compassion, open-mindedness and rigour.

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Continuing chemotherapy gives better length and quality of life (QoL) than giving it intermittently.

Chemotherapy can improve QoL by shrinking tumours and improving cancer-related symptoms, but it can impair QoL by damaging normal tissues and causing treatment related side-effects. A major practical question for patients with breast cancer who are responding to chemotherapy is whether it is better to continue it until disease progression, or to stop after some number of cycles, reserving further cycles for subsequent progression.

The seminal trial addressing this question was designed by Alan Coates and reported in the New England Journal of Medicine in 1987. This Australia New Zealand Breast Cancer Trials Group study compared two strategies of giving chemotherapy in advanced breast cancer: Continuing chemotherapy gives better cure rate and longer survival than intermittent treatment. But it also increases toxicity.

These findings suggested that the association between QoL and survival was related to cancer-related symptoms. They were compatible with a simple explanation that patients perceived disease progression before it was clinically evident, but also with a more complex causal relationship where QoL influenced survival duration. Subsequent observational studies showed that differences in coping styles and adjustment strategies were associated with differences in overall survival and in QoL over time in patients with melanoma that was localised or metastatic. Styles of coping and adjustment were also associated with survival in women with metastatic breast cancer. These studies suggested that the use of minimisation and avoidance were associated with longer survival and led to a randomised trial to test the benefits of encouraging patients to use these coping styles and adjustment strategies.

Small benefits are judged sufficient to make adjuvant chemotherapy worthwhile.

Quality of life research that shaped oncologists' thinking and practice

Abstract
Alan Coates is a pioneer of quality research in oncology. This paper reviews three threads in his extensive program of quality of life research that have had enduring influences on how we think about cancer and manage it. The studies produced counterintuitive conclusions to three pragmatic questions: 1) How long should chemotherapy continue in responding patients with advanced cancer? 2) Is baseline quality of life prognostic in people with advanced cancer? 3) What benefits are needed to make adjuvant chemotherapy worthwhile? This research was done predominantly in people with breast cancer and melanoma, but its implications extend to the management of all malignancies.

Martin Stockler University of Sydney and Sydney Cancer Centre, Royal Prince Alfred and Concord Hospitals, NSW Email: stockler@med.usyd.edu.au

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COSA, CANCER COUNCIL CALL FOR CANCER TRAINING IMPROVEMENTS IN MEDICAL EDUCATION INQUIRY

The Clinical Oncological Society of Australia (COSA) and The Cancer Council Australia recently provided a joint submission to a Department of Education, Science and Training (DEST) study aimed at determining how Australian medical schools can ensure undergraduates have the right skills, knowledge and professional attitudes to become successful interns and continue their professional development after graduation.

The submission, prepared by The Cancer Council’s advocacy hub with expert advice from the joint Oncology Education Committee and COSA Council, drew heavily on the Ideal Oncology Curriculum to make a number of recommendations designed to ensure cancer management skills in undergraduate and postgraduate medical students reflected the disease’s impact on the community.

It was the latest in a series of joint submissions to public consultations focusing on reform of the medical sector in preparation for population ageing. Other recent inquiries include the Productivity Commission’s review of the medical workforce, which looked at systemic barriers to effective practice through workforce planning and service delivery, and a study into the economic impact of changes in medical technology.

Copies of the joint submissions to these consultations are available at www.cancer.org.au/policy_submissions.

Background

Key stakeholders across Australia have been engaged in widespread debate about medical training in universities, prompting the former Minister for Education, Science and Training, Dr Brendan Nelson, to commission a study that essentially asked the question: “What makes for successful medical education?”

The study looked into graduate learning outcomes, including expected skills and knowledge, and the transition to internship and postgraduate specialist training. It was first proposed by Minister Nelson in an address to the Australian Doctors’ Fund in February 2003.

A roundtable discussion with peak medical bodies was held in May 2003 to discuss the scope and focus of the study, which led to the establishment of a steering committee tasked with clarifying the scope of the study and identifying the relevant strands of research required. The steering committee endorsed several complementary research methodologies for three separate but related strands of research, to investigate the educational outcomes required and how well those requirements are being met.

The research will be completed through a combination of contracted consultancies and DEST activities, which included the public consultation to which COSA and The Cancer Council responded.

Strands 1 and 2 are examining the knowledge, skills and professional attitudes required to prepare graduates for internship and future specialist training, while Strand 3 is examining models of clinical education and the use of clinical teachers in medical education.

The findings will be analysed and consolidated in a final report to inform the future development of undergraduate medical education in Australia, which is expected to be presented to the new minister, Julie Bishop, early in 2007.

COSA/The Cancer Council Australia response

The study’s terms of reference examined undergraduate and postgraduate competencies, ‘readiness’ and attitudes, and undergraduate clinical education models that addressed the need for greater efficiency at the intern level and as preparation for postgraduate training.

A centrepiece of the response by COSA and The Cancer Council was our concern about the decline in cancer management skills observed in medical students and graduates over the past 10-15 years, at a time when the burden of cancer is increasing in step with population ageing.

Much of the evidence to support our recommendations was based on a comparative study published in the Medical Journal of Australia in 2003, indicating that recent medical graduates had less exposure to cancer patients than those who had been trained 11 years earlier.1 The submission also drew upon two previous studies that demonstrated that the comparative reduction in skill levels was part of an alarming, longer-term trend.2 3

As a more general point, COSA and The Cancer Council emphasised that much-needed improvements in cancer management training can be applied to all clinical disciplines and are particularly relevant to communications skills, medical ethics and the principles of life-long learning – all essential to continual improvement in the healthcare system and among individual professionals.

COSA and The Cancer Council’s key recommendations in the context of the terms of reference are that:

1. DEST identifies the improvement of cancer management competency as a core medical education priority.
2. Minimum standards in cancer management competency for graduates be established nationally, along with a mechanism to monitor continual improvement in postgraduate cancer skills and knowledge.
3. DEST scopes ways in which COSA and The Cancer Council Australia’s Ideal Oncology Curriculum can be adopted throughout Australian medical schools.
4. Undergraduates and interns perform minimum clinical cancer management practice and that a cancer exit exam, based on the outline developed by COSA and The Cancer Council, be incorporated into relevant medical curricula.
5. DEST explores options to ensure students in rural locations have adequate access to clinical experience in all elements of multidisciplinary cancer care, including modalities such as radiation therapy for which there is limited local infrastructure.
6. DEST notes the decline in interns’ cancer management competency observed in recent studies and identifies reversing this trend as a priority for graduates and in prevocational and postgraduate training.
7. DEST supports the introduction of a national system of credentialing for cancer professionals, to help ensure that postgraduate training in major clinical disciplines translates to ongoing adherence to best practice.
8. DEST explores opportunities to translate the increase in Australian Government support for independent cancer clinical trials into improvements in medical education.
9. DEST identifies improved communication skills as an increasingly important competency for students involved in all areas of cancer management.

An increased understanding of the role of complementary medicines and patient interest in them be incorporated into medical curricula where appropriate.

The increased role general practitioners play in cancer prevention and early detection, particularly in the diagnosis and treatment of skin cancer, be factored into prevocational and postgraduate training.

Training modules in the prevention and treatment of chronic disease be developed nationally, according to current epidemiological evidence and projections.

The role of practising clinicians as on-the-job trainers of medical undergraduates and interns be formally recognised and supported through national train-the-trainer and incentives schemes.

COSA and The Cancer Council Australia, through The Cancer Council’s advocacy hub, will continue to monitor developments. Cancer Forum readers who would like to express their interest in the process should contact their local COSA Council representative to be informed about this and any other advocacy/policy activity.

References


18TH LORNE CANCER CONFERENCE

9 – 11TH FEBRUARY 2006

After visiting Phillip Island last year, the Lorne Cancer Conference returned to its spiritual, and now refurbished, home at Lorne. Grey skies kept the lure of the surf at bay and everyone inside the seminar room for three days of presentations, covering an exciting program with a focus on oncology and targeted drug therapies.

The first day featured sessions on apoptosis, tumour suppressors and molecular therapeutics. Highlights included Doug Green’s surprising story of the glycolytic enzyme, hexokinase 2 (HK2), and Lyndon’s idea that HK2 is a ‘switch’ that is activated in cancer cells and not in normal cells. A genetic screen was used to identify GAPDH as the major gene that promoted mitochondrial recovery and cell survival in cells lacking a functional caspase-dependent death mechanism. GAPDH is often over-expressed in cancer, but previously it was assumed to be important only for glycolytic metabolism and was not associated with cell survival. Saul Rosenberg (Abbot Laboratories) presented the development of a new drug, ABT-373, that inhibits members of the anti-apoptotic Bcl-2 family. Along with Jerry Adams (Walter and Eliza Hall Institute), who presented in a later session, Rosenberg described how ABT-373 antagonised Bcl-2 proteins to render tumours more sensitive to chemotherapeutic agents, while exhibiting very low toxicity in normal and cancerous
ABL was expressed in pre-B cells from wild type ARF deletions. Sherr presented a model where BCR-leukaemia, but only ALL is commonly associated with lymphoid leukaemia (ALL) and chronic myelogenous who presented on the ARF tumour suppressor and evidence that suggests it is transmitted as an infectious disease. A surprise guest, Anne-Maree development of leukaemia, with microRNA expression presented work showing the role of microRNA in the epimutation is weak and may result in complex family histories. Victoria Richon (Merck Research Laboratories, California San Francisco) described the use of an epigenetic silencing repair genes MLH1 or MSH2. Individuals were identified by which they engage apoptotic pathways. Other sessions on Friday focused on the genetic basis of by the compound alone. The final day featured sessions on oncogenes, molecular therapeutics and ageing. George Demetri (Dana-Farber Cancer Institute, Boston) delivered an inspiring account of his successful treatment of Gastrointestinal Stromal Tumours (GIST) with Imatinib. Demetri highlighted the importance of PET for functional analysis of cancer treatment and detailed the progress being made in treating Imatinib resistance. In another session on the topic of ageing and cancer, Cynthia Kenyon (University of California San Francisco) described a model for studying the effects of ageing on tumour progression using long lived C. elegans mutants, which spontaneously form germ line tumours. The Ashley Dunn oration was delivered by Elizabeth Blackburn (University of California San Francisco), who was the first to characterise the telomerase enzyme. Results from her laboratory have shown that downregulating telomerase by RNA interference rapidly induced growth arrest in cancer cells, without requiring uncapping or substantial shortening of the telomeres. In addition, microarray analysis showed that the knockdown of telomerase changed the expression of many genes – including downregulation of genes implicated in metastasis and angiogenesis. Curiously, expression of a dominant-negative mutant telomerase template RNA produced a very different outcome, uncapping telomeres and rapidly inducing apoptosis in cancerous and pre-cancerous human cells. Her work promotes telomerase as a potential target for anti-cancer therapies. Many thanks and congratulations must be extended to the organisers for assembling such an excellent array of speakers and to the speakers themselves for the high quality of their research and presentation. Thanks must also go to The Cancer Council Australia, the principal sponsor of the Lorne Cancer Conference and for generously sponsoring the first plenary session and the cancer epigenetics session. The CBRC welcomes Emily Brennan as our new research assistant trainee. Emily recently completed her honours thesis in psychology at the University of Melbourne, exploring the influence of message frames, disease familiarity and stage-of-change on smokers’ receptivity to new health warnings about smoking-related diseases. Emily is providing research support for a range of tobacco-related projects including the Population Survey for Quit Victoria.

**News**

**n Centre for Behavioural Research in Cancer (CBRCC) WA**

Dr Owen Carter has received five-years’ funding to begin the Highway Tobacco Control Research Fellowship at CBRCC until 2011.

**n Centre for Health Research and Psycho-oncology (CheRP) NSW**

After four years with CheRP, Deborah Bowman is leaving us to pursue a primary school teaching career.

**n Cancer Research Prevention Centre (CPRC) Queensland**

The CPRC has appointed four new research fellows: Dr Shere Leigh Lawler (Sun Protection) and Dr Katrin Haasdorf (Tobacco Control) joined the Centre in October 2005 and November 2005 respectively; and Dr Marina Reeves (Physical Activity and Nutrition) and Dr Takemi Sugiya (Physical Activity and the Environment) will take up their positions with CPRC in April 2006. Paul Gardner and Alesha Smith joined CPRC in March after being awarded PhD scholarships in Behavioural and Population Health Studies for Cancer Prevention by the Cancer Council of South Australia. In December 2005, Alesha Smith joined CPRC as a postdoctoral researcher in a project to test the impact of a media campaign about the new graphic warning labels on the smoking behaviours of adolescents.

**n Tobacco Control Research Evaluation (TCRE) SA**

TCRE had a number of oral and poster presentations accepted for the UCIC World Cancer Congress and the 13th World Conference on Tobacco or Health.

**Research in the pipeline**

Impact of graphic health warnings and mass media campaign on adolescent smoking behaviours

Victoria White and Melanie Wakefield, along with Edith Szabo, are investigating the impact of the new graphic health warnings on cigarette packs on: 1) adolescents’ awareness of health warnings; 2) perceptions of cigarette brand image; 3) thoughts about smoking; and 4) smoking behaviours. A further aim is to determine the impact of a media campaign about the new graphic warnings on adolescents’ responses. In March 2006, Australia introduced new graphic health warnings on cigarette packs. The introduction of these new warnings was accompanied by a national advertising campaign. An additional advertising campaign promoting the new health warnings will be run in Victoria as well as several other states in May 2006. Currently there is little information on the impact of graphic health warning labels on the smoking behaviours of adolescents. This study builds upon data collected as part of the 2005 Victorian component of the Australian Secondary Students Alcohol and Drug (ASSAD) survey. A sample of schools that took part in the Victorian component of the ASSAD survey in 2005 will be randomly allocated to one of two follow-up conditions. Half of the sample will complete surveys on smoking behaviours and issues relating to the new warning labels approximately four to six weeks after their introduction (April 2006), while the second half will complete the same survey approximately four to six weeks after the launch of the media campaign promoting the new warning labels (June–July 2006). The design will allow us to investigate the impact of the new warning labels on adolescents’ attitudes and behaviours regarding smoking before and after the May media campaign. How does Quit advertising influence calls to the Victorian Quitline?

The aim of this project, being led by Sarah Durkin, is to better understand the relationship between calls to the Victorian Quitline and various aspects of Quit Victoria’s advertising, in the first instance utilizing historical records of advertising on television and radio and calls...
PASS is funded by a Targeted Cancer Prevention Grant from Queensland Health. It focuses on sun exposure, protective behaviours, social norms and the environmental attributes of sporting settings for young adults who compete in soccer, hockey, tennis and surf sports. The study methods (quantitative, qualitative and observational) and aims to:

- examine the interrelationships between physical activity and sport participation and sun exposure in young adults;
- identify relevant attributes of the settings in which sun exposure takes place, for physically active and sedentary young people;
- make recommendations on settings-based approaches that can most appropriately address sun exposure in young adults; and
- identify relevant attributes and norms of the social networks (particularly sporting clubs and less formal groups), through which sun protection behaviours may be encouraged.

Data collection was completed in December 2005 and a report on the study will be presented to Queensland Health at the end of April. Results of the study will be reported in the next issue of Cancer Forum.

**TCRE**

Pilot study to evaluate The Cancer Council South Australia’s support and information pack

Approximately 250 recently diagnosed cancer patients will be recruited through their oncologist, to review the newly developed support and information pack. A postal survey will be sent to all consenting patients four to six weeks after they received the pack from their oncologist. This questionnaire has been adapted from the survey instrument used by The Cancer Council NSW to evaluate their state’s pack. One follow-up call will be made to non-respondents offering them the opportunity to complete the survey by telephone. Results of this pilot study will help to shape the design and contents of the final version of the pack for distribution in South Australia.

The smoke-free pregnancy project

The smoke-free pregnancy project by Quit SA is underway in four South Australian hospitals including the Lyell McEwin Health Service and the Women's and Children's Hospital. The project aims to establish an effective and sustainable set of interventions to reduce the harm caused by smoking among pregnant women in South Australia. It incorporated several phases. One of these phases involved the training of antenatal staff and their colleagues in smoking cessation, so that they were able to conduct brief smoking interventions with pregnant women on presentation to the antenatal clinics. These staff were followed up six months after the intervention was rolled out in September 2004 to assess usage of the brief intervention and usage of a case note insert named the smoke-free assessment and intervention form. In addition, a case note audit was undertaken. Results will be available in April 2006.

GP prostate cancer decision-making workshop evaluation

The Cancer Council South Australia’s Primary Health Care Project Officer is coordinating a series of prostate cancer decision-making workshops for GPs. The workshops aim to present facts about prostate cancer testing to GPs and encourage them to initiate discussions around this with their male patients. Workshops are scheduled every two months from 2006 and will be evaluated using a post-workshop questionnaire and a three-month telephone follow-up survey to assess appraisals of the workshop and use of the knowledge gained in the workshop.

Evaluation of The Cancer Council HelpLine

TCRE is working with The Cancer Council South Australia to undertake an evaluation of The Cancer Council HelpLine, which offers information and resources to those with cancer-related questions and concerns. The project aims to look beyond satisfaction with the service (which has been found to be very high), instead examining the impact of the helpline on the cancer journey among those who have been diagnosed with cancer. Approximately 40–50 in-depth interviews will be conducted between April and June 2006, with an evaluation report of the findings available by August of this year.

Evaluation of the Cancer Counselling Service

TCRE is working with The Cancer Council South Australia to conduct an evaluation of the newly established Cancer Counselling Service, in order to examine the impact of the service on the distress levels of cancer patients. HelpLine callers will be assessed for distress and other psychosocial outcomes and these outcomes will be compared among those who elect the Cancer Counselling Service, those who elect an alternative counselling service and those who elect no counselling. Approximately 150 cancer patients will be interviewed between April and June 2006 and evaluation results will be available in August 2006.

Evaluation of National Youth Tobacco-Free Day

TCRE is working in partnership with Quit SA to determine the levels of participation in National Youth Tobacco-Free Day, scheduled to take place on 5 April 2006. The day involves a large event held in Rundle Mall along with promotional events held at various schools and youth service facilities. TCRE will assess the level of participation and satisfaction with the central event, and will interview a sample of groups sent promotional materials to monitor the extent to which they were used for promotion and event development. Evaluation results will be available in August 2006.
New results
n CBRC
Can home smoking restrictions influence adolescents' smoking behaviours if their parents and friends smoke?
Edith Szabo, Victotna White and Jane Hayman examined the effects of home smoking restrictions and the smoking behaviours of parents and friends on adolescents’ smoking behaviours. This analysis was based on data from the Victorian component of the 2002 Australian Secondary Students Alcohol and Drug (ASSAD) survey. Research suggests that the presence of a total ban on smoking in the home is associated with a reduced likelihood of tobacco experimentation among adolescents. While past research has examined the effects of smoking behaviour on this association, no study has investigated the influence of friends’ smoking behaviour. Analyses showed that students living in homes with a total ban on smoking were least likely to be susceptible to smoking or to have experimented with smoking. While the effect of home smoking restrictions on adolescent smoking was strongest when neither parent smoked, the effect was not influenced by the smoking behaviour of an adolescents’ coterie.
The results suggest that home smoking bans reduce the likelihood of an adolescent trying tobacco regardless of their friends’ smoking behaviours. It was concluded that if parents adopt strong home smoking bans they will reduce some of the influence of friends’ smoking behaviour on the smoking behaviour of their adolescent children. The paper is in press in the journal Addictive Behaviors.

Observed use of sunglasses in public outdoor settings around Melbourne, Australia: 1993–2002
Madagelna Lagerlund, Helen Dixon, Julie Simpson (Cancer Council Victoria), Matthew Spittal, Hugh Taylor (Centre for Eye Research Australia, University of Melbourne) and Suzanne Dobbinson examined trends in the use of sunglasses in outdoor settings around Melbourne between 1993 and 2002. This study was based on a serial cross-sectional observational survey that assessed sun protection behaviours, including use of sunglasses, from 1993–2002, and other variables hypothesised to predict sun-related behaviour. Predictors of the use of sunglasses (sex, age, socio-economic status (SES), activity level and setting, size of social group, and weather conditions) were assessed using multivariate logistic regression. Overall, 36% of people observed wore sunglasses and there was only a slight increase over the years. Sunglasses use was most common among golfers, tennis players, teenagers, males and people in lower SES areas. The paper is in press in the journal Preventive Medicine.

n CBRC
Impact of smoking imagery in youth-oriented magazines
CBRC assembled a mock youth lifestyle magazine from various pages of other youth magazines that incorporated five photographs of smokers associated with positive attributes such as fun, glamorous, sexy, social success, rebellion and power. An identical second version of the magazine was also produced but without the tobacco paraphernalia digitally erased. A total of 357 young people aged 14–17 were recruited, with equal numbers of smokers and non-smokers. Half the smokers and non-smokers were asked to look through the smoking version of the magazine and the other half through the non-smoking version. They were then asked their impressions of various aspects of the magazine, such as the people in photographs, the kind of people who might purchase the magazine and what images they could recall. This was followed by questions encompassing attitudes towards smoking and future intentions to smoke. Smokers were significantly more likely than non-smokers to associate smoking with being cool, sexy, fashionable, glamorous, fun, attractive, popular, tough and independent, but not rebellious. A comparison of smokers and non-smokers who viewed the smoking magazine suggested that the smoking depictions made a greater impression upon the smokers than non-smokers; more smokers made unprompted mention of such imagery than non-smokers (52% vs 34%). However, no evidence was found of the smoking imagery impacting on the impressions teenagers formed of any aspects of the magazine; their rated urge to smoke; their intentions to initiate or continue smoking in the future; or their magazine purchase intentions. The exception was that smokers who viewed the smoking magazine had significantly higher associations between smoking and ‘sexiness’ in comparison to their counterparts who viewed the non-smoking magazine, while the reverse was true for non-smokers. Smoking imagery appears to have merely reinforced pre-existing notions towards smoking in the present study, but does not preclude a cumulative effect of such imagery over time, nor potential impacts of similar imagery portrayed on higher impact media such as movies. The results are currently being prepared for submission to a scientific journal.

Cancer in the workplace
There are little previous data to suggest the impact on employment of individuals undergoing cancer treatments or their carers. The Cancer Council WA tried to determine the extent of the problem with a mail-out survey to cancer survivors and employers. CBRC was asked to assist in analysis of the results and to conduct several follow-on interviews and focus groups. Of the cancer sufferers responding to the survey, two-thirds stated that they continued to work while undergoing treatment, suggesting that the workplace is an important factor in the journeys of many cancer sufferers. Nine-in-ten carers suggested that they too continued to work. Fortunately, a large majority of respondents from both of these groups suggested that at no time did they feel they were treated unfairly or unsympathetically by their employers. Although the methodology was exploratory, we might tentatively assume from these data that workplace discrimination related to cancer treatment is the exception rather than the rule. The consultations highlighted the important role the workplace can have in facilitating the cancer journey of sufferers, by providing a mentally cathartic semblance of continuity while their cancer treatment progresses, and ongoing exposure to the social support networks provided by co-workers. The research yielded nine recommendations to employers. The full report is available at the CBRC website: www.cbrc.curtin.edu.au/reports.htm.

n CHiRP
Training in communication skills from a distance: an oxymoron or reality?
A national team initially led by the late Professor Jill Cockburn has collaborated on a National Health and Medical Research Council funded research grant to examine the effectiveness of consultation skills training with oncologists at improving outcomes for people with cancer. The team comprises Ali Girgis and Deborah Bowman from CHiRP; collaborators from the universities of Newcastle, Sydney and Queensland; the Peter MacCallum Cancer Centre and the Pam McLean Cancer Communications Centre, along with clinical colleagues from a number of major Australian oncology clinics. We have developed an innovative consultation-skills training program for oncologists, with a particular focus on recognising emotional and psychological cues that indicate possible dysfunction and initiating appropriate management for these. The program is delivered over a six-month period, beginning with a two-day interactive face-to-face workshop facilitated by both an oncologist and a psychologist or psychiatrist with experience in consultation skills training. Based on an evidence-based model, clinicians rehearse aspects of the consultations with actors as simulated patients and self-assess the way that they dealt with psychological issues. The remaining sessions are conducted by video-conference, with the facilitators working from a central location and the doctors and actors participating from one of the four remote, convenient locations. Nineteen oncologists from major cancer centres across Australia and 375 of their patients participated in a randomised controlled trial to assess the program’s effectiveness. The intervention was assessed in terms of patient outcomes – improving patients’ quality of life and preventing patients’ psychological morbidity; and doctor outcomes – improving doctors’ detection of psychological issues in a simulated consultation and reducing risk of burnout among doctors. Results suggest the intervention is highly acceptable to doctors. Furthermore, there were significant differences in the intervention group in both patient and doctor outcomes. Compared to patients of the control doctors, patients of the trained doctors showed significantly reduced levels of anxiety at one week from baseline. There were also trends to improved anxiety levels, reduced psychological and patient care and support needs reported by patients at three months from baseline and reduced depression levels at one week from baseline. Trained doctors’ patients also felt significantly more involved in the consultation. Improvements in doctor outcomes in the trained versus the control doctors included better detection of anxiety in simulated patients at six months post-intervention, higher levels of expression of basic empathy, and detection of distress at 12 months.
The Cancer Council welcomes new CEO

The Cancer Council Australia welcomes new Chief Executive Officer, Professor Ian Olver, who is looking forward to the challenge of leading Australia’s peak national non-government cancer control agency from this month.

The Cancer Council Australia’s President, Mrs Judith Roberts AO, said the role of CEO was one of the nation’s most important community sector positions and Professor Olver was well-placed to take on the role.

“For many years Professor Olver has shown an extraordinary personal commitment to the fight against cancer, through his work in clinical research, publication across a range of cancer-related areas and his involvement in delivering services at the frontline of cancer care, including in remote Indigenous communities,” Mrs Roberts said.

Professor Olver takes on the role of CEO of Australia’s largest federated health charity following the retirement of long-serving CEO Professor Alan Coates.

“He brings a diverse range of skills and will continue to provide the national leadership we have seen from Professor Coates in the face of unprecedented challenges in cancer control, in particular the projected growth in cancer incidence,” Mrs Roberts said.

Professor Olver believes the cancer control landscape is evolving, meaning all involved will need to adapt quickly and effectively to ensure the challenges are met.

“It is an important time in cancer control. With the ageing population the number of cancer cases is expected to increase by more than 30 per cent in the next five to 10 years,” Professor Olver said.

“I am particularly keen to see the establishment of Cancer Australia, which will be a very important government agency for the coordination of cancer control in Australia and I look forward to working in collaboration with it.”

Professor Olver points to several key issues currently facing the cancer community, including the implementation of a national bowel cancer screening program.

“An effective bowel cancer screening program is essential in reducing the death rate from Australia’s second biggest cancer killer,” he said. “The announcement last year of the Commonwealth Government’s bowel cancer screening program is welcome news and we look forward to the roll-out of the program.

“Another key consideration moving forward is how we fund high-cost drugs that can have significant impacts on survival and quality of life of cancer patients and also reduce the risk of cancer recurrence. Herceptin is currently receiving significant media attention, but there are more drugs to come that will fall into the same category.”

Professor Olver said prevention would continue to be a key Cancer Council goal and the challenge for those working in the prevention arena would be to communicate the need for Australians to access a single site and download up-to-date resources with the click of a mouse.

“The directory will be updated as new resources become available and revised resources are released – ensuring that primary care professionals have access to the most current information.”

Melbourne GP Dr Adrian Dabscheck said the directory was a welcome resource for general practitioners.

“The resource directory will be a valuable tool for GPs. You can spend so much time searching for information – but having this new one-stop-shop will make it much easier to find reliable, evidence-based information,” Dr Dabscheck said.

The primary care resources directory can be accessed via The Cancer Council Australia website at www.cancercouncil.org.au.
Position statements

New position statements
The Cancer Council Australia has issued a new position statement on cervical cancer screening.

The statement provides recommendations relating to cervical cancer screening including:
- Under the provisions of the current National Cervical Screening Policy, women aged 18 to 70 who have ever been sexually active are recommended to have a Pap smear every two years as part of the National Cervical Screening Program.
- In the absence of sufficient evidence to suggest that alternative screening technologies are more effective than the conventional Pap test, a patient-centred approach for individual decisions about screening methodologies is recommended.
- In line with emerging evidence, The Cancer Council Australia supports the move towards the introduction of a three-yearly cervical screening interval in Australian women in conjunction with long-term evaluation in terms of invasive cervical cancer incidence and mortality.

All positions statements can be viewed on The Cancer Council Australia's website at www.cancer.org.au/positionstatements.

Medical and Scientific Committee news
Following his appointment as Chief Executive Officer of The Cancer Council Australia, Professor Ian Olver has stepped down as Chair of The Cancer Council's Medical and Scientific Committee.

Dr Stephen Ackland, immediate past President of COSA will take on the role of committee chair.

The Committee is the principal advisory committee on medical and scientific matters for both The Cancer Council Australia and COSA.

# Advances in Cancer Research (Vol 91)

GF Vande Woude and G Klein (eds)
Elsevier Academic Press
ISBN: 0-12-006691-2 200 pages plus index
RRP: A$256.30

This book forms part of a valuable series covering a variety of aspects of biomedically-oriented cancer research. The series generally provides state-of-the-art summaries on topical areas. In this edition, the editors have included five papers on diverse topics authored by leading experts in their field. At least two of these chapters provide a particularly topical update on two areas that are of great clinical interest, namely the BRC-ABL tyrosine kinase inhibitor, Imatinib and Histone Deacetylase Inhibitors, which are increasingly finding their way into clinical trials. The other three papers cover prostate cancer and the Met Hepatocyte Growth Factor Receptor, Keratinocyte Growth Factor/FGF7 (KGF) and its potential role in epithelial protection and repair and the Raf-1 Kinase Inhibitor Protein (RKIP).

The paper by Brian Druker provides an informative overview of the molecular biology underpinning chronic myeloid leukemia, development of the BCR-ABL inhibitor Imatinib and pertinent clinical trial information. Important observations on mechanisms of drug resistance and relapse are presented, as well as its increasing role in other diseases, such as gastrointestinal stromal tumours. A personal perspective is provided on ‘lessons learned from clinical trials’ on patient and dose selection, as well as translating the success of Imatinib to other cancers.

Paul Marks, Victoria Richon

and colleagues provide a useful summary on the various classes of Histone Deacetylases and Histone Acetyltransferases (HDACs and HATs), which play a critical role in modulating chromatin structure and the pattern of gene transcription. Their recognised disruption in certain cancers is summarised, including the role that HDACs play in mediating oncogenic activity in certain tumour types including leukemia/lymphoma and breast cancer.

An overview on the various HDAC inhibitors under development is provided, with some insights into their effect on gene expression, non-transcriptional effects and synergy with anticancer agents. Some data on xenograft models is reported, as well as an extensive list of clinical trials underway with a large number of HDAC inhibitors. Anecdotal evidence to date, provided from Phase I studies and early Phase II data suggest that HDAC Inhibitors are worthy of further investigation.

Geoff Lindeman
The Walter and Eliza Hall Institute and Royal Melbourne Hospital, Victoria

# An Introduction to the Use of Anticancer Drugs

Imran Rafi
ISBN: 0-7506-8830-0 194 pages plus index
RRP: $75.00

As suggested by the title, this book will provide healthcare workers who come into contact with cancer patients with an overview of the principles of drug treatments in this rapidly evolving field. The author, a senior lecturer
in general practice and primary care with a special interest in oncology, identifies medical students, doctors in all medical specialties, general practitioners, pharmacists and nurses as the book's intended audience. Although clearly not written for those who specialise in preparing, prescribing or delivering anticancer drugs, this text is ideally suited to students or clinicians seeking an introductory text on cancer drug therapy.

The first chapter presents an introduction to the principles of drug therapy in cancer, giving 10 pages over to a brief review of the role and limitations of this treatment modality. Tumour growth models, the mechanism of action of the major drug classifications and treatment scheduling. The following chapter provides the reader with an introduction to the principles and conduct of clinical trials of anticancer drugs and the related regulatory, ethical and quality of life issues.

Perhaps the most useful chapters in this text are chapters three, four and five, comprising almost two-thirds of the book. These chapters provide summaries of the properties, clinical use and toxicities of individual anticancer drugs, presented by classification. Toxicities of cancer drug therapies to each body system are discussed and tumour-specific descriptions of common drug therapy protocols are presented. The treatment of breast, colorectal, lung, head and neck and other common solid tumours are discussed. Despite addressing the management of multiple myeloma and lymphomas, leukaemia does not appear.

In the final chapters, emerging treatment options are addressed, both in general terms and by major tumour type and issues involving drug interactions in the cancer patient are flagged. Several of these chapters conclude with a short list of suggestions for further reading. A somewhat useful list of abbreviations and limited glossaries of cancer chemotherapy terms and regimes are included at the front of the book and an appendix provides a list of websites for both general cancer and tumour-specific information.

A particularly helpful feature of this book is the precis provided on issues in the treatment of each of the specific tumours discussed, providing a neat summary of the biology, treatment options, common protocols and treatment for some cancers. An accompanying reference list suggests important studies worth review for each tumour type. These will be helpful to readers who are looking to rapidly review the state of knowledge in regards to therapy for particular cancers. However, despite (or perhaps because of) its brevity, this readily portable text will provide a useful and easy-to-navigate introductory reference to drug therapy in cancer.

Trevor Saunders
Peter MacCallum Cancer Centre, Victoria

bowel cancer: foundations for practice
B Borwell (ed)
Whurr Publishers 2005
ISBN: 1-86156-452-X  244 pages plus index
RPP: $23.99

Barbara Borwell describes the book as being "designed and written to assist the reader in embarking on a bowel cancer journey from its evolution and treatment to patient and family centred care". She continues to state that the purpose of this book is to provide a comprehensive introduction to bowel cancer for all health professionals involved in the care of patients and families and to these ends she fulfils a need. Her background in the field of specialist nursing, with the majority being in cancer nursing, has given her a commitment to patient focused care and multidisciplinary team working.

The author is English and the introduction offers a historical background into the organisational and cultural changes, which evolve in the context of improving outcomes through managed clinical networks accountable with providing patient centred services. Opportunities and challenges for the multidisciplinary team are discussed followed by vision for the future. Once past this section, which has limited relevance for the Australian audience, the book has three sections, comprised of 14 chapters. The first section entitled "The nature of bowel cancer" covers the biological basis of bowel cancer, prevention and screening through to diagnosis and staging. Section two is the treatment of bowel cancer, which includes background to surgery, surgical management, chemotherapy and radiotherapy. Section three has a large focus on the management and care of patients with bowel cancer. This section looks at the psychological aspects of care, promoting a patient centred approach, community care, nutrition, professional issues, then complimentary therapies and help and support for cancer patients and their families. Each chapter is easy to read and understand and at the conclusion of each there is a concise dot-point summary of the key points and an extensive list of references. Some chapters have the added advantage of further readings and useful websites that allow the reader to explore the topic in greater detail.

The inclusion of the "Promoting a patient-centred approach to care" chapter highlights how when care is organised, it potentiates and improves the outcome of the treatment and further how patient education and psychosocial support improvements also increase the chances of survival from the disease. "Continuity and community care" emphasises communication, collaboration and coordination as some of the key points in caring for patients, which is useful and relevant information for all health professionals and personnel from other agencies to practice in the care of these patients.

In summary, book is beneficial to nurses, who are the target audience, to help develop skills both theoretically and practically in order to further enhance the quality and effectiveness of patient care.

Michelle Carey
Concord Community Nursing Service, NSW

Breast Cancer Answers
Dr Bruce A. Feinberg
Jones and Bartlett (2005)
ISBN: 0-7637-3465-9   111pages plus index
RPP: $33.00

This book has been written for women newly diagnosed with breast cancer. Its author, Dr Feinberg, describes Breast Cancer Answers as "an outgrowth of my consultations with patients" designed to help reinforce and clarify information on breast cancer and its treatment.

The book aims to answer many of the questions that a newly diagnosed woman may have about her cancer and its subsequent treatment, from diagnosis through to the completion of treatment and ongoing surveillance. Each chapter builds on the information given in the previous chapter and the book has been designed to be easily read from cover to cover in one evening. Illustrations are used to accompany the narrative and to reinforce and clarify the content.

The book begins with a short introduction by the author on how to use it most effectively. It is then divided into three sections and uses a case study format to describe the breast cancer journey to the reader. Section one examines the time before surgery and starts with a comprehensive explanation of the basic science of breast cancer. It ends with an overview of the surgical options including breast reconstruction. It explains some quite complex concepts using simple analogies and illustrations effectively.

Important key words and terms are highlighted in red and can be found in the glossary. Section two examines the planning of systemic treatment and the current systemic treatment for breast cancer. All of the information is current and the author also explains in some detail how standards of care are developed and integrated into clinical practice. Section three touches on issues such as alternative therapies, prevention, advanced cancer and effective follow-up.

The main limitation of this book is that it has been written predominately for American women. Some of the analogies used are specific to the US. The book was also written to fill a gap identified by the author in the American market for quality information on breast cancer. Australian women have access to the National Breast Cancer Centre resources, which are comprehensive, evidence-based and free.

This book is a concise and comprehensive source of information for women newly diagnosed with breast cancer. It is very easy-to-read and the illustrations are extremely helpful in explaining some quite difficult and complex concepts. It is a good starting point for women wanting more information ($33 is not prohibitive) and an excellent resource for specialist breast care nurses and doctors to have at hand for their patients.

Elisabeth Black
NSW Breast Cancer Institute, Westmead Hospital, NSW
Cancer of the Skin

DR Rigel, LM Dzubow, DS Reintgen, JC Bystryn, R Marks (eds)
Elsevier Saunders (2005)

ISBN: 0-7216-0544-3  684 pages plus index
RRP: $327.80

This book is targeted mostly at the practising clinician who diagnoses and treats skin cancer. It has a distinctly North American orientation, from its editorship and authorship, to its content. This will limit its relevance to many practitioners in Australia experienced in dealing with skin cancers on an almost daily basis. While the stated emphasis is on diagnosis and management of skin cancers, the two largest sections are devoted to generic therapeutic considerations and ‘other’ skin cancers ie. other than basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma. The opening 90 pages address various issues relating to biology, epidemiology and prevention, while the closing pages deal with indoor tanning, photodocumentation of skin cancer and “medical and legal aspects of skin cancer patients.” There is also an accompanying CD of photo images used in the text.

Strong points of the book include: the chapters on the molecular genetics of skin cancer/tumour development and some of the more unusual cancers; the range of photographs of (early) melanomas and of BCCs; and the comprehensive coverage of operative and other management techniques, especially of advanced skin cancer.

Limitations are: the curious order of topics (for example the book opens with a chapter explaining the cellular processes of metastasis of skin cancer, mostly melanoma); the uncoordinated and in some cases conflicting repetition of the same topics by different authors across contiguous chapters; and lack of, or parochial, evidence bases for some topics of fundamental importance to the treating clinician (particularly parts of the opening 100 pages where in some chapters there are whole tracts of facts and figures without a single reference cited).

Overall, despite its idiosyncratic ordering, the book is well presented. Formatting highlights include the ‘key points’ in boxed text at the beginning of each chapter, high quality photographs and diagrams and clear tables, even of complex data. The real downside for an Australian audience at least, is the book’s lack of global perspective, leading to an unusual balance favouring the exotic rather than the common in seeking to cover the development and management of cancers of the skin.

Adèle Green
Queensland Institute of Medical Research

Dx/Rx Lung Cancer

CG Azzoli
Jones and Bartlett Publishers (2006)
ISBN: 0-7637-2641-9  123 pages plus index
RRP: $55.00

This book on lung cancer is one of the Dx/Rx Oncology series. Dx/Rx Lung Cancer is divided into 12 chapters ranging from epidemiology of lung cancer through to diagnosis and staging, the various treatment options available for small cell lung cancer/non small cell lung cancer, the treatment of common complications of lung cancer, separate chapters for malignant mesothelioma and malignant thymoma and the last chapter, 'What the Future Holds' makes for interesting reading.

Dx/Rx: Lung Cancer is not a difficult book to read. Each chapter is concisely written and well organised into an outlined bulleted format and highlights the importance of thorough staging in current lung cancer management. The list of references at the end of most chapters is quite short, though current. I wonder whether this may frustrate those who seek more information. References to recently completed clinical trials is consistent throughout the book.

Current chemotherapy and radiotherapy regimes are very well documented as are side-effects and current treatments.

My one criticism of this book is that it does not include the importance of the multidisciplinary team in any of its directions for care regarding patients with a lung cancer diagnosis.

In conclusion, I found that Dx/Rx Lung Cancer to be a valuable and handy resource and I have no hesitation in recommending it. This slim book would fit perfectly in a busy resident’s pocket, in an oncology ward library and would be a useful resource for most healthcare practitioners as a very reliable and up to date tool for those involved in the treatment of lung cancer.

Beth Ivimey
Prince of Wales Hospital, NSW

Dx/Rx: Upper Gastrointestinal Malignancies: Cancers of the Stomach and Esophagus

M Shah
Jones and Bartlett (2006)
ISBN: 0-7637-4743-2  160 pages plus index
RRP $56.10

This book is one from a series titled Dx/Rx Oncology. This is an American publication with the author and series editor coming from the Division of Gastrointestinal Oncology at Memorial Sloan Kettering Cancer Centre in New York.

This handbook focuses on the practical management of stomach and oesophageal malignancies. As the title suggests, it reviews the diagnosis and treatment of these cancers with an emphasis on current practice standards and also highlighting points of contention. The layout is very easy to read and has a logical sequence, but at the same time is comprehensive. It is well organised, with a dot point format being used throughout the book.

In the introduction Shah gives statistics on the worldwide scope of these cancers. Together these two malignancies are second only to lung cancer in global cancer deaths. In western countries the incidence of both gastric cardia and oesophageal adenocarcinoma are increasing more rapidly than for any other type of cancer. The prevalence and mortality statistics underscore the relevance of gastrointestinal malignancies to all healthcare professionals in oncology.

The book is divided into three sections, the first being gastric cancer. Within this section are individual chapters on: epidemiology and pathology; staging; surgery; locally advanced gastric cancer; and treatment of metastatic disease and common non-adenocarcinoma gastric cancers. Section two is titled oesophageal cancer. The chapter topics covered are: epidemiology, staging;
management of locally advanced disease; treatment of metastatic oesophageal cancer. Section three covers both the cancers and contains two chapters, the first is common and unusual complications and the final chapter is a look into the future discussing stem cells and chemotherapy. In the epilogue the author summarises areas where questions still remain unanswered regarding disease management.

This book summarises the diagnostic and treatment issues for oesophageal and gastric cancers in a succinct and well organised manner and would be a useful addition to the library of any health professional dealing with people with these types of cancers.

Meg Rogers
Peter McCallum Cancer Centre, Victoria

**Dx/Rx: Leukemia**

JIM Burke
Published by Jones and Bartlett (2006)
ISBN: 0-7637-2738-5  208 pages including index
RRP: US$65.00

Part of the Dx/Rx Oncology series this pocket-size handbook is a ‘current, quick and concise’ reference for wards and clinics as stated by the editor. However, the editor does not clarify who will find this a useful reference. Judging by the medically technical terminology and the clear and concise emphasis on diagnosis and treatment this is not a book for junior staff, nursing or medical. Written by a physician who is board certified in haematology, oncology and internal medicine, this reference book is a handy guide for those who diagnose and prescribe for patients with leukaemia, as in fact the title suggests.

The book is well set out and moves logically from one leukaemia to another, including related myeloproliferative disorders, less common leukaemias and aplastic anaemia. However the last chapter of this book deals with plasma cell neoplasms and the question has to be asked whether perhaps this is slightly incongruous? In a series of clear and concise reference handbooks does this not warrant its own book?

The information in this book is thorough. Each chapter outlines the disease process in detail under headings such as epidemiology, classification, pathology and treatment. Headings vary slightly from chapter to chapter but all topics use a bulleted format and incorporate tables and pathology slides for ease of information. This succinct format allows the entire discussion of leukaemia and related disorders to be covered comprehensively in nine chapters and 206 pages.

Diagnostic factors and treatment options for each subtype or stage within each category of leukaemia make this a very valuable reference tool. The author states that the treatment protocols he describes are current professional recommendations and acknowledges that different treatment centres may differ in their use of these protocols. This is emphasised by the use of such terms as ‘common practice’ or ‘in many studies’ or ‘the most commonly used induction regime’. Recommendations are based on current research and the reader is directed to these references at the end of each chapter.

Overall Dx/Rx: Leukemia appears to be a comprehensive and valuable reference for qualified physicians who want a quick and easy guide for current diagnostic factors and recommended treatments of all categories of leukaemia.

Clare Backhouse
Leukaemia Foundation of NSW

**European Society for Medical Oncology: Handbook for Advanced Cancer Care**

R Catane, NI Cherny, M Klöke, S Tanneberger, D Schrijvers (eds)
Taylor and Francis (2006)
ISBN: 0-415-37530-4  266 pages plus index
RRP: $22.50

This useful handbook provides, with a distinctly European flavour, a valuable small textbook covering the aspects of palliative medicine necessary for the practice of medical oncology. In the introductory four chapters the distinctive goals of palliative medicine and its relationship with oncology are explored. These chapters contain many familiar definitions and concepts, but they are anchored simply and persuasively within a discussion of the limits of oncology practice. The focus is on the different goals of care in relation to different phases of cancer, however it does not underestimate how difficult the transition from curative to palliative goals can often be.

The second part focuses on the main modalities of active treatment for patients with advanced cancer – surgery, radiotherapy and anti-cancer drug treatments. In each of these succinct chapters, the focus is on the rationale for decision making. Discussion of these principles is both sensible and wise and unpacks the thinking processes underlying the best advice we are likely to receive from colleagues in these various disciplines. I found the chapter on radiation oncology particularly helpful. Despite their brevity, each of these chapters provides a good summary of the major clinical problems and highlights the key evidence supporting good practice.

The core of the book is made up of the chapters on symptom management. These cover the many physical sources of distress for patients with advanced cancer, but also locate these within their broader context – that treatment options may vary with the stage of disease and the goals of care and that symptoms which relate to psychological or spiritual distress will very rarely be alleviated by pharmacological strategies alone. The chapter on pain is particularly good in this regard and includes the important concept of pain with risk factors for inadequate pain control, as initially developed by Bruera – an important syndrome that must be recognised and responded to appropriately. The content of all of these chapters is generally very useful and evidence based and where controversy or inadequate evidence is a problem, this is mostly flagged.

The remainder of the book includes valuable content on psychiatric and psycho-oncology topics, bereavement, communication, geriatric patients with cancer and some starting points for responding to the existential and spiritual issues which are such an intense aspect of caring for patients with advanced cancer. One of the most intriguing and enjoyable chapters was that on self-care, which presents a very culturally appropriate screening tool for clinician distress – the ‘emotional dosimeter’. This I commend to readers as a novel but effective approach to monitoring one’s own well-being. Unfortunately, as is common with much self-care advice in the literature, the diagnosis is easy, but the solutions are sparser.

In general this small book contains a wealth of wise and succinct advice, a good index and is judiciously rather than generously referenced, with many useful summaries and some clear tables. Occasional oddities of phrasing hint at the extremely multilingual origins of the many authors, but the chapters are generally extremely readable and conceptually well organised.

Christine Sanderson
Southern Adelaide Palliative Services, South Australia

**Fast Facts: Skin Cancer**

K Agnew, B Gilchrist, C Bunker
Health Press (2005)
ISBN: 1-903734-63-0  103 pages plus index
RRP: $44.00

Fast Facts: Skin Cancer is suitable for a wide readership from medical students and general practitioners through to the general population.

The text is divided into seven chapters, examining topics such as epidemiology, pathogenesis, clinical features, management, prognosis, prevention and also future trends in the treatment of skin cancer.

The chapters flow logically giving a broad understanding of the incidence and risk factors, before going on to describe the basis of malignancy and its treatments. All chapters are colour coded which makes finding the topic of choice simple.

Each chapter concludes with key points, which pull together the topic discussed and key references, which act as useful pointers to further source information.

Useful tables in an easily readable format are contained
throughout the text, covering subjects such as risk factors, scoring method for the dermoscopic diagnosis of invasive melanoma and the American Joint Committee on Cancer Staging System for melanoma. There are detailed photographs with accompanying explanations, which make essential visual aids and highlight the subtlety in presentation and diagnosis of skin lesions. These photographs the full range of skin lesions, from benign, premalignant to malignant lesions. The photographs bring significant clarity which would have been lost on description alone.

The management section discusses differing types of treatments such as surgery, biopsy, photo dynamic therapy, radiation and topical preparations, as well as the instances in which these treatment modalities would be recommended. It was also reassuring to read that patients should be referred to multidisciplinary centres in cases where the treating practitioner was not familiar with current treatment regimes.

Discussion of inherited disorders such as Gorlin’s syndrome and genetic predisposition were interesting and could prove helpful when assessing familial and skin cancer risk. I found the glossary at the beginning of the book helpful, however inclusion of some of the genetic terminology may have been beneficial.

This text is written from a US and UK perspective and while the basic principles remain the same, there is variation within the Australian setting. The incidence of skin cancer is higher in the Australian population and this may be due to climatic factors and ancestry of the population. Other treatments such as lymphoscintigraphy for stage two melanoma are standard practice in Australia and are not only used in clinical trial setting.

The chapter on prevention is applicable to all populations and is useful information to be aware of when educating on sun avoidance and types of preventive garments that should be worn to reduce risk. Overall this is a useful factual short text that could be used to supplement and assist health professionals globally in the diagnosis and prevention of skin cancer.

Monica Tucker
Sydney Melanoma Unit, NSW

Loss, change and bereavement in palliative care
P Firth, G Luff, D Oliver (eds)
Open University press (2005)
RBP: $54.96

Loss, change and bereavement in palliative care is a book of some 200 pages in easy to understand language with contributions from many authors. Each author presents their topic in a manner that either allows application to clinical practice or makes clinicians stop and assess the practice currently in place.

This book, while reporting largely on the experience of research within the UK, is applicable to the Australian culture and healthcare system citing references from Australian research data. The book is divided into the initial areas of the need for evidence-based research through to the application of research within the clinical setting. There is acknowledgement throughout regarding a flawed methodology in previous work, coupled with previous studies being based on very small numbers. There is also the notion that bereaved people do not want to be bothered by engaging within the research process. To date, the research conducted with bereaved clients does not provide an evidence-base to support this notion.

Palliative care is identified as a late comer to ‘user involvement’. This is seen to be due to the fact that as a service provider palliative care already provides a strong culture of listening and thus advocating on a client’s behalf. “However, offering a voice is not the same as accessing people’s own voice.” (p.120)

The opportunity afforded to grieving individuals to contribute to research enables an account from first hand experience and thus is a sound source of expertise. This in turn can be of benefit to those ensnared in grief to move on with their lives.

There are practical examples that can be readily applied to clinical practice. This book looks at pre and post-death bereavement issues. It highlights areas that require special attention as well as identifying social groups that are at risk of exclusion from support.

It challenges all of us who are in the area of service provision to identify those at risk of unmet needs, to assess coping styles that will be solid predictors of poor bereavement outcomes and to review and critically appraise intervention models. To date research findings demonstrate that not all commonly held ways of supporting bereaved people are supported by evidence.

Finally the challenge is mounted for service providers to look at models of bereavement care that focus on identifying strengths and promoting resilience. This is a move away from models that focus on identifying risk and vulnerability factors.

Ensuring that users of bereavement services are seen as fundamental to policy development and service provision will enable the resilience required for individuals to overcome adversity.

Kate Swetnam
Southern Adelaide Palliative Services, South Australia

Mosby’s Dictionary of Medicine, Nursing & Health Professions
P Harris, S Nagy, N Vardaxis
Elsevier Australia (2005)
ISBN: 0-7295-3734-4 2134 pages
RBP: $82.50

This dictionary had immediate appeal as it has been specifically written for an Australian and New Zealand audience, with the editors using the US published Mosby dictionary as a guide to writing a reference relevant to our region of the world. It is a very user friendly and comprehensive dictionary and would be of use to students, nurses, medical practitioners, allied health professionals and medical secretaries.

The dictionary begins with a colour atlas of human anatomy with each system covered by well-labelled diagrams. The dictionary itself contains extensive information. Alphabetical entries are well identified with each word highlighted in bold text. The description following each word is indented which, again, makes it easy to read the meaning. There are many full colour photographs and diagrams within the text, which enhance and clarify definitions that may not be adequately described by words alone.

As the dictionary targets an Australian and New Zealand audience, it contains spelling familiar to us, but it is also cross-referenced to the US spelling that some of us have adapted to over the years. It contains abbreviations of common terms which are also cross-referenced. Other inclusions are tumour markers and their indications, word roots and local pronunciation, useful tips and some historical information.

Common diseases are listed and not only describe the disease, but contain subheadings that include incubation period, observations, interventions and care considerations. Commonly prescribed and over the counter medications are listed generically and include indications, contraindications and adverse effects.

There are 19 appendices and among the inclusions are units of measurement, assessment guides, medical terminology, normal reference values, nutrition, health promotion and immunisation and many more topics. A section on the use of herbs and alternative medicine includes common herbs and supplements, traditional and popular uses, precautions and contraindications, as well as herb-drug interactions. A CD-ROM which includes a complete collection of all the images within the book and a printable version of the colour atlas of human anatomy accompanies the dictionary. The CD-ROM also contains the full text to accompany the appendix on nursing diagnosis as this only appears as a
A minor criticism of the dictionary is that the attempt to de-identify individuals is not always successful. I think the editors have produced a quality dictionary and I would highly recommend it as a valuable resource for all health professionals.

Jayne Maidens
Royal North Shore Hospital, NSW

New Technologies in Radiation Oncology

W Schlegel, T Bortfeld, AL Grosu (eds)
ISBN: 3-540-00321-5   447 pages plus index
RRP $US269.00

The editors of New Technologies in Radiation Oncology intend this as a textual reference for those entering radiation oncology from a health professional background or from a physics background. The text is an excellent, comprehensive introduction to the developing areas of radiation oncology, but I feel that one would need a strong understanding of basic radiotherapy principles before attempting to make sense of this text.

The text in my opinion would appeal to those transferring from a medical physics degree into specialising in radiation oncology, but I feel that one would need a strong understanding of basic radiotherapy concepts and imaging techniques.

The text covers many aspects of radiation therapy: imaging, planning, treatment and questions and answers, ensuring the target audience remains informed of all aspects of the radiotherapy technology developments. Included are well researched topics such as cone beam CT, brachytherapy and image fusion/production, as well as case studies to demonstrate the specific usefulness of new technologies. The authors present a very practical, pragmatic approach to the technological advances from experts who are in touch with the information required to understand their technologies thoroughly.

The use of case studies would also appeal considerably to radiation therapists and registrars, as it is easy to see how the technology can be easily applied and what would be indications/contraindications of the use of these new technologies. The relevance of the texts to the clinical environment is further enhanced with an impressive list of leading European contributors, many of whom were directly involved in developing these new technologies and have some years of experience as test sites prior to the technology being released.

The topics are arranged in a very logical fashion leading the reader to an increasingly deeper understanding of the technologies that are currently in use and how the future technologies relate to these. The text is also supported by a very well integrated use of diagrams. The use of formulas may be a little hard for non-physicists to comprehend, but the formulas are also be useful for radiation oncology registrars to further consolidate their understanding of radiotherapy concepts and imaging techniques.

The use and how the future technologies may be a little hard for non-physicists to comprehend, but the formulas are
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<th>Name of Meeting</th>
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<tr>
<td>April</td>
<td>European Association for Cancer Research 19th Annual Meeting</td>
<td>Budapest, Hungary</td>
<td>Federation of European Cancer Societies, Avenue E. Mounier 83, 1200 Brussels. Tel: +32 2 775 02 05. Fax: +32 2 775 02 00. E-mail: <a href="mailto:secretariat@fecs.be">secretariat@fecs.be</a>.</td>
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<tr>
<td>2006</td>
<td>American Association for Cancer Research (AACR) 97th Annual Meeting</td>
<td>Washington DC, United States</td>
<td>American Association for Cancer Research (AACR), Philadelphia, PA. Tel: +1 215 440 9300. Fax: +1 215 351 9165. E-mail: <a href="mailto:meetings@aacr.org">meetings@aacr.org</a>. Web: <a href="http://www.aacr.org">www.aacr.org</a>.</td>
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<td>5-9</td>
<td>The American Society of Breast Surgeons 7th Annual Meeting</td>
<td>Baltimore, United States</td>
<td>The American Society of Breast Surgeons, Marti Boyer, 10440 Little Patuxent Parkway Suite 810, 21044 Columbia. Tel: +1 410 992 5472. Fax: +1 410 992 5472. E-mail: <a href="mailto:tforte@breastsurgeons.org">tforte@breastsurgeons.org</a>. Web: <a href="http://www.breastsurgeons.org">www.breastsurgeons.org</a>.</td>
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<td>20-22</td>
<td>5th European Oncology Nursing Society (EONS) Spring Convention</td>
<td>Innsbruck, Austria</td>
<td>EONS – 5th EONS Spring Convention, Brussels, Belgium. Tel: +32 2 775 02 01. Fax: +32 2 775 02 00. E-mail: <a href="mailto:EONS06@fecs.be">EONS06@fecs.be</a>. Web: <a href="http://www.fec.be/conferences/eons5">www.fec.be/conferences/eons5</a>.</td>
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<td>28-30</td>
<td>1st Scientific Conference of Baltic Society for Pediatric Oncology and Hematology</td>
<td>Vilnius, Lithuania</td>
<td>UAB COMBILAS, Renata Baulyte, Jaakto g 12, LT-011 Vilnius. Tel: +370 5 2120001. Fax: +370 5 2120001. E-mail: <a href="mailto:renata@balticconference.com">renata@balticconference.com</a>. Web: <a href="http://www.balticconference.com/bosub2006">www.balticconference.com/bosub2006</a>.</td>
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<tr>
<td>May</td>
<td>Oncology Nursing Society (ONS) 2006 Congress</td>
<td>New Orleans, United States</td>
<td>Oncology Nursing Society (ONS), Pittsburgh, Pennsylvania, PA. Tel: +1 866 257 4667/1 412 859 6100. Fax: +1 877 369 5497/1 412 859 6162. E-mail: <a href="mailto:customer.service@ons.org">customer.service@ons.org</a>. Web: <a href="http://www.ons.org">www.ons.org</a>.</td>
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**CALENDAR OF MEETINGS**

- **Date** | **Name of Meeting** | **Place** | **Secretariat** |
- 6-8 | Reasons for Hope Scientific conference | Montreal, Canada | Canadian Breast Cancer Research Alliance, Susan Wall, 1000 - 790 Bay Street. M5G 1N5 Toronto. Tel: +1 416 596 6598. Fax: +1 416 596 1714. E-mail: info@cbica.ca. Web: www.cbica.ca/language/default.aspx?thisUrl=%2FDefault%2FAisc.htm. |
- 6-12 | 14th Scientific Meeting and Exhibition for Magnetic Resonance in Medicine | Washington, United States | International Society for Magnetic Resonance in Medicine, Berkeley, USA. Tel: +1 510 841 1899. Fax: +1 510 841 2340. E-mail: info@ismrm.org. Web: www.ismrm.org. |
- 14-17 | 11TH International Congress on Oral Cancer (SCODC) | Grado, Italy | ORL Dept. – Ospedale Civile di Udine, Udine, Italy. Tel: +39 432 552 801. Fax: +39 432 554 062. E-mail: gentemenniran.oslo@telenor.com. Web: www.ismrm.org. |
- 16-17 | Diagnostic & Interventional Radiology in Clinical Oncology | Moscow, Russia | N.N. BLOKHIN RUSSIAN CANCER RESEARCH CENTER (NNBRCRC) - Office of International Affairs, 24, Kashiynskaya Street, 115478 Moscow. Tel: +7 095 324 1504. Fax: +7 095 323 5355. E-mail: info@eso.ru. Web: www.eso.ru. |
- 18-20 | Ethics in Oncology | Bled, Slovenia | European School of Oncology, Rita De Martini, Via del Bollo 4, 70123 Milan. Tel: +39 02 8464527. Fax: +39 02 8464545. E-mail: info@eso.ru. Web: www.eso.ru. |
- 18-20 | 6th Nordic Mammography Screening Symposium | Copenhagen, Denmark | Dept. of Epidemiology Institute of Public Health, University of Copenhagen, c/o International Symposium Services, Hellerup, Copenhagen, Denmark. Tel: +45 570 237 823. Fax: +45 570 237 888. E-mail: mammogr@symposium.dk. Web: www.mammogr@symposium.dk. |
- 24-26 | 10th Annual Meeting of European Musculo-Skeletal Oncology Society (EMSOS) | Moscow, Russia | European School of Oncology, N N Blokhin Russian Cancer Research Centre, Office of International Affairs, Moscow, Russia. Tel: +7 95 324 1504. Fax: +7 95 323 5355. E-mail: info@eso.ru. Web: www.eso.ru/eng/index.htm. |
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<th>Secretariat</th>
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<tr>
<td>1-2 April</td>
<td>Head and Neck Course</td>
<td>Hong Kong Medical Centre, Queen Mary Hospital, Sassoon Road, Pokfulam</td>
<td>Tel: +852 22 918 0232 Fax: +852 22 918 1186 Email: <a href="mailto:HKICC05@hku.hk">HKICC05@hku.hk</a> Web: <a href="http://www.hku.hk/surgery">www.hku.hk/surgery</a></td>
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<tr>
<td>20-26 June</td>
<td>2006 Annual Meeting – American Society of Clinical Oncology</td>
<td>Atlanta United States</td>
<td>American Society of Clinical Oncology Annie Allender 1900 Duke St Ste 200, 22314 Denver Tel: 1 703 299 0158 Fax: 1 703 299 0255 Email: <a href="mailto:meetings@asco.org">meetings@asco.org</a> Web: <a href="http://www.asco.org">www.asco.org</a></td>
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<tr>
<td>7-9 July</td>
<td>European Association for Cancer Education (EACE) - 19th Annual Scientific Meeting</td>
<td>Enschede Netherlands</td>
<td>Saxon Hospicholen Inge Geenink Handelikade 75 Postbus 501, 7400AM Deventer Tel: 31 570 663 683 Fax: 31 570 663 611 Email: g.m.geneeskunst.nl Web: <a href="http://www.eso.org/">www.eso.org/</a></td>
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<tr>
<td>11-13 July</td>
<td>2006 Komen Foundation Mission Conference: Many Faces- One Voice (breast cancer)</td>
<td>Washington DC United States</td>
<td>Susan G. Komen Breast Cancer Foundation 2100 N. Central Expy, Dallas, TX, 75201 Tel: +1 972 701 2127 Fax: +1 972 853 4301 Email: <a href="mailto:breastcancer@komen.org">breastcancer@komen.org</a> Web: <a href="http://www.komen.org">www.komen.org</a></td>
</tr>
<tr>
<td>15-16 July</td>
<td>Familial Cancer - Inside Track Conference</td>
<td>Madrid Spain</td>
<td>European School of Oncology 1124 Locust St Philadelphia, PA 19107 Tel: +1 215 568 1622 Email: <a href="mailto:s.clemmons@imedex.com">s.clemmons@imedex.com</a> Web: <a href="http://www.imedex.com/cancer.com/markets/">www.imedex.com/cancer.com/markets/</a></td>
</tr>
<tr>
<td>15-17 July</td>
<td>6th International Conference on the Adjunct Therapy of Malignant Melanoma</td>
<td>Stockholm Sweden</td>
<td>Congres Sweden AB P.O. Box 5619, Karlskoga 118 85 Stockholm Tel: 0046 8 659 6600 Fax: 0046 8 661 9125 Email: <a href="mailto:bith-manabohm@congress.se">bith-manabohm@congress.se</a> Web: <a href="http://www.congress.com/markets/">www.congress.com/markets/</a></td>
</tr>
<tr>
<td>15-18 July</td>
<td>11th Congress of the European Haematology Association (EHA-11)</td>
<td>Amsterdam Netherlands</td>
<td>Eurocongress Conference Management Amsterdam, Netherlands Tel: +31 20 670 3411 Fax: +31 20 673 7306 Email: <a href="mailto:abha@eurocongress.com">abha@eurocongress.com</a> Web: <a href="http://www.eurocongress.com/">www.eurocongress.com/</a></td>
</tr>
<tr>
<td>18-21 July</td>
<td>9th Cancer Research UK Beatson International Cancer Conference</td>
<td>Glasgow Scotland</td>
<td>Beatson Institute for Cancer Research Glasgow, United Kingdom Tel: +44 141 724 0855 Fax: +44 141 338 0426 Email: <a href="mailto:wheelock@beatson.gla.ac.uk">wheelock@beatson.gla.ac.uk</a> Web: <a href="http://www.beatson.gla.ac.uk/summits/conferences/">www.beatson.gla.ac.uk/summits/conferences/</a></td>
</tr>
<tr>
<td>25-28 July</td>
<td>Tumour Vascularisation: New Targets and Therapies</td>
<td>Cirencester United Kingdom</td>
<td>British Association for Cancer Research Barbara Cavill c/o The Institute of Cancer Research, 235-241 Fulham Rd, London SW10 9NH Tel: +44 20 7738 4200 Fax: +44 20 7738 4200 Email: <a href="mailto:info@beaconcare.org">info@beaconcare.org</a> Web: <a href="http://www.beaconcare.org/">www.beaconcare.org/</a></td>
</tr>
<tr>
<td>3-7 August</td>
<td>3rd World Congress of the International Federation of Head &amp; Neck Oncologic Societies (IFHONS)</td>
<td>Prague Czech Republic</td>
<td>International Federation of Head &amp; Neck Oncologic Societies (IFHONS) c/o Guarant International spol.sr.o Prague, Czech Republic Tel: +420 284 001 484 Fax: +44 20 7738 4200 Email: <a href="mailto:info@ifhons.org">info@ifhons.org</a> Web: <a href="http://www.ifhons.org/">www.ifhons.org/</a></td>
</tr>
</tbody>
</table>
### CALENDAR OF MEETINGS

<table>
<thead>
<tr>
<th>Date</th>
<th>Name of Meeting</th>
<th>Place</th>
<th>Secretariat</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-26</td>
<td>4th International Conference on Gastroenterotological Carcinogenesis</td>
<td>Honolulu, United States</td>
<td>The University of Texas M.D. Anderson Cancer Centre Houston, United States Tel: +1 713 792 2222 Fax: +1 713 794 1724 Email: <a href="mailto:eriemery@mdanderson.org">eriemery@mdanderson.org</a> Website: <a href="http://www.manderson.org">www.manderson.org</a></td>
</tr>
<tr>
<td>21-23</td>
<td>2006 Gastrointestinal Oncology Conference</td>
<td>Arlington, United States</td>
<td>International Society of Gastrointestinal Oncology (ISGO) Mr. Robert Ross 200 Broad hologue Rd, 11747 Malville Tel: +1 390 8390 Fax: +1 393 5091 Email: <a href="mailto:emak@emak.org">emak@emak.org</a> Website: <a href="http://www.emak.org">www.emak.org</a></td>
</tr>
<tr>
<td>27-28</td>
<td>European School of Oncology Course (ESO): Skin Melanoma</td>
<td>Istanbul, Turkey</td>
<td>European School of Oncology (ESO) Milano Italy Ph: +39 2 8546 451 Fax: +39 2 8546 4545 Email: <a href="mailto:conferences@esoo.org">conferences@esoo.org</a> Website: <a href="http://www.cancerw.org/esoo">www.cancerw.org/esoo</a></td>
</tr>
<tr>
<td>27-Oct</td>
<td>14th International Conference on Cancer Nursing</td>
<td>Toronto, Canada</td>
<td>International Society of Nurses in Cancer Care (ISNCC) Cheshire, UK Tel: +44 116 270 3309 Fax: +44 116 270 3673 Email: <a href="mailto:conferences@isncc.org">conferences@isncc.org</a> Website: <a href="http://www.isncc.org">www.isncc.org</a></td>
</tr>
<tr>
<td>29-Oct</td>
<td>31st European Society for Medical Oncology (ESMO) Congress</td>
<td>Istanbul, Turkey</td>
<td>ESMO Congress Vanareno-Lugano, Switzerland Tel: +41 91 973 1919 Fax: +41 91 973 1918 Email: <a href="mailto:congress@esmo.org">congress@esmo.org</a> Website: <a href="http://www.esmo.org">www.esmo.org</a></td>
</tr>
<tr>
<td>7-9</td>
<td>International Dermoscopy Course and Conference</td>
<td>Warsaw, Poland</td>
<td>Dept. Dermatology CSK MSWA Dr. Lidia Rudnicka, M.D., PhD Wolska 137, 02-507 Warszawa Tel: +48 22 842 22 90 Fax: +48 22 508 14 92 Email: <a href="mailto:lrd@deimix.com">lrd@deimix.com</a> Website: <a href="http://www.deimix.pl/dermesia.html">www.deimix.pl/dermesia.html</a></td>
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<tr>
<td>13-16</td>
<td>Perspectives in Melanoma X</td>
<td>Amsterdam, Netherlands</td>
<td>Imédx 70 Technology Drive, 30065 Alpharetta Tel: +1 770 751 7332 Fax: +1 770 751 7334 Email: <a href="mailto:lchammons@imidex.com">lchammons@imidex.com</a> Website: <a href="http://www.imedex.com">www.imedex.com</a></td>
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<tr>
<td>13-17</td>
<td>International Congress on Hormonal Steroids/Hormones and Cancer</td>
<td>Athens, Greece</td>
<td>Eramus Conferences Tours &amp; Traical S.A. Mrs. Penelope Mitrogianni I, Kolofontos &amp; Evridikis str., 161 21 Athens Tel: +30 210 725 7693 Fax: +30 210 725 7532 Email: <a href="mailto:info@eramus.org">info@eramus.org</a> Website: <a href="http://www.eramus.org">www.eramus.org</a></td>
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<tr>
<td>Date</td>
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<tr>
<td>November</td>
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<tr>
<td>2-4</td>
<td>7th Meeting of the International Society of Geriatric Oncology (SIGOG)</td>
<td>The Hague, Netherlands</td>
<td>SIGOG - International Society of Geriatric Oncology - by T. Romaryk</td>
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<td>Gevers Deynootweg 62 2586BEN The Hague Tel: +31 70 3318444 Fax: +31 70 3318442</td>
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<td>Email: tariana.com/sigogg-onyology.com Web: <a href="http://www.cancerworld.org/sigog">www.cancerworld.org/sigog</a></td>
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<tr>
<td>5-8</td>
<td>3rd Asian Pacific Organization for Cancer Prevention (APCP) General Assembly</td>
<td>Bangkok, Thailand</td>
<td>3rd Asian Pacific Organization for Cancer Prevention (APCP)</td>
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<tr>
<td></td>
<td>Conference: &quot;Empowering Cancer Prevention in the Asia Pacific&quot;</td>
<td></td>
<td>Neppu, Japan Tel: +61 1 809 7644 Fax: +66 2 955 9986</td>
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<td>Email: <a href="mailto:tiamasvachi@apcp.org">tiamasvachi@apcp.org</a> Web: <a href="http://www.apcp.org">www.apcp.org</a></td>
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<tr>
<td>5-9</td>
<td>48th American Society for Therapeutic Radiology and Oncology (ASTRO) Annual</td>
<td>Philadelphia, United States</td>
<td>American Society for Therapeutic Radiology and Oncology (ASTRO)</td>
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<tr>
<td></td>
<td>Meeting</td>
<td></td>
<td>Fairfax, Virginia, United States Tel: +1 703 227 0170/502 1550</td>
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<td>Fax: +1 703 502 7852 Email: <a href="mailto:meetings@astro.org">meetings@astro.org</a></td>
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<td>Web: <a href="http://www.astro.org">www.astro.org</a></td>
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<tr>
<td>5-10</td>
<td>XVIII FIGO World Congress of Gynecology and Obstetrics</td>
<td>Kuala Lumpur, Malaysia</td>
<td>AIDS Conventions and Events Sdn Bhd Kuala Lumpur, Malaysia Tel: +60 3 4252 9100</td>
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<td>Fax: +60 3 4257 1133 Email: <a href="mailto:cancer.office@2006.com">cancer.office@2006.com</a></td>
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<td>Web: <a href="http://www.figo2006kl.com">www.figo2006kl.com</a></td>
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<tr>
<td>7-10</td>
<td>18th EORTC-NCI-AARC Symposium on Molecular Targets and Cancer Therapeutics</td>
<td>Prague, Czech Republic</td>
<td>Federation of European Cancer Societies (FECS) Brussels, Belgium Tel: +32 2 775 0201</td>
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<td>Fax: +32 2 775 0200 Email: <a href="mailto:FECS2006@fece.org">FECS2006@fece.org</a></td>
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<td>Web: <a href="http://www.fecs.be">www.fecs.be</a></td>
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<tr>
<td>9</td>
<td>American Society for Therapeutic Radiology and Oncology (ASTRO) Annual Meeting</td>
<td>Philadelphia, United States</td>
<td>American Society for Therapeutic Radiology and Oncology (ASTRO)</td>
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<td></td>
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<td>12500 Fair Lakes Circle Suite 375 22033 Fairfax Tel: +1 703 227 0170/502 1550</td>
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<td>Fax: +1 703 502 7852 Email: <a href="mailto:meetings@astro.org">meetings@astro.org</a></td>
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<tr>
<td>9-10</td>
<td>Satellite Meeting “Modeling for Detection of Environmental Carcinogens and</td>
<td>Chiang Mai, Thailand</td>
<td>Asia Pacific Organization for Cancer Prevention (APCOP) Division of Epidemiology and Prevention, Aichi Cancer Center, Research Institute 1-1kanokodien, Chikuzia ku 467-86 Nagoya Tel: +66 1 809 7644</td>
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<td>Modifying Agents in the Asian Pacific”</td>
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<td>Fax: +66 2 955 9986 Email: <a href="mailto:tiamasvachi@apcp.org">tiamasvachi@apcp.org</a></td>
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<td>Web: <a href="http://www.apcp.org">www.apcp.org</a></td>
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<tr>
<td>9-11</td>
<td>2006 ONS Nurse Practitioner Conference</td>
<td>Pittsburgh, United States</td>
<td>Oncology Nursing Society (ONS) 125 Enterprise Drive 15275- Pittsburgh,</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Pennsylvania, USA Tel: +1 866 204 4667/1 412 859 6100 Fax: +1 877 369 5497</td>
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<td>Email: <a href="mailto:customer.services@ons.org">customer.services@ons.org</a> Web: <a href="http://www.ons.org">www.ons.org</a></td>
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<tr>
<td>10-12</td>
<td>ONS 2006 Institutes of Learning</td>
<td>Pittsburgh, United States</td>
<td>Oncology Nursing Society (ONS) 125 Enterprise Drive</td>
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<td>15275- Pittsburgh, Pennsylvania, USA Tel: +1 866 257 4667/1 412 859 6100</td>
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<td>Fax: +1 877 369 5497/1 412 859 6162 Email: <a href="mailto:customer.services@ons.org">customer.services@ons.org</a> Web:</td>
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<td><a href="http://www.ons.org">www.ons.org</a></td>
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<tr>
<td>21-22</td>
<td>Cancer World Conference on Improving Cancer Services</td>
<td>Brussels, Belgium</td>
<td>European School of Oncology Marzana Cassese Viale Beatrice d’Este 37</td>
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<td>20122 Milan Tel: +0039 02 8546 4522 Fax: +0039 02 8546 4545</td>
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<td>Email: <a href="mailto:mcassese@esooncology.org">mcassese@esooncology.org</a> Web: <a href="http://www.cancerworld.org">www.cancerworld.org</a></td>
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<tr>
<td>29-Dec</td>
<td>13th Congress of the European Society of Surgical Oncology (ESSO 2006)</td>
<td>Venice, Italy</td>
<td>ESSO 2006 Conference secretariat – Federation of European Cancer Societies</td>
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<tr>
<td></td>
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<td></td>
<td>(FECS) Brussels, Belgium Tel: +32 2 775 0205 Fax: +32 2 775 0200 Email:</td>
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<td><a href="mailto:ESSO2006@fece.org">ESSO2006@fece.org</a> Web: <a href="http://www.fecs.be">www.fecs.be</a></td>
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<tr>
<td>December</td>
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<tr>
<td>10-14</td>
<td>International Meeting on Cancer</td>
<td>Texas, United States</td>
<td>The Cancer and Bone Society Conference Secretariat 2025 M Street, NW, Suite</td>
</tr>
<tr>
<td></td>
<td>Induced Bone Disease</td>
<td></td>
<td>800 20036 Washington Tel: +1 202 367-1138 Fax: +1 202 367-2138 Email:</td>
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<td><a href="mailto:admin@cancerandbonesociety.org">admin@cancerandbonesociety.org</a> Web: <a href="http://www.cancerandbonesociety.org/">www.cancerandbonesociety.org/</a></td>
</tr>
<tr>
<td>12</td>
<td>The American Society of Hematology</td>
<td>Florida, United States</td>
<td>American Society of Hematology - ASH 1900 M Street, NW Suite 200 20036-</td>
</tr>
<tr>
<td></td>
<td>48th Annual Meeting and Exposition</td>
<td></td>
<td>Washington DC Tel: +1 202 857 1118 Fax: +1 202 857 1164 Email:</td>
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<td><a href="mailto:admin@hematology.org">admin@hematology.org</a> Web: <a href="http://www.hematology.org/meetings/2005/index.cfm">www.hematology.org/meetings/2005/index.cfm</a></td>
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</table>
**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.

**MEMBERS**
The Cancer Council ACT
The Cancer Council New South Wales
The Cancer Council Northern Territory
The Cancer Council South Australia
The Cancer Council Tasmania
The Cancer Council Victoria
The Cancer Council Western Australia
Queensland Cancer Fund

**AFFILIATED ORGANISATIONS**
Australasian Association of Cancer Registries
Clinical Oncological Society of Australia Inc
Palliative Care Australia

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Vice President
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Members
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Professor C Gaston
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Professor D Hill AM, PhD
Hon S Lenehan BA, DipMan, MBA, FAICD
Dr A Penman
Assoc Professor S Smiles RN, RM, ICC, BHA, GradDipPSEM
Dr K White PhD

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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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President Elect
Assoc Professor D Goldstein MBBS, FRACP

Executive Officer
Ms M McJannett

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Professor L Kristjanson RN, BN, MN, PhD
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Cancer Research
Clinical Research Professionals
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Lung Oncology
Medical Oncology
Melanoma and Skin
Neuro-oncology
Palliative Care
Pharmacy
Psycho-Oncology
Radiation Oncology
Regional and Rural Oncology
Social Workers
Surgical Oncology

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

Membership fees for 2006
Ordinary Members: $160
Associate Members: $100
(includes GST)