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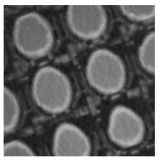

CANCER FORUM

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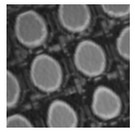

Progress in cancer control: the Alan Coates effect

Alan Coates: an appreciation

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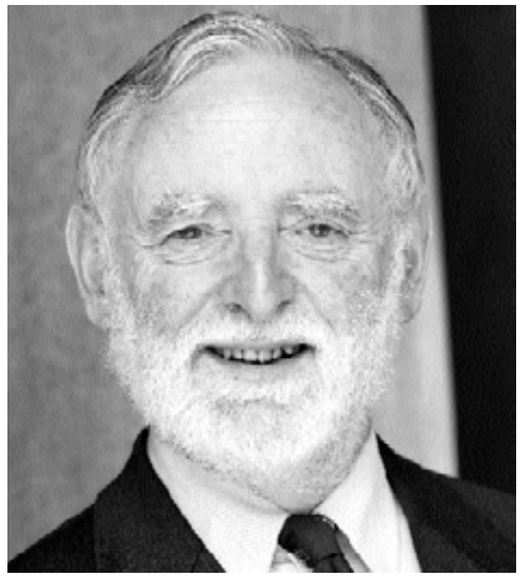
The last 50 years have seen major changes in cancer management. There have been great advances in prevention, early diagnosis and cost effective management with much emphasis on "holistic" care involving multidisciplinary teams with a commitment to the best possible care for all phases of cancer management 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.



Retiring CEO of The Cancer Council Australia, Professor Alan Coates AM.

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.

Progress in cancer control: the Alan Coates effect

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Upon Alan Coates' retirement after eight years as Chief Executive Officer (CEO) of The Cancer Council Australia we have chosen 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 control.

In this Forum, a number of Australia's leading oncologists and researchers discuss important advances in the prevention, early detection and management of cancer. Many highlight the role Alan Coates has played; others focus on developments that Alan helped facilitate or championed. It is evident that he has directly or indirectly influenced people, perceptions and progress across the whole spectrum of cancer control in Australia and overseas.

Through a mixture of history, clinical practice and science these articles provide a context and description of Alan's life and work. They highlight the breadth and diversity of his knowledge, clinical experience and interests, as well as the personal qualities, which combined to great benefit in his role at The Cancer Council Australia. As Ray Lowenthal attests, in addition to his apparent knowledge and skills, Alan brought to this role a previously unheralded capacity for leadership, skilful advocacy, networking and organisational management.

While the subjects of these articles vary widely, a number of themes emerge. In references to Alan's contribution to cancer control, key words and phrases are often repeated: evidence, multidisciplinary care, collaboration, quality of life. Lowenthal describes The Cancer Council's many achievements under the stewardship of a CEO who was "collaborative rather than antagonistic". Andrew Coates acknowledges Alan's "cross-disciplinary vision". Sue Pendlebury notes his insistence on "evidence of efficacy" and formation of multidisciplinary teams before the term was used in the cancer care context. John Forbes praises his colleague's "remarkable breadth of scientific knowledge, his humanity and his wise counsel".

Ian Tannock questions whether the increasing commonness of PSA testing is in fact "progress" in cancer management, apart from effectively curing asymptomatic prostate cancer. Toronto-based Tannock argues that for many men knowledge of their PSA is harmful, creating an anxiety he terms "PSAitis", and subjecting them to investigations and treatments that adversely affect their quality of life rather than permitting them to live peacefully with asymptomatic prostate cancer.

As has been the case in other countries, the debate about PSA screening has been contentious. In presenting The Cancer Council's position Alan has endured professional and personal criticism. The Cancer Council does not support population-based screening of asymptomatic men for prostate cancer because there is not yet direct evidence of a net benefit in terms of reduced mortality. Despite claims of the opposite, Alan has in fact done many Australian men a great service by his unswerving espousal of this evidence-based position. He has taken great efforts to explain the value of a patient-centred informed decision-making approach to PSA testing in place of mass screening that could, as Tannock argues, be more harmful than beneficial.

In the next three articles, John Thompson, Andrew Coates and Rick Kefford discuss advances in the management of melanoma: Thompson provides a historical perspective of progress in surgical management; Coates explains how cross-disciplinary collaboration has enhanced "mapping" of melanoma metastases; and Kefford provides an update on developments in the field of experimental therapies. As these authors and others have noted, Alan Coates contributed greatly to improving treatment of melanoma, largely through his long service with the Sydney Melanoma Unit, involvement in clinical trials and commitment as a clinician, researcher and CEO of The Cancer Council to the development of evidence-based management guidelines. Kefford cites some of the pioneering contributions made by Alan in investigating systemic treatment of melanoma. What lay beneath the published literature was a gifted and highly principled unwavering commitment to clinical science and to multidisciplinary care that continues to inspire all those with whom he works and has made him the deeply respected mentor of many Australian oncologists. In a tribute to his father's "cross-disciplinary vision", Andrew Coates illustrates the potential benefits to be gained from 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.

The articles by Frazer, Forbes and Pendlebury describe world-leading research by Australian clinicians that has improved, or is poised to advance, the prevention and management of cancer. These are appropriate inclusions in a Forum dedicated to a man who has not only personally been at the forefront of cancer research but has, in his various capacities, been a great advocate for and supporter of research, particularly clinical trials.

Frazer outlines the viral aetiology of cervical cancer and the development, and potential, of vaccines based on human papillomaviruses to greatly reduce the cervical cancer burden. Cervical cancer is a particular problem in Aboriginal communities within Australia and in many of our near neighbour countries, where prevention through screening is not currently feasible. Alan has demonstrated, through his work with The Cancer Council Australia and internationally with the International Union Against Cancer, a consistent interest in improving cancer control in the Australian Indigenous community, 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 trials 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 the challenge in managing breast cancer – and the fundamental objective of multidisciplinary care – is to "optimally integrate" all treatment modalities. She acknowledges Alan's leadership in supporting truly multidisciplinary clinics, developing guidelines and fostering discussion and collaboration.

Forbes also acknowledges Alan's global leadership with respect to quality of life studies – high on the ANZ Group's agenda from the beginning – and development of quality of life measurements "as the norm rather than an add-on for many trials". Alan's commitment to focusing on patients' quality of life is also the subject of the final triptych of articles, by three of Australia's leading oncologists, researchers and advocates for the improvement of cancer management and care: Ian Olver, Martin Tattersall and Martin Stockler.

While Olver details developments in antiemetic therapy regimens intended to reduce distressing side effects of chemotherapy for many cancer patients, Tattersall examines a series of published papers about cancer patients' perceptions of the burden of chemotherapy. But both note the continuing resonance of a 1983 study by Coates et al that highlighted Alan's commitment and drew others' attention to the needs and perceptions of patients with respect to quality of life. As Tattersall notes, this and subsequent papers in the series co-authored by Alan, "illustrate [his] skills in measurement and analysis" and provide insight into Alan's career-long focus on the needs and concerns of patients.

Martin Stockler also highlights Alan's quality of life research and published articles that have "had enduring influences on how we think about cancer and manage it". His article highlights three areas of practice in which Alan's commitment to thoughtful and well-designed studies have produced counterintuitive conclusions that have shaped oncology practice. Key to each was the notion of incorporating patients' attitudes and opinions into judgements about treatment, which has proved to be of great benefit to patients in terms of both their treatment outcomes and involvement in decision making.

In summary, this Forum lauds Alan's major contributions to cancer research, particularly: the management and support of clinical trials; the treatment, care and support of people with cancer – both as a clinician and an advocate; public awareness and understanding of cancer; and enhancing Government funding and commitment to improving cancer control in this country. As Stockler concludes, it is Alan's contribution to "thinking" as well as practice in oncology that will be his legacy.

We suspect there is more to come.

Alan Coates and The Cancer Council Australia

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Abstract

Alan Coates was appointed the inaugural Chief Executive Officer of The Cancer Council Australia (then the Australian Cancer Society) in 1998 and has since amassed achievements in the areas of advocacy, alliances and member services. Under his stewardship, The Cancer Council Australia has become recognised as Australia's peak non-government cancer control organisation, influencing and guiding national cancer control policy and action. His rare combination of intellect, clinical knowledge, leadership, skilful advocacy and diplomacy has greatly contributed to reducing the burden

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 academic oncologist, but 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 output until then had been largely on the theme of cancer management rather than prevention, whereas the latter obviously would be a major focus 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's stewardship, the ACS 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 and the public as much more. Successive Ministers for Health were soon turning to Alan for authoritative advice. Indeed, the respect accorded him is exemplified by a quote from current minister Tony Abbott, who in 2005 stated that he had made policy decisions in the hope of getting "a better report card from Professor Coates". By astutely making appointments of staff with the appropriate skills, Alan presided over an organisation that cooperated with its member bodies (the state and territory Cancer Councils) to: greatly increase income from donations, sales and grants; largely unify the organisations by creating a common logo and (mostly) common nomenclature; and effectively address differences or disputations to ensure clear and consistent public communications.

For Alan too this was a 'win-win' situation. Despite the demands of the new job, Alan was able to carry on and indeed extend his work with global cancer organisations, including his involvement in international breast cancer trials groups. During the period of his appointment Alan continued to publish prodigiously. In fact, he has been a key author on a number of important recent papers that have advanced the treatment of breast cancer.[1,2]

None of this came easily. Let's not pretend otherwise. As in the political sphere, federal-state disagreements sometimes were stark, especially in the early days. There were times when wrangling between Alan's upstart federal organisation and some of its larger, longer-established state counterparts threatened to break the new entity. But Alan had a vision for the role of a national cancer body and held his ground. In the end all recognised that the greater good would come from collaboration rather than conflict.

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, now mostly 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 includes ACN (Australian Cancer Network), COSA (Clinical Oncological Society of Australia), NCCI (National Cancer Control Initiative), NHPAC (National Health Priorities Action Council), CSG (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 the model The Cancer Council 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 Australia and allies is the 2003 publication Optimising Cancer Care in Australia.[3] This is a carefully crafted, evidence-based work that has had, and continues to have, considerable sway over the development of government policies at both state and federal levels. There is no other work like it and it proved to be an influential tool in The Cancer Council's efforts 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 the Bush,[4] the report of a conference that was held at The Cancer Council Australia's initiative. It highlighted the inequities suffered by cancer patients residing in Australia's rural and remote communities and their need for special assistance was made pointedly self-evident. The specific cancer control needs of Australia's Indigenous people were brought into 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 Australia's National Cancer Prevention Policy, the only comprehensive guide to effective measures for preventing cancer in Australia, also occurred during Alan's tenure.

The Australian Cancer Network, an organisation supported by The Cancer Council Australia – which was and continues to be superbly steered by Emeritus Professor Tom Reeve AC CBE – has produced a number of highly influential Clinical Practice Guidelines.[5-6] The aim is to guide clinical behaviour to minimise unjustified variability between treatment recommendations arising from different specialists or different geographical locations. Although initially some clinicians were fearful the guidelines would adversely affect their freedom to make decisions in the best interests of their individual patients, in fact the opposite has proved to be the case. Guidelines give the evidence base that underlies optimal clinical decision-making. Overall there is little doubt they have contributed significantly to improving the survival statistics of cancer patients in Australia, which now are among the best in the world. Alan, through his work in this sphere, has shown how a clinician can influence more widespread treatment decisions than just those of 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 advocacy was complemented by representation on many government forums and by influential submissions made to numerous government inquiries. Cancer has become recognised as a National 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 – following 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, concatenate eight years of effort into a single set of figures from 1998 to 2005, in which the Federal Government increased its four-year cancer-specific funding from $8 million to $189 million. Although The Cancer Council did not act alone in bringing about this outcome, its role was crucial. In particular, for the 2004 federal election The Cancer Council produced a policy document, Cancer Priorities: Issues for the Federal Election, the core elements of which were largely adopted by both major parties. The setting up of the new national umbrella organisation Cancer Australia, due to be established in 2006, will be a prime tribute to the success of Alan's advocacy. For patients and the general public it will spearhead the introduction of many of the outstanding cancer control initiatives for which The Cancer Council has been advocating for years.

Alan's success in advocacy is underpinned by his experience as a cancer clinician and his encyclopaedic familiarity with the scientific literature – he never makes statements that cannot be supported by evidence, which he can quote chapter and verse. But he also has a knack of being able to explain complex technical points in ways that are understandable by the non-expert; thus he is much in demand by the media. In this role he has greatly enhanced the public profile of the Cancer Councils and their recognition as a trusted, independent source of information. Furthermore, he has shown an understanding of the need to think beyond the scientific – successful advocacy means also facing up to the financial, political and social aspects of policy-making. Although not shying away from making points firmly where he deems this necessary, his overall approach to government has been collaborative rather than antagonistic. Much work never gets public recognition – for example the central behind-the-scenes role of The Cancer Council in the 2003 decision of the

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 player in town though there was certainly initial jostling for 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 adviser 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 strategies. Our relationship with the American Society of Clinical Oncology, the world's premier clinical cancer organisation, was strengthened when Alan was elected as the first non-American member of its Board of Directors, a tribute to his international reputation.

All this was done in a way that enhanced rather than subsumed 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 developing its own methods of fundraising. However the state and territory organisations (each being a member of the ACS/The Cancer Council Australia) soon realised that they could gain considerable benefit by coordinating these activities. Indeed, such collaboration was one of the major activities of the ACS prior to the appointment of Alan as its first CEO. Under Alan's stewardship, such activities have been greatly strengthened, with measurable success. There has been reduction of duplication and conflict, coordination of effort and production of uniform supporting materials for events such as Australia's Biggest Morning Tea, Daffodil Day, Pink Ribbon Day, and so on. There have been annual increases in fundraising event income, with almost quadrupling of national revenue since 1998, from $7.3 million to $27.3 million in 2005.

These funds underwrite cancer research projects and sustain state and territory prevention, patient support and information services – the vital local face of the Cancer Councils.

A small triumph has been the near uniform national adoption of The Cancer Council brand. In 1998 each state and territory had its own name and logo. The federal body, the Australian Cancer Society, was distinct again. Now there is a national logo – the daffodil – and, with the exception in 2006 of only one state, uniformity in 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 brand has provided a combined dividend worth 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

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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. Here I suggest that there is no proof that knowledge of PSA improves the average life expectancy, either 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 (PSAitis), that it identifies disease in many men that

"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 many prostate cancer support groups, and the American Cancer Society, recommend that all men older than 50 with reasonable life expectancy, should have their serum PSA measured. A raised serum PSA would then lead to further investigation to rule out prostate cancer and to treat prostate cancer if it is found. Many would also apply the directive to those who have been treated for localised prostate cancer by prostatectomy or radiotherapy, so that recurrence can be detected early and to those men who have advanced disease. Is this good advice? Alan Coates and I share not only a long-time friendship, but are also men of a certain age who have made a conscious decision not to know their PSA. Here I will outline arguments to suggest that for many men knowledge of their PSA may be harmful rather than beneficial.

I will not examine in detail the arguments for and against PSA screening, which have been widely discussed elsewhere.[1-3] I know from the experience of giving talks to prostate cancer support groups that men diagnosed with prostate cancer by PSA screening, who have no evidence of disease after treatment by prostatectomy or radiotherapy, believe firmly that PSA screening has saved their lives. Indeed for some of them it undoubtedly has. However this is not proof of overall benefit and many of those so diagnosed and treated would have died of other causes without discovery of their occult prostate cancer in the pre-PSA era.[2,4,5]

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.[6] 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 most men become functionally impotent within two years after either treatment – nerve-sparing or not.[7,8] As Talcott[9] 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 they will provide 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 ultrasound-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 benefit. Black et al[10] 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 the prostates of elderly men, some of them will develop bleeding or infection and a consequent death a few months later from pulmonary embolism is likely to be reported as "unrelated". Slippery-linkage indeed.

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 their disease. In 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.[11] 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 those most 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.[12]

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 they 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 from earlier therapy for those without evident metastases,[13] the trial had substantial flaws. I know of no reliable evidence that early treatment will improve their longevity, as opposed to waiting 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 – PSAdynia or PSAitis - anxiety about PSA, is a major problem for patients who are otherwise without symptoms due to their disease.[14,15]

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.[16] 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 1986 and a large study in the New England Journal of Medicine from 1987[17] established the end of peaceful coexistence between occult deposits of prostate cancer cells and their asymptomatic hosts. Entering the terms PSA and prostate cancer into Medline now identifies more than 8000 papers. No longer do men arrive for their annual check-up in blissful ignorance that they harbour asymptomatic prostate cancer. Instead they arrive flustered and anxious, sometimes with graphs or computer print-outs – consumed by knowledge of their PSA. For many men PSAitis 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.

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SURGICAL MANAGEMENT OF MELANOMA: HAVE WE MADE ANY PROGRESS IN 100 YEARS?

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Abstract

In the early 20th Century, excision of all primary melanomas with >5cm 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 (<1mm) 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 staging and prognostic 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

Treatment of the primary melanoma

In 1907, William Sampson Handley[1] reported pathways along which melanoma spread 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 database, he advocated wide local excision of the primary melanoma, regional lymph node dissection and amputation in selected cases. Nearly a century later, revised management policies are introduced only when they can be justified by carefully planned and well conducted large-scale randomised controlled trials. It is nevertheless instructive to review the history of melanoma management from the surgical point of view, because it highlights some of the difficulties that are inevitably encountered when management policies are based on anecdotal experiences and retrospective rather than prospective studies.

Such was the paucity of information available to guide melanoma management policies in the early 20th century that even by 1935 Sampson Handley had treated "only 8 to 10 cases, apart from hopelessly inoperable ones".[2] Hogarth Pringle in 1908 had also recommended excising tumour and adjacent skin down to and including the deep fascia.[3] These important historical documents became the basis of melanoma treatment for many subsequent decades, especially when strengthened by Olsen's report that atypical melanocytes were often found within 5cm of the primary tumour.[4] During this period excisions 10cm or more in diameter, with correspondingly large skin grafts, were regularly performed at melanoma treatment centres around the world. This radical surgical management of primary melanoma initially developed in response to the almost universal presentation of patients with locally advanced tumours.

The recommendation to always excise very widely down to and including the deep fascia, was subsequently abandoned[5, 6] and 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[7] and Sweden,[8] 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 other 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.[3] This proposal established the basis of regional lymph node treatment for 60 years. The policy was founded on the earlier premise by Snow[9] 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 (ELND) for all patients with higher-risk tumours. Some earlier randomised but poorly stratified trials undertaken by the World Health Organization (WHO) Melanoma Program[10] and North American groups[11] 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 1874[12] had categorically stated that lymphatic drainage never crossed the midline. He later modified this to exclude sites within 5cm of each side of the original vertical and horizontal dividing lines of the body. This concept was embraced by most practitioners until quite recently, when it became obvious from preoperative lymphoscintigraphy performed in large numbers of patients that, particularly on 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.[13] Later, more carefully stratified randomised trials, the Intergroup Melanoma Surgical Trial[14] and the WHO Melanoma Program Trial[15] in which either blue dye or radio-colloid tracer 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 postitive during follow-up had the poorest prognosis. The principal criticism of this latter trial was that the sample size did not allow sub-group analysis. The other crucial outcome in the WHO trial was that 36 patients with clinically negative but histologically postitive nodes who had an ELND (NO+), had a significantly better five-year survival rate (48% versus 27%; p<0.04) than those 25 patients with clinically negative nodes not undergoing ELND, who subsequently developed clinically and histologically overt lymph node disease (N1) (Figure 1). Thus the immediate dissection of positive but subclinical node metastases appeared to result in improved long-term survival. This clinical trial observation provided an incentive to pursue development and validation of the less invasive technique which has subsequently revolutionised the treatment of higher-risk patients – sentinel node (SN) biopsy.

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.[16] 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%

Figure 1

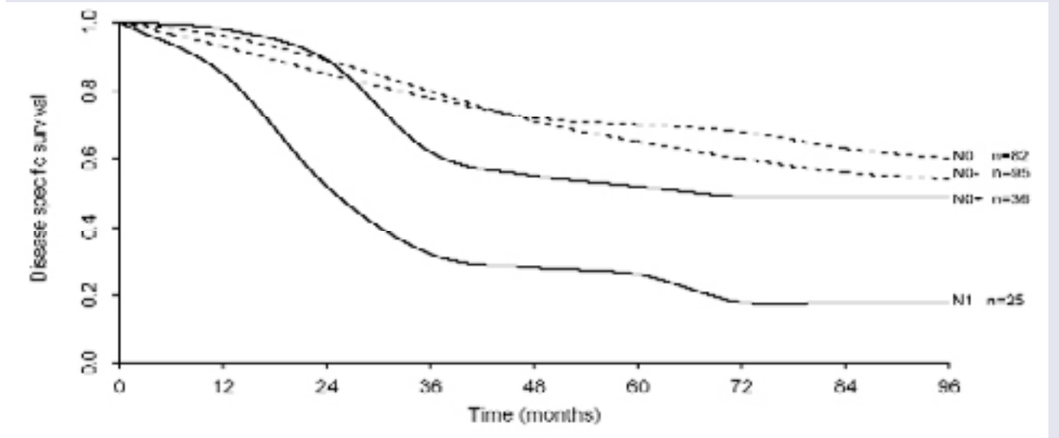
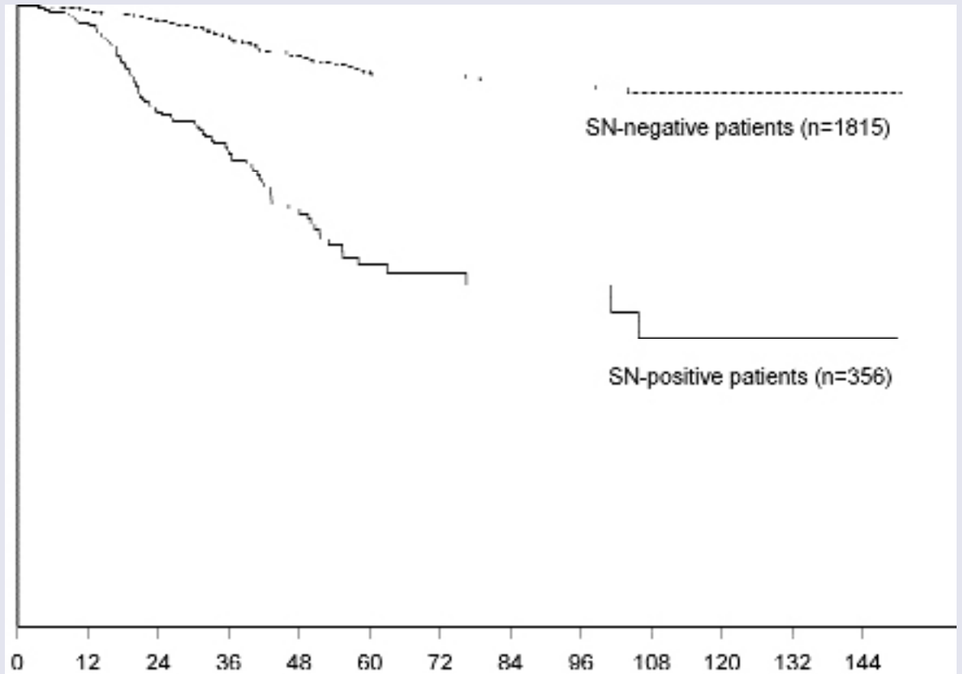


Figure 2



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 States[18] and Australia.[19] 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 lymphoscintigram, 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.[22-27] 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 experience[28] 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 (MSLT-I),[29,30] have recently been reported[31] at an international meeting and a paper documenting the outcome of this trial was submitted for publication in mid-February 2006. The MSLT-I results indicate

that there is no significant overall survival advantage between those patients with intermediate thickness melanomas randomised to receive wide excision of their primary melanoma together with SN biopsy and those having wide excision alone. However, patients who are SN positive appear to have a significantly better survival outcome if they have an immediate completion 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). Publication of the full MSLT-I results is awaited with great interest. The morbidity of the SN biopsy procedure is low[30] and the suggestion that performing an SN biopsy may increase the rate of intransit metastasis has been convincingly disproved by four large retrospective studies from the MD Anderson Cancer Center, the John Wayne Cancer Institute and the SMU,[32-35] and most recently by the MSLT-I results.[31]

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 (ie. non-SN) metastases in their regional nodes. A second international multicentre trial (MSLT-II), designed to answer this question, commenced patient accrual in late 2004. 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 node field and have a complete node dissection 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.

Thus while there is strongly suggestive evidence of a survival benefit for node-positive patients having SN biopsy, there is still no absolute proof of this. However, even if no survival benefit is ever able to be demonstrated, there are still compelling reasons to perform SN biopsy.[36,37] The procedure undoubtedly provides the most accurate staging that is currently available. It also provides the most reliable estimate of prognosis and allows patient selection and stratification for adjuvant therapy (such as with interferon alpha) and for adjuvant therapy trials.

Minimally 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.[38,39] SNs containing metastatic melanoma produce spectra with characteristic peaks of taurine, choline 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, 41]

The role of surgery for apparently isolated metastatic disease

It has been known for many decades that local melanoma recurrences and intransit 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.[25] 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 metastases[42-44] and five-year survival rates exceeding 20% after complete resection of lung metastases.[45,46] 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. ■

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MAPPING THE HUMAN BODY: THE IMPORTANCE OF CROSS-DISCIPLINARY THINKING

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Abstract

The history of scientific thought is marked by spikes of revolutionary thinking, followed by periods of evolutionary consolidation. Both are essential components in the continued development of our understanding. Generally, the revolutionary spikes are instigated by a few (or often one) maverick thinkers who are willing to reassess the conventional wisdom and set out in a new direction. These revolutionary spikes are temporally well spaced, but even during the evolutionary periods, there is a requirement for continual reassessment of the relevancy of other disciplines to one's own. This paper examines one such example of the combination of disciplines (radiography and geography) that might otherwise be considered disparate and goes on to make some general observations about the importance of such

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 marked 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 however, 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)[1] 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 theme is a layer of data that is linked geographically to other data layers of different themes. A GIS can be used to project combinations of geographical interrelationships of the various data layers onto a single map. Conversely, individual themes can be separated from 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 they have a location in relation 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 must be terrestrial (or, occasionally, ex-terrestrial, 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 fields can be recorded. This is achieved by injection of the radiopharmaceutical Technetium-99m-antimony sulphide colloid (^{99m}Tc-Sb_2S_3) 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 are computer 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 channels, interval nodes (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)[2]). Lymphoscintigraphy has shown these concepts to be incorrect in a large proportion of patients.

Mapping the primary lesions and their draining node fields allows the researcher to quantify the divergence of paths actually taken from those predicted by Sappy 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 (ArcViewR). The images produced 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 the locations and depth 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 the 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 nodes and any 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 initial 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 about 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 technological 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 as simple as entering some 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 the revolutionary breakthroughs made have very often come with the introduction of ideas from outside the field.

Acknowledgements

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FORUM

Melanoma: narrowing the sights on an evasive enemy

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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 this signalling pathway include the cell cycle regulator cyclin D1 and the melanocyte-specific transcription factor, Mitf. Newly tested inhibitors of the RAF pathways, like sorafinib, 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 bosentan. Considerable hope is also provided by recent Phase II trials with monoclonal antibodies such as ticilimumab and ipilimumab, which inhibit immunosuppressive cell signalling.

Metastatic melanoma

Melanoma is remarkable for variability in its pattern of spread.[1] 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 hind-quarter amputation.[2] 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 disease 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.[3] 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.[4] 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.[5]

In a recent revision of the American Joint Committee on Cancer (AJCC) Staging System for Melanoma,[6] Stage IV melanoma has been subdivided into three prognostic groups. The M1 category includes those patients with lymph node and/or subcutaneous metastases and has a median survival of >12 months and a two-year survival of 15-20%. The M2 category has pulmonary metastases +/- subcutaneous or lymph node involvement, and has a median survival of 9-12 months and a two-year survival of 10%. The M3 category has other visceral involvement, or any site with an elevated serum lactate dehydrogenase (LDH). Although non-specific, the LDH is an independent prognostic factor for patients with metastatic disease[7] 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,[8] has been standard best systemic therapy for metastatic melanoma since the early 1970s[9] and its use in Australia was pioneered by Gerald Milton and William McCarthy at Sydney Melanoma Unit.[10] 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%.[11-13] However, in recent Phase III prospective randomised trials, in which dacarbazine has been standard therapy, response rates were 6.8-13%.[14-16] The use of combinations of cytotoxic drugs, such as the widely used 'Dartmouth' regimen – consisting of cisplatin, dacarbazine, carmustine and tamoxifen, show no advantage over dacarbazine alone.[11,17] The addition of potent cytokines like interleukin-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.[18]

Predictors of response to dacarbazine include good performance status and disease confined to the skin, subcutis, lymph nodes and lungs.[19,20] The median duration of response is five to six months.[12] 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.[21,22]

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 photosensitivity reactions may occur.

Both temozolomide and dacarbazine are prodrugs of the active alkylating agent 5-(3-methyl-1-triazeno)imidazole-4-carboxamide (MTIC). Unlike dacarbazine, which requires metabolic activation, temozolomide spontaneously converts to MTIC 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.[14] Temozolomide is not available under the Australian Pharmaceutical Benefits Scheme (PBS) for metastatic melanoma. The fact that temozolomide penetrates the central nervous system[23] 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.[15] 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. The DNA repair enzyme O6-alkylguanine-DNA alkyltransferase (AGT) is thought to be the main determinate of resistance to dacarbazine

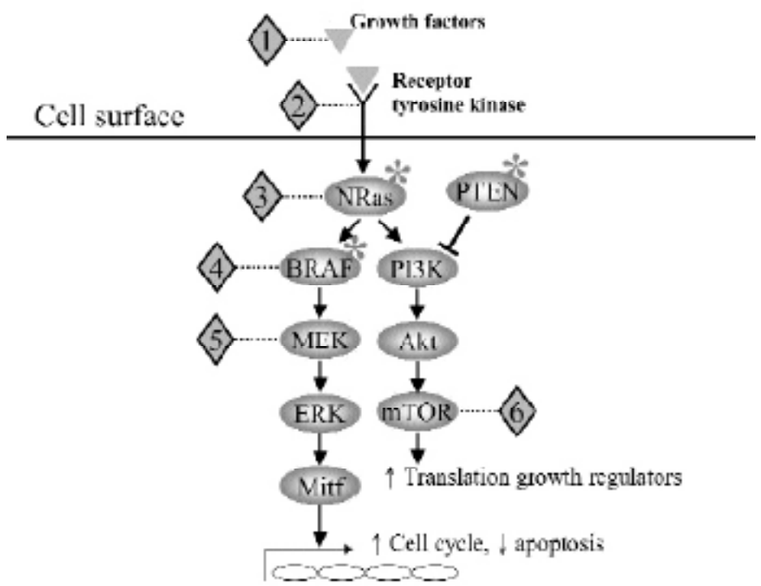


Figure 1. Molecular targets in melanoma: the RAS/RAF pathway

Targets undergoing experimental inhibition in melanoma therapy (diamonds) are:

1) ligands for receptor tyrosine kinases (bevacizumab);
2) receptor tyrosine kinase inhibitors (imatinib);
3) farnesyl transferase inhibitors (tipifarnib)
4) RAF inhibitors (sorafenib);
5) MEK inhibitors;
6) mTOR inhibitors (temsirolimus). Red asterisks denote genes commonly altered in established melanomas.

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); Mitf: 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 lomeguatrib, an agent that inhibits AGT and therefore may sensitise 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 MEK-ERK-Mitf, or PI3K-Akt-mTOR. Mitf triggers the transcription of a suite of genes involved in regulation of cellular proliferation, apoptosis and migration. mTOR promotes the translational efficiency of growth regulatory gene products. PI3K is inhibited by PTEN.

Constitutive activating mutations in NRas, BRAF and PTEN are among the most common somatic oncogenic mutations in established melanomas, indicating the importance of these pathways in the deregulation of melanocyte growth.[24-26] The pan-RAF inhibitor sorafenib (BAY 43-9006) has minimal activity in metastatic melanoma as a single agent,[27,28] but in a Phase II trial in combination with the cytotoxic drugs carboplatin and paclitaxel in patients with metastatic melanoma, 60% of whom had received prior therapy, 14 of 35 patients achieved partial responses.[29] Response did not depend upon the presence of an activating RAF mutation,[30] as sorafenib is "promiscuous" in its effects against RAF family members. The combination of carboplatin/paclitaxel +/- sorafenib is now in Phase III clinical trial in many centres in Australia. Cutaneous reactions constitute the major toxicity of sorafenib.

Apoptosis regulators

The genetic locus CDKN2A is a melanoma susceptibility gene[31] and it is also altered in a large number of established melanomas. It produces two protein products, $p16^{INK4A}$ (p16) and p14ARF (ARF) (Figure 2). When defective, p16 is unable to inactivate CDK4 and 6, which phosphorylate Rb, releasing the transcription factor E2F leading to cell cycle progression.[32]

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 releasing its binding partner hdm2.[33] This probably contributes to the natural resistance of melanoma cells to apoptosis (programmed cell death) in response to cytotoxic, radiation and

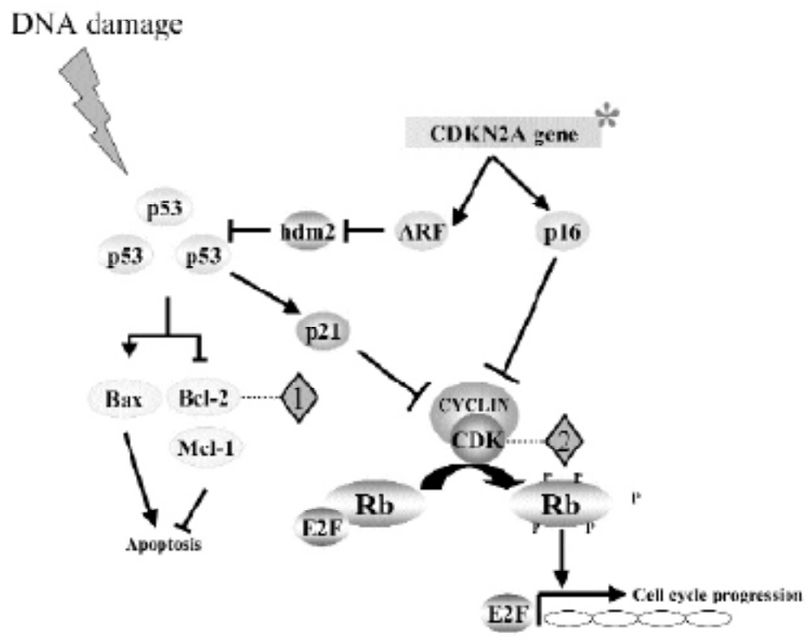


Figure 2: Molecular targets in melanoma: apoptosis and cyclin kinase inhibitors

Targets undergoing experimental inhibition in melanoma therapy (diamonds) are:

1) antisense oligonucleotide to bcl-2 (oblimersen, "Genasense");
2) CDK inhibitors (flavopiridol). The asterisk denotes a gene commonly altered in established melanomas.

Legend: CDKN2A: cyclin dependent kinase inhibitor-2A gene; CDK: cyclin dependent kinase; Rb: retinoblastoma protein; p16: p16INK4A, 16,000 MW protein; ARF (p14ARF): 14,000 MW alternate reading frame protein; bcl-2: B-cell lymphoma derived sequence 2; Mcl-1: myeloid cell leukaemia sequence 1; hdm2: human double minute chromosome–associated protein 2; E2F: E2F cell cycle regulated transcription factor; p21: 21,000 MW protein; RB: retinoblastoma protein; Bax: Bcl-2 associated X protein.

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.[34] These are important molecular vulnerabilities in melanoma. Oblimersen is an antisense oligonucleotide 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 ever conducted 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.[35] 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,[36] 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.[37,38] 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.[39]

Anti-angiogenic agents

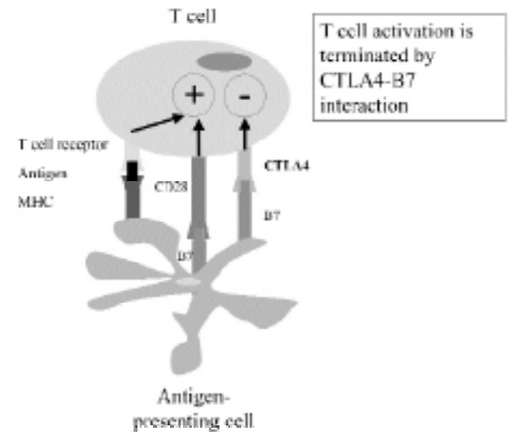
Thalidomide has a variety of anti-tumour effects, which include immuno-modulation and anti-angiogenesis. It has been tested in small cohorts of pre-treated patients with metastatic melanoma, but failed to show convincing evidence of activity.[40] A large Phase III trial of a potent thalidomide analogue, lenalidomide, showed no benefit over placebo.[41] Thalidomide has been tested in combination with a number of agents, including interferon-alpha[42] and dacarbazine.[43] Only a small trial in combination with temozolomide showed some trend towards improved response rates and survival in a preliminary report.[44] 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.[45]

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 suggest potential clinical activity of MEDI-522.[46] Bosentan, an endothelin receptor antagonist used in the treatment of primary pulmonary hypertension, may modulate anti-proliferative and anti-angiogenic activities in melanoma.[47,48] A Phase II Trial of bosentan in patients with metastatic melanoma suggested some clinical activity[49] and Phase III Trials are now underway testing the combination of dacarbazine with or without bosentan.

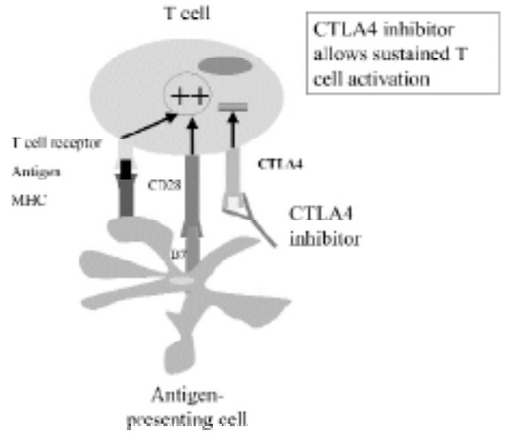
Immunomodulators

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.[50] Despite the presence of detectable immune responses in 30–60% of patients, tumours regress in only a few vaccine-treated patients

Figure 3: Anti-CTLA4 monoclonal antibody therapy



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 CD 28 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.[51] 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.[52] 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 ticilimumab (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[53,54] and are in Phase II and III Trials in many Australian centres. The major toxicity involves autimmune-type reactions in skin, colon and endocrine organs.[55]

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 obvious tumour regressions. New trial platforms are urgently required. One such design is 'Treat, Resect, 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 notoriously treatment-resistant phenotype through acquisition of a bewildering array of molecular advantages. 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

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Abstract

Cervical cancer can be attributed to infection with a subset of high risk human papillomaviruses. While anogenital 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 can be entirely attributable to an infectious agent, human papillomavirus (HPV). Shope showed that papillomavirus could cause cancer 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[1] and strengthened by the epidemiological studies of the International Agency for Research on Cancer (IARC) on the global association of HPVs with cervical cancer.[2] Thus, observations of Rigoni-Stern in the 19th century on the prevalence of cervical cancer among nuns and prostitutes, suggesting an infectious agent, were

vindicated. Human papillomaviruses appear also to be important in the aetiology of other anogenital cancer including vulval and anal cancer and contribute to the aetiology of some head and neck cancer.

Papillomaviruses and cervical cancer

Papillomaviruses come in at least 200 different varieties,[3] in four broad groups.[4] Two groups infect the genital tract of humans, one associated with genital warts and one associated with genital cancer. Detailed epidemiological evidence gathered by IARC and others has allowed the conclusion that a subset of about 10 human papillomaviruses, termed high risk genital HPVs, are responsible for ~100% of cervical cancer, with two types (HPV16 and HPV18) accounting for more than 75% of cancers in most countries. 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 oestrogen.[5] 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 HPVs.

The natural history of infection with high risk human papillomavirus

Infection of the genital tract with high risk HPVs is extremely common, with up to 50% of women becoming infected during the first five years after commencing sexual intercourse.[6] 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,[7] 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 (HSIL) in squamous 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. Physical destruction of high grade 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 also incorporate use of vaccines designed to prevent infection with the papillomaviruses (PVs) 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 PV.[8,9] However, human PVs cannot be grown in the laboratory and vaccines for human PVs are therefore based on virus like particles (VLPs).[10-13] The current vaccines are constructed using recombinant DNA technology from the L1 major capsid protein of the relevant 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.[14,15]

Clinical trials of HPV vaccines

Initial studies in humans demonstrated that VLPs administered with alum or AS04 adjuvant induce HPV type specific antibody[15-20] and protect against infection with the corresponding HPV type.[21-23] 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 HPVs, also HSIL/CIN2, 3 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 (Cervarix™ and Gardasil™) 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 (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 cancer screening programs because they protect against only two types of HPV associated 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 in women and vaccine efficacy in males is yet to be established, though antibody studies available to date suggest that duration of protection will be long-lasting with high and stable levels of antibody observed in vaccinated subjects up to four years after vaccination.

Immunotherapeutics to eliminate HPV infection and cervical cancer

Immunotherapeutics designed to eliminate existing HPV infection are also being considered as a part of a broad strategy to prevent cervical cancer. Therapeutic vaccines have no precedent in human immunotherapy and HPV therapeutic vaccines are at an earlier stage of development than HPV prophylactic vaccines. These products are generally targeted at viral non-structural proteins and are expected to induce killer T-cells which can eliminate virus infected cells in the cervix. Although several possible vaccine products based on HPV16 E6 and E7 protein have been subjected to early phase clinical trials,[24] there are significant scientific and technical challenges to meet before such vaccines become available for routine clinical use. No surrogate markers of effective immunotherapy have been identified, though helper T-cell responses particularly to viral non-structural proteins E2 and E6 may correlate with clearance of persisting HPV infection. Animal models of HPV infection suggest that a major problem with HPV infection may not be a lack of vaccine immunity, but rather a problem with targeting effector T-cells to the HPV infected tissue.[25]

Conclusions

Cervical cancer is a preventable disease. Future strategies to reduce the cervical cancer burden, particularly in the developing world where screening is not available, are likely to focus on HPV prophylactic vaccines based on VLPs. Deployment will depend on development of a strategy for delivering vaccines to young women and, in the developing world, on the availability of adequate funding for the vaccines.

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The Australia New Zealand Breast Cancer Trials Group: some contributions to breast cancer trials

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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 Australia New Zealand Group is currently conducting 46 trials encompassing prevention and early and advanced disease. In the Australia 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 Australia New Zealand Breast Cancer Trials Group Statistical Centre is contracted out to the National Health and Medical Research Centre Clinical Trials Centre. The Australia 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 multidiscipline collaboration. The Breast Cancer Institute of Australia was established to foster education and involvement of consumers in research. Important contributions have already been made by Australia New Zealand Breast Cancer Trials Group researchers to

The Australian New Zealand Breast Cancer Trials Group (ANZ BCTG) had its origin in 1975. At that time new advanced breast cancer trials in Cardiff were comparing first line treatment with tamoxifen or chemotherapy and initiating quality of life measurements in cancer 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) by Bernard Fisher and colleagues[1] and the CMF trial from the Istituto Nazionale Tumori, Milan, by Gianni Bonadonna and colleagues.[2] The CMF trial, investigating 12 months of adjuvant CMF versus no adjuvant chemotherapy for women with positive nodes, showed that after 27 months median 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, but the results from both adjuvant trials were sufficiently striking to change practice and launch a new era of randomised clinical trials (RCTs) evaluating various new adjuvant systemic therapy regimens. The recent early and strikingly positive results from the first trastuzumab adjuvant trials are likely to have a similar impact.[3,4]

In January 1977, Dr Jan Stjernsward from the Lausanne Branch of the Ludwig Institute of Cancer Research (LICR) invited a small group of researchers[i] to a meeting in Lausanne to discuss the implications of these results and the possible conduct of trials by a new international collaborative group. This in turn resulted in the formation of the Ludwig Breast Cancer Study Group (LBCSG), and LBCSG trials I-IV were planned (the final design being completed on a table napkin in a Lausanne Hotel) and commenced in 1978. These initial four adjuvant trials were a logical extension of the Milan CMF trial and emerging data suggesting that tamoxifen might be a valuable adjuvant therapy for postmenopausal women.

From the outset, the new LBCSG was substantially influenced by Australian and New Zealand researchers who actively pursued collaboration and rigorous science. Because the advantage for CMF in the Milan trial seemed less in postmenopausal women (and was not separately significant for this group), LBCSG trials III and IV retained a control arm – subsequently confirmed as a wise decision. The 20-year CMF results were published in 1995[5] and by this time it had become apparent that CMF had less effect in postmenopausal women. Overall, there was a 34% reduction in relative risk of relapse and a 26% reduction in the relative risk of death. In premenopausal women, DFS was 37% and 26% 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 Trialists' Collaborative Group (EBCTCG) Overviews for evidence that chemotherapy does indeed provide advantages for postmenopausal women.[6]

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 similar outcomes for women with advanced breast cancer.[7] Pioneering studies of quality of life (QoL), using LASA (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.[8]

i Those invited to the first "LBCSG" meeting included Kurt Brunner, John Forbes, Percy Helman, Ken Stanley, Carl-Magnus Rudenstam, John Simpson, Martin Tattersall, Marvin Zelan. They were soon joined by Alan Coates, John Collins, Ian Russell, Franco Cavali, Juri Lintner, and Hans-Jorg Senn. Aron Goldhirsch and Richard Gelber became very actively involved soon afterwards

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 oncologists[ii] returned to Australia and New Zealand 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.[11] 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 time was not plausible, so adjuvant 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 for some 2000 years. The largest of the initial LBCSG adjuvant trials had just 491 patients. It soon became apparent that clinical trials introduced new standards of care – in LBCSG I-IV, lymph nodes had to be counted and examined, pathology protocols were standardised, follow-up was according to an agreed 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 trial I (premenopausal with 1-3 positive nodes), had 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 the forerunner 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 therapy is 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 (ISBCSG) 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 were important 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 LBCSG continued with a new name and structure, the IBCSG, which has since built on the substantial contributions of the LBCSG. The ANZ BCTG continued its strong support for the new IBCSG trials, contributing 20% of total international accruals and many of the scientific ideas.

In 1978 advanced breast cancer was increasingly being treated with cytotoxic chemotherapy, particularly in the US. ANZ BCTG 7801/7802 was the largest advanced 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.[9] Today the availability of tissue from women with advanced breast cancer is becoming very important to reliably selecting optimal treatments based on biological assays; increasingly we are able to identify

ii The first "ANZ BCTG Group" included Michael Byrne, Alan Coates (first appointed SAC Chair), John Collins, John Forbes (first Group Coordinator), Grantley Gill, Ron Kay, John Levi, Ray Lowenthal, Don McNeil (first Statistician), Stuart Renwick, Ian Russell, John Simpson, Ray Snyder, Eric Stevens, Martin Tattersall and Robert Woods

the many patients who do benefit from chemotherapy and targeted therapies. In 2006 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[6] 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 new 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 hormone sensitive tumours), combination rather than single agent chemotherapy and anthracycline containing chemotherapy regimens. The demonstration in the overviews of reduced rates of contralateral breast cancer for women taking adjuvant tamoxifen, was a sound basis for IBIS I and other tamoxifen prevention trials.[10,11]

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 rapid than the five-yearly EBCTCG overviews involving much broader patient groups. The first CMF trial involved 386 pre and post-menopausal women. The initial adjuvant aromatase inhibitor trials, evaluating anastrozole, exemestane and letrozole, collectively involved more than 22,000 patients;[12-14] the tamoxifen duration trials and tamoxifen prevention trials both involved more than 20,000 women. The importance of collaboration has never been more apparent.

The Breast International Group (BIG) was established to increase accrual for the large trials needed to address important questions in patient subgroups - including use of taxotere, trastuzumab (Herceptin), aromatase inhibitors and new targeted therapies directed against cellular molecular targets. The ANZ BCTG is a founding member of BIG and has also collaborated with other groups to contribute to other trials. This collaboration has involved trials for ductal carcinoma in situ, as well as prevention with Cancer Research UK and the International Breast Cancer Intervention Group (IBIS), the Clinical Trials Service Unit at Oxford (ATLAS), the North American Intergroup (menstrual cycle and surgery timing trial and the new endocrine trials in younger women), trials of the Breast Cancer International Research Group (BCIRG, now CIRG) and groups established to conduct the ATAC (Arimidex Tamoxifen Alone or Combined)[14] and IES (International Exemestane Study).[13] This collaboration has been valuable and has provided early access to new agents and quality research for researchers and patients.

Growth of the ANZ BCTG

The ANZ Group has continued to conduct its own advanced breast cancer trials. Accrual has generally been adequate for this however wider collaboration is required for trials where treatments are targeted to smaller patient subgroups. The ANZ Group has built an international reputation for its work with advanced breast cancer, from ANZ 7801/02 through trials of intermittent versus continuous therapy, endocrine modalities, high dose CT and new agents. From the beginning, the ANZ Group has explored QoL studies and helped establish QoL measurements as the norm rather than an add on for many trials – led globally by Alan Coates.[15]

The ANZ BCTG is a breast cancer clinical trials research group which uniquely encompasses trials for prevention and both early and advanced breast cancer. The ANZ BCTG model includes an elected Board of Directors, responsible for legal and financial affairs; the Scientific Advisory Committee (SAC) responsible for setting the scientific agenda; the Operations Office which is responsible for all aspects of conduct of the research program; and the ANZ BCTG Statistical Centre currently contracted to the National Health and Medical Research Council (NHMRC) Clinical Trials Centre. The Group Coordinator and SAC Chair are appointed by the Board. The SAC is not representative – it simply requires individuals with the knowledge and ability to contribute to the scientific agenda of the group.

The ANZ BCTG established the Breast Cancer Institute of Australia (BCIA) as an operating division for education, consumer involvement and fundraising. Australia does not have a 'National Cancer Institute' to provide infrastructure and operational funding for collaborative groups; hence, the BCIA is vitally important to help the ANZ BCTG to conduct its clinical trials research program in accord 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 substantially by involving consumers in the research agenda. CAP members comment on all ANZ BCTG protocols, particularly on patient materials and issues that will affect accrual to the trial. The IMPACT program now includes mentoring of individual consumers at the group's Annual 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 300 researchers in 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 46 trials are being conducted, including: (i) follow-up 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 20-98) and the only trial of continuous versus sequential aromatase inhibitor adjuvant therapy (BIG 1-98/IBCSG 18-98); (iii) trials open to accrual and; (iv) trials with endorsement from the SAC to be commenced.[17] 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 a key part of 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 metastatic process and new 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.

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Local therapy in a systemic world: the evolution and incarnations of adjunct radiotherapy for breast cancer

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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 to be treated. Alan was a leader 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

In farewelling Professor Alan Coates it is easy to consider matters in evolutionary terms. How far back must we go to reach an era in which he has not dominated the breast cancer literature?

Halsted described his mastectomy in a paper in 1894.[1] There was at that time no adjuvant therapy. The discovery of the properties of radiation a small number of years later led to its rapid inclusion in the treatment of breast cancer.[2] It was an era in which there was no systemic therapy, certainly no chemotherapy. Radiotherapy remained for over 70 years, the sole modality for reducing the risk of recurrence after surgery for breast cancer. It clearly worked. The role for radiation therapy in reducing the risk of local recurrence has not been disputed.[3] During the 1980s as clinical trials confirming the benefits of adjuvant chemotherapy on survival became widespread, the benefits of radiotherapy on survival and even its role in reducing local recurrence once chemotherapy was employed, was seriously questioned.

Postmastectomy radiation therapy: historical data

The early randomised trials of radiotherapy after mastectomy did little to enhance the value of the modality.[4-8] We can look at them now and all were seriously flawed in some way, be it statistically,[4,5] in terms of the dosing for the radiation,[5-7] or in terms of the volume of the patients treated,[4,5,7,8] usually an unacceptable amount of cardiac inclusion. The best of the trials was the Stockholm I Trial.[8] It was started in 1971 and included 960 patients with operable disease. The study compared adjuvant radiotherapy with modified radical mastectomy alone. There was a clear improvement in the recurrence-free survival with radiotherapy ($p<0.001$) and in the higher risk group with node-positivity as well as improvement in both loco-regional recurrence ($p<0.001$) and distant metastases ($p<0.01$). With follow-up there was a non-significant trend to improved survival.[9] This was set against an emerging literature of a decreased survival for those patients undergoing adjuvant radiotherapy.[10-14] The publications of Cuzick highlighted this and pointed specifically at an excess of cardiac deaths in those early trials reviewed.[14]

Chemotherapy alone however, did not adequately address local control.[15-17] While there was a small reduction in the rates of local relapse, patients at medium to high risk continued to accrue local recurrences, with the rates increasing over time. Even the introduction of high dose chemotherapy did not reduce the rate of local chest wall recurrence. This era however, where many patients received adjuvant systemic therapy without radiotherapy, has allowed us to identify those groups of patients at highest risk of local recurrence. The largest of these data series is from the International Breast Cancer Study Group,[17] an analysis of 5352 women, which is able to identify that for node negative patients, factors associated with increased risk of loco-regional relapse were vascular invasion and tumour size greater than 2cm for premenopausal women and vascular invasion for postmenopausal women. The 10-year cumulative incidence of locoregional failure was 16% for premenopausal and 19% for postmenopausal women. For the node positive group, the number of nodes and tumour grade were important for pre and postmenopausal groups, the additional predictors of vascular invasion for premenopausal women and tumour size for postmenopausal women. The 10-year risk of local relapse was 35% for the high-risk premenopausal group and 34% for the postmenopausal group. Clearly for such a group of patients the delivery of postmastectomy radiation is important. The challenge is to deliver the treatment without the late principally cardiac morbidity.

Postmastectomy radiation therapy: the modern era

In the past 15 years, the development of new equipment and techniques, coupled with an expansion of radiobiological understanding of dose-response relationships for breast cancer, has revolutionised the delivery of radiotherapy for this disease. Modern radiotherapy avoids direct irradiation of the heart and delivers a more effective dose to the regions most at risk of recurrence. Evidence is emerging that this is now converting the reduction in breast cancer deaths to improvements in overall survival.

The publication of two randomised trials in 1997 by Ragaz[18] and Overgaard[19] were the first suggestions of such improvements. Both trials showed significant improvements in overall survival, in addition to the benefits of their chemotherapy. The Overgaard trial (9% at 10 years) and the Ragaz trial (10% at 20 years),[20] showed improvements in overall survival from the addition of radiotherapy. A separate cardiac substudy with the Overgaard study showed no excess cardiac morbidity.[21] Such single institution data needs confirmation however, and that has been achieved with the publication of a meta-anlaysis.[22] The most compelling evidence that the effect is truly a reflection of improved delivery and targeting of the radiotherapy, as opposed to confounders in surgery and chemotherapy, came earlier this year. Gebski et al[23] published a sophisticated analysis of all postmastectomy radiotherapy studies according to the biologically equivalent dose delivered, the region and volume included in the target volume and whether the radiotherapy was delivered in a truly adjuvant situation or to compensate for inadequate surgery. They demonstrated in a meta-analysis of trials using optimal radiation therapy dose, delivered to appropriate target volumes, that there was an improved overall survival benefit. Furthermore, the relative risk reductions in all-cause death were calculated to be greatest for those at greatest risk of death, with a 16% reduction in the risk of death for this group. A 13% relative risk reduction was seen for the medium risk group and 7.8% for the low risk group. This is consistent with the clinical benefits seen in the Ragaz and Overgaard studies.

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).[24] 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 mastectomy in this group of women who have chosen to keep their breast.

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 Coates 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,[25] a clinic in which systemic and local therapy decisions are optimally integrated must remain an ideal.

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ANTIEMETIC RESEARCH: SOLVING PATIENT PROBLEMS

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Abstract

A study which showed that patients ranked nausea and vomiting as their most distressing side-effects of chemotherapy reinforced the need to discover more effective antiemetics. Nausea and vomiting impact on patients' quality of life. It is important to have patients rank their own adverse experiences and this may differ from an observer's assessment. A breakthrough in ameliorating acute post chemotherapy emesis occurred with the introduction of the 5 hydroxytryptamine$_3$ antagonists. However, a repeat of patients' ranking of the severity of side-effects of chemotherapy after the introduction of these drugs still showed nausea and vomiting ranking in the top three. This was due to poor control of delayed emesis, which occurs after 24 hours. A study comparing clinicians' predictions of the severity of patients' emesis against their actual experience post chemotherapy showed that clinicians underestimated delayed emesis by up to 28%. The next development in antiemetics was the advent of the neurokinin$_1$ receptor antagonists. When added to ondansetron and

A study reported by Coates et al in 1983 is often quoted in the antiemetic 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 select 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.[2] A group of 832 chemotherapy naive patients who received chemotherapy of high or moderate emetic potential completed both the European Organization for Research and Cancer Core 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 all 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 following high-dose cisplatin, found that the directly observed and patient recalled number of emetic episodes correlated very well ($r = +0.98$, $p < 0.025$).[3] Subjective sensations such as nausea can really only be assessed by the patient and observers would need to question the patient to record their severity. Fetting and colleagues reported a significant relationship between patients self reporting of nausea and that of observers in a study of emesis after high dose cyclophosphamide.

We examined three of our randomised antiemetic studies to investigate the relationship between patient and observer assessments.[4] In one parallel subjects study there was no significant difference between the patients and nurses assessments of the number of vomiting episodes, but the duration of vomiting, the severity and duration of nausea and the side-effects of the antiemetic were given higher scores by the nurses. The high scoring for emesis by the nurses however, may just have reflected their frequent prospective recording as compared to the retrospective recording by the patients at 24 hours. Differences in duration may just reflect differences in the frequency of recording. In two cross-over studies the patients recorded more vomiting episodes than the nurses, while the nurses recorded more anxiety and sedation than the patients. This resulted in the patients detecting a difference in the side-effects of the antiemetics not detected by the nurses. Here the nurses recorded the number of vomiting episodes at the end of an eight hour shift. The result may have been different if they had recorded the number of vomiting episodes each hour as occurred in the parallel design study. Therefore there are differences between patient and observer assessments of nausea and vomiting which may just reflect the method and 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$_3$ antagonists

Emesis following chemotherapy became particularly problematic with the introduction of cisplatin in the mid 1970s. It was recognised that antiemetics should be given prophylactically to prevent emesis, but the available drugs were ineffective. The main antiemetics tried were the dopamine antagonists, particularly metoclopramide which blocked the D_2 receptor, thought to mediate emesis.[5] 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 sporadic extrapyramidal reactions.[6] It is little wonder that patients rated nausea and vomiting so high in the list of the worst side-effects of chemotherapy.

A breakthrough in the control of acute chemotherapy induced emesis occurred with the recognition that the 5 hydroxytryptamine$_3$ ($5HT_3$) receptors in the small intestine were involved in triggering the acute emetic response to cytotoxics. The first of the $5HT_3$ 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 metoclopramide 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.[7] A $5HT_3$ receptor antagonist combined with dexamethasone became the gold standard given prophylactically to prevent acute post chemotherapy induced emesis.[8] This resulted in complete protection from cisplatin-induced acute emesis ranging from 70-90%.[9]

Patients' perceptions

Ten years after the initial study reported by Coates et al, and following the introduction of the $5HT_3$ receptor antagonists, the study on patient perceptions of the side-effects of chemotherapy was repeated.[10] There was a change in the ranking of side-effects by severity, but nausea was still ranked first. Vomiting was now ranked fifth behind 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 others. A French study in 100 patients noted the shift from physical to psychosocial concerns and ranked fatigue as the most severe physical symptom.[11] A trial in the Netherlands replicated Coates' survey in patients who had received $5HT_3$ antagonists and found that nausea and vomiting were still ranked in the top three toxicities.[12]

These results are not surprising when the $5HT_3$ literature is analysed. Although very effective for preventing acute vomiting after chemotherapy, if a $5HT_3$ 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%.[13,14] 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.[15]

Clinicians' predictions of emesis

With the advent of the $5HT_3$ 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) emetic potential.[16] 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 after HEC by 21% to 28% and delayed nausea after MEC by 28%. Moreover delayed symptoms could appear without acute symptoms after HEC (emesis, 38%; nausea, 33%) and MEC (emesis, 19%; nausea, 21%).

Neurokinin$_1$ receptor antagonists

Somewhat fortuitously, the next major breakthrough in antiemetic development addressed the issue of delayed nausea and vomiting after chemotherapy. This was the development of the neurokinin$_1$ receptor antagonists; the first to market being aprepitant.

In two large phase III placebo controlled trials performed in South America (Poli-Bigelli et al) and in centers from North America, Europe and Australia (Hesketh et al), patients receiving their first cycles of cisplatin >70mg/m^2 had aprepitant for three days added to intravenous ondansetron; 32mg 30 minutes before cisplatin with oral dexamethasone 20mg on day one followed by oral dexamethasone, 8mg twice daily from days two to four in the study arm and compared to ondansetron and dexamethasone alone.[17,18] Combining the trials 1099 patients were enrolled. For acute emesis the response in the aprepitant patients was 82.8% versus the control group 68.4% ($p<0.001$) for Poli-Bigelli study and aprepitant 89.2% versus controls 78.1% ($p<0.001$) for Hesketh. The biggest 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.[19] Also, more patients receiving aprepitant reported no impact of chemotherapy induced nausea and vomiting on their daily lives.

Similar benefits were seen when aprepitant was used as part of the antiemetic regimen to control the acute and delayed nausea and vomiting after combination chemotherapy with an anthracycline and cyclophosphmide.[20]

Patients' expectations

What is required now is a repeat of the Coates' study to see if the control of acute and delayed emesis by the triple therapy of ondansetron, dexamethasone and aprepitant really has decreased the patients' ranking of post chemotherapy nausea and vomiting as among the most severe of side-effects. We also need to understand more about what influences patients' perceptions of side-effects.

A lack of adequate pharmacological explanations for side-effect variation following chemotherapy suggests psychological factors may contribute to the experience of side-effects. Our research aimed to determine if patients' expectations were associated with toxicities.[21] Eighty-seven chemotherapy-naive patients rated their expectations of 20 common side-effects before treatment and then rated their experiences 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 to patients. It also allows assessment of whether therapeutic interventions have altered the patients' perceptions. In the antiemetic literature such studies were used to justify the research effort to find new antiemetics, then highlight the limitations of the impact of the $5HT_3$ antagonists. Ultimately the NK_1 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.

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

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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. The Sydney branch of the Ludwig Institute for Cancer Research, established at the University of Sydney 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 expectancy of those patients was 44 weeks.[1] At the time, most chemotherapy was

In August 1980, Alan Coates was recruited to join the staff of the Sydney Branch of the Ludwig Institute for Cancer Research. He was to remain at Royal Prince Alfred Hospital (RPAH) until he took up his current position as Chief Executive Officer of The Cancer Council Australia (then the Australian Cancer Society) in 1998. His extensive and distinguished clinical and research contributions over these years are reviewed in this issue of Cancer Forum. I am reviewing a series of papers presented with the title On the receiving end from 1983 to 1996.[2-7] These papers span time during which cancer chemotherapy expanded rapidly, along with developments in supportive care. The papers illustrate Alan Coates' skills in measurement and analysis and also document changes over a 10-year timeframe in patient perception of the relative importance of different side-effects of chemotherapy. These changes mirror changes in cancer chemotherapy and supportive care and the evolution of patient-centred care. Moreover, the co-authorship of these six papers indicates that collaboration with Alan Coates has been a passport to distinction in clinical cancer research.

The first paper in the series reported a survey of 99 English-speaking outpatients who attended medical oncology outpatients at RPAH who had received chemotherapy within the four-week period before study entry.[2] Patients had received a median of three cycles of their current therapy. Two sets of cards were 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 described 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 symptoms selected 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[3] 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 symptoms identified as important in the earlier studies.[4] These items formed a new instrument (GLQ-8) for measuring aspects of QoL. One hundred and sixty-six patients completed both the GLQ-8 and five previously validated LAA scales, together with the visual analogue version of the Spitzer QL Index. The new scales showed high reliability, with retest correlation coefficients exceeding 0.8 for most items. Correlations were in general higher for the GLQ-8 items than for the five older LASA items. It was concluded that the GLQ-8 and GLQ uniscale were convenient and reliable instrument measuring aspects of patient's QoL in patients receiving cancer chemotherapy. The fourth paper in the series extended cross validation of the GLQ-8 against three established measures of QoL, mood and psychological adjustment to cancer.[5] Correlations were high and it was concluded that the regular inclusion of practical indicators of aspects 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 an average of 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 whiles receiving chemotherapy and a shift from concerns about physical to psychosocial issues.

The final paper[7] 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. ⓝ

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Quality of life research that shaped oncologists' thinking and practice

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Abstract

Alan Coates is a pioneer of quality of life 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.

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 advanced 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 for giving chemotherapy in advanced breast cancer: continuing it until disease progression (continuous) versus stopping it after three cycles and restarting at evidence of further progression (intermittent).[1] The underlying hypothesis was that intermittent chemotherapy would be preferable because it would give equivalent anti-cancer effects with less toxicity.

The results were unexpected and controversial. QoL improved during the first three cycles of chemotherapy despite its side-effects. More importantly, QoL was better with continuous chemotherapy than with intermittent. Subsequent follow-up showed that continuous chemotherapy also yielded superior survival duration.[2] This trial established that chemotherapy could improve both length and QoL in people with advanced cancer. It remains one of the strongest pieces evidence that chemotherapy is beneficial in advanced cancer.[3]

The observation that changes in QoL were significant predictors of survival in this trial raised the question of whether baseline QoL scores might also be prognostic.[1]

QoL is a prognostic factor in advanced cancer

Subsequent studies in advanced breast cancer showed that QoL scores were highly significant predictors of survival, regardless of whether they were assessed by patients or their doctors.[4] The prognostic significance of QoL scores was corroborated in a trial of adding interferon to dacarbazine for advanced melanoma,[5] and subsequently, in patients with a range of metastatic cancers being treated in routine clinical practice in several countries.[6] Observations of women in early breast cancer trials showed that ratings of QoL after they relapsed were associated with overall survival, but ratings before relapse were not associated with outcome.[7]

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[8] and in QoL over time in patients with melanoma that was localised[9] or metastatic.[10] Styles of coping and adjustment were also associated with survival in women with metastatic breast cancer.[11] 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

International randomised trials in the 1970s and 1980s established that adjuvant chemotherapy could improve relapse free and overall 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.[12] 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.[13,14] 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.[15,16] 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.[19]

Alan Coates has made a substantial, enduring contribution to thinking and practice in oncology. These studies have shown how to improve 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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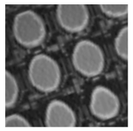

COSA, Cancer Council call for cancer training improvements in medical education inquiry

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 inquires include the Productivity Commission's review of the medical workforce, which looked at systemic barriers to best practice from education through to 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 success in 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 2005.

A roundtable discussion with peak medical bodies was held in May 2005 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 and cultural 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:

- DEST identifies the improvement of cancer management competency as a core medical education priority.
- 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.
- DEST scopes ways in which COSA and The Cancer Council Australia's Ideal Oncology Curriculum can be adopted throughout Australian medical schools.
- 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.
- 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.
- 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.
- 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.
- DEST explores opportunities to translate the increase in Australian Government support for independent cancer clinical trials into improvements in medical education.
- 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 COSA Council representative to be informed about this and any other advocacy/policy activity. n

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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 oncogenesis 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 glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and its role in protecting cells from caspase independent death. Numerous reports have now shown that cells with inactivated caspase cascades can still die in response to mitochondrial apoptotic signalling. 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-737, 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-737 antagonised Bcl-2 proteins to render tumours more sensitive to chemotherapeutic agents, while exhibiting very low toxicity in normal and cancerous

cells. Interestingly, B-cell lymphomas and other tumours associated with translocations involving Bcl-2, underwent apoptosis when treated with the compound alone.

Friday delivered an action-packed program, beginning with a session on cancer epigenetics sponsored by The Cancer Council Australia. One of the major themes of the conference was the genetic regulation of senescence and ageing. David Sinclair (Deptartment of Pathology, Harvard University) gave the first presentation in this session, showing his recent work on SIRT-1, the mammalian homologue of a family of histone deacetylases (HDACs) called sirtuins. Sirtuins are known to prolong the lifespan of simple organisms such as yeast and Drosophila. He presented data showing that mammalian sirtuins, like those in simpler organisms, delay aging by associating and stabilising highly repetitive DNA, but that this association decreases with age – stressing the links between epigenetic silencing by this family of HDACs, genomic instability, and ageing. Robyn Ward (St Vincent's Hospital, Sydney) presented her findings on the role of epigenetic mutations in hereditary non-polyposis colorectal cancer (HNPCC). HNPCC is a cancer predisposition caused by heterozygous germline mutations of the DNA mismatch repair genes MLH1 or MSH2. Individuals were identified that do not carry mutations in these genes, but instead carried soma-wide monoallelic silencing of MLH1. The clinical outcomes of these individuals demonstrated the monoallelic silencing epimutation is functionally equivalent to heterozygous mutation, but examination of family members demonstrated that the inheritance of the epimutation is weak and may result in complex family histories. Victoria Richon (Merck Research Laboratories, Boston) and Ralf Lindemann (Peter MacCallum Cancer Centre) delivered reports respectively on the progress of clinical trials with HDAC inhibitors and the mechanism by which they engage apoptotic pathways.

Other sessions on Friday focused on the genetic basis of cancer and apoptosis. Gerard Evans (University of California San Francisco) described the use of an oestrogen-receptor regulated p53 protein to investigate the role of p53 in tumour suppression and found evidence that p53's DNA damage response is separate from its role as a tumour suppressor. Perhaps even more intriguingly, Carlo Croce (Ohio State University) presented work showing the role of microRNA in the development of leukaemia, with microRNA expression being used to predict disease progression in chronic lymphocytic leukaemia. A surprise guest, Anne-Maree Pearse (Tasmanian Department Primary Industry), told the colourful story of the facial tumour disease in Tasmanian devils and described the cytogenetic evidence that suggests it is transmitted as an infectious allograft when the temperamental animals bite each other.

The first plenary session was sponsored by The Cancer Council Australia and was delivered by Charles Sherr (St Jude Children's Research Hospital, Tennessee), who presented on the ARF tumour suppressor and its role in childhood leukaemia. The BCR-ABL fusion protein is an important initiating event in both acute lymphoid leukaemia (ALL) and chronic myelogenous leukaemia, but only ALL is commonly associated with ARF deletions. Sherr presented a model where BCR-ABL was expressed in pre-B cells from wild type and ARF null mice, showing that the ARF deletion was required for these BCR-ABL expressing cells to induce leukaemia in mice. Additionally, these cells were resistant to treatment with high doses of kinase inhibitors, suggesting that loss of ARF deletions may be important in resistance to Imatinib. ARF does not necessarily need to be deleted in cancer, but can be inactivated by epigenetic silencing or by over expression of specific repressor proteins. Sherr presented evidence that dominant mutations in the ARF binding partner nucleophosmin can trap ARF in the cytoplasm and lead to partial suppression of its tumour suppressor function.

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.

Stephen Loughran and Rohan Steel
Walter and Eliza Hall Institute, Victoria

Australian behavioural research in cancer

News

- Centre for Behavioural Research in Cancer (CBRC) Victoria

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' reactions to newspaper articles about smoking-related diseases. Emily is providing research support for a range of tobacco-related projects including the Population Survey for Quit Victoria.

- Centre for Behavioural Research in Cancer (CBRCC) WA

Dr Owen Carter has received five-years' funding to become the Healthway Tobacco Control Research Fellow at CBRCC until 2011.

- Centre for Health Research and Psycho-oncology (CHeRP) NSW

After four years with CHeRP, Deborah Bowman is leaving us to pursue a career in primary school teaching. Deb's most recent work at CHeRP has included managing the trial of communication skills training with oncologists and the development of palliative care referral guidelines. Deb has been a valuable member of our team and we wish her well in her new vocation.

- Cancer Research Prevention Centre (CPRC) Queensland

The CPRC has appointed four new research fellows: Dr Sheleigh Lawler (Sun Protection) and Dr Katrin Hausdorf (Tobacco Control) joined the Centre in October 2005 and November 2005 respectively; and Dr Marina Reeves (Physical Activity and Nutrition) and Dr Takemi Sugiyama (Physical Activity and the Environment) will take up their positions with CPRC in April 2006. Paul Gardiner and Alesha Smith joined CPRC in March after being awarded PhD scholarships in Behavioural and Population Health Studies for Cancer Prevention by CPRC, funded by Queensland Health. In December 2005, Adele Spencer (Logan Project Manager) and Fiona Porter (Logan Intervention Trial Telephone Counsellor) joined the Centre. Research Fellow, Dr Ester Cerin, left CPRC to move to The University of Hong Kong in January 2006, but will maintain collaborative links with the Centre. Research Assistant Phoebe Kearey accepted a position with The Queensland University of Technology in December 2005. Logan Project Manager Kirsty Pickering accepted a job offer from Queensland Health in December 2005. Logan Project Telephone Counsellor Melissa Harvey has taken time out to oversee home renovations.

- Tobacco Control Research Evaluation (TCRE) SA

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

Research in the pipeline

- CBRC

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 the 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 utilising historical records of advertising on television and radio and calls

from January 2002 through to December 2005. The study is investigating the impact of different styles of anti-tobacco advertising and whether factors such as the time of day and the type of program within which ads were played, influence the number and nature of calls received. For example, the study is seeking to determine whether ads played within comedy, news or drama programs, all else being equal, might yield different numbers of calls, or whether the style of anti-tobacco advertising might interact with the program type in driving call volume. While these kinds of research questions will be investigated in the current dataset, the study will set up a system to enable ongoing monitoring of advertising and Quitline calls into the future, in order to provide Quit Victoria with immediate feedback on the relative effectiveness of future campaigns, and information about the optimum level of advertising to drive Quitline calls. The information from this project also has the potential to enable prediction of Quitline calls for future campaigns.

- CBRCC

UV Index sundial

In Australia comprehension of the Ultraviolet (UV) Index is suboptimal and only 37% of Australians report using it once or more per month during summer. Criticism of the UV Index includes that it does not allow real-time feedback of UV conditions of immediate relevance to observers. To this end, the New Zealanders have developed a motorised UV Index sign that uses a UV sensor and computer to give real-time measurements throughout the day. Whilst admirable, the system is expensive, requires a power source and ongoing maintenance of its working parts. CBRCC plans to test a far cheaper concept in the form of a UV Index sundial. Researchers in Italy developed a working model of a UV Index sundial in 2003 that was accurate to within an average of +/-7.2% (less than 1 UV Index integer). It is planned to develop a UV Index sundial, in collaboration with the Australian Radiation Protection and Nuclear Safety Agency and the University or Rome, for the latitude and atmospheric conditions of Perth and display it at several beaches and public swimming pools around the metropolitan area. Researchers will record the time people spent outdoors and also observational measures of sunscreen application and protective clothing use. A free sunscreen stand will also be provided and net use of sunscreen will assessed by weight. These measurements will be compared to a rotation of control locations where the UV Index sundial will not be displayed. In this way, the usefulness of providing UV Index sundials to motivate people to adopt greater sun protection behaviours will be directly assessed. If the results are successful UV Index sundials could be adopted around Australia at outdoor recreational areas and contribute to a reduction in the incidence of sunburn, skin cancer and premature death.

- CHeRP

Reaching national consensus on cancer-related practice, knowledge and attitude items

The Cancer Council Australia, through its Public Health Committee, has commissioned Afaf Girgis and Chris Paul to undertake a small project to reach national consensus on cancer-related practice, knowledge and attitude items. The aim is to agree a small core set of items that can be included in state-based surveys as they arise, allowing us to gain a national picture of common items of interest, which can be monitored over time. Representatives from the state-based behavioural research groups are all participating in this consensus process.

Prospective study of non-participants to a smoking cessation intervention trial

Of all risk factors for disease, tobacco smoking is responsible for the greatest burden on the health of Australians and is estimated to kill approximately half of its long-term users. Estimates from the 2004 National Drug Strategy Household Survey indicate that around 2.8 million Australians (17.4% of people aged 14 years and over) smoke tobacco on a daily basis. Cigarette smoking in Australia causes around 40% of male deaths and 20% of female deaths before the age of 65 years and is responsible for 143,000 hospital separations annually. Evidence from randomised controlled trials (RCTs) provide the strongest test of the efficacy of smoking cessation interventions. RCTs establish the size of effect of an intervention in a particular context in a sample who are eligible and willing to receive the intervention. In many smoking cessation RCTs, a substantial proportion of eligible subjects choose not to participate. Not only are data on this non-participating group necessary to assess the proper context and generalisability of an RCT, but the smoking-related attitudes, intentions and behaviours of non-participants also represent an important research priority in their own right. CHeRP, in collaboration with Hunter New England Population Health, is currently undertaking an RCT that examines the effectiveness of proactive telephone counselling for smoking cessation in a non-volunteer population. Households selected randomly from the NSW Electronic White Pages are contacted to establish if there are any adult daily smokers in the household. One daily smoker per household is randomly selected and invited to participate in the RCT. If the smoker refuses to participate in the RCT, the interviewer invites them to participate in a short baseline interview to assess their quitting-related attitudes, intentions and behaviours. During this baseline interview RCT non-participants are also invited to participate in seven and 13-month post-baseline interviews so that their cessation rates and attitudes can be assessed longitudinally as well as compared to their RCT participant counterparts.

- CPRC

Physical Activity, Sun and Sport (PASS)

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 uses multiple 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 svelte young adults;
- 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 influenced.

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 participants 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 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 12 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 for 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, Victoria 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 influence of parental smoking 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 can reduce some of the influence of friends' smoking 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

Madgalena Lagerlund, Helen Dixon, Julie Simpson (Cancer Epidemiology Centre, The 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 those observed on sunny days, in no shade or partial shade, in parks/gardens and at pools/beaches. Less active people and those on their own or in pairs were also commonly observed wearing sunglasses, as were people observed in higher socio-economic areas, females, people aged between 20 and 50 years of age and people donning head and clothing cover. It was concluded that use of sunglasses should be encouraged among the population in general and especially among golfers, tennis players, teenagers, males and people in lower SES areas. The paper is in press in the journal Preventive Medicine.

n CBRCC

Impact of smoking imagery in youth-orientated magazines

CBRCC 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, glamour, sex, social success, rebellion and power. An identical second version of the magazine was also produced but with 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.

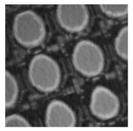
Cancer in the workplace

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. CBRCC 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 CBRCC website: www.cbrcc.curtin.edu.au/reports.htm.

n CHeRP

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 Afaf Girgis and Deborah Bowman from CHeRP; 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-appraise 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



NEWS & ANNOUNCEMENTS

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 better understand the potential consequences of risky behaviours and to adopt healthier lifestyles.

"The Cancer Council has been a vocal advocate for effective cancer prevention programs, implementing successful SunSmart campaigns and being involved in Quit campaigns," he said. "We need to continue to communicate effectively with the Australian public, ensuring the messages about quitting smoking, being SunSmart, maintaining a healthy diet and engaging in physical activity are taken on board and translated into behaviour changes – for themselves and their families."

"One-stop-shop" for primary care cancer resources

A new web-based directory of cancer resources for primary care professionals will provide quick and easy access to national, state and territory information.

The new directory, developed by The Cancer Council Australia's General Practice Committee, provides a single access point to a range of cancer resources including guidelines and advice on prostate, breast, bowel, ovarian and skin cancer, as well as issues associated with screening and psychosocial care for cancer patients.

"Previously, primary care professionals would need to find resources from a range of websites or contact a variety of different cancer organisations," Chair of the Committee, Rebecca Russell said. "Now, they can 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.

Here's hoping

With a target of more than $8 million, Daffodil Day is hoping for a big response to the launch of its 2006 creative campaign.

Based around the theme of hope in defeating cancer and hope for those living with or in some way affected by cancer, the campaign aims to inspire people to participate in Daffodil Day on Friday 25 August.

Once again the ever popular Dougal Bear (dressed by mambo this year) heads the list of merchandise, which includes funky yellow 'hope' wristbands and more than two million daffodils.

Chief Executive Officer of The Cancer Council Australia, Professor Ian Olver, said significant advances had been achieved through cancer research, prevention and early detection programs. "Over the past decade, we have seen a significant reduction in the cancer mortality rate in Australia of 17%. Continuing your support for Daffodil Day will help ensure this figure continues to fall," Professor Olver said.

Funds raised during Daffodil Day activities will contribute directly to Cancer Council initiatives in cancer

cancer.org.au/primarycare.

Cancer professional development study underway

Cancer professionals, GPs and counsellors are being asked to contribute to a scoping study designed to improve cancer professional development in Australia, as part of the Australian Government's Strengthening Cancer Care package.

The scoping exercise is being undertaken by a consortium comprising Clinical Oncological Society of Australia, The Cancer Council Australia, the National Breast Cancer Centre, the Royal Australian College of General Practitioners and the University of Sydney's Centre for Innovation in Professional Health Education (CIPHE). The consortium applied successfully for the Commonwealth contract late last year. CIPHE, which specialises in professional health education, is managing the project under the guidance of the other consortium members.

Phase 1 of the project is a scoping exercise, including a literature review, audit of currently available tools for cancer professional development and widespread consultation to determine the needs and views of the three professional target groups.

As part of the consultation, cancer professionals, GPs and counsellors are being asked to complete an online survey which, along with general information about the project, is available at http://www.cancercpd.org.au/.

Phase 2 of the project, which is not part of the current contract and will be dependent on the results of Phase 1, will look at devising professional development packages in response to identified need.

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.

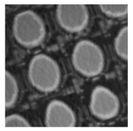
All positions statements can be viewed on The Cancer Council Australia's website at www.cancer.org.au/positionstatements.

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-orientated 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

Elsevier Butterworth Heinemann (2006)

ISBN: 0-7506-8830-0 194 pages plus index

RRP: $75.00

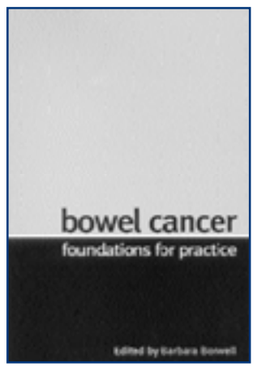
As suggested by the title, this book will provide healthcare workers who come into contact with cancer patients with an overview of the principles of drug treatments in this rapidly evolving field. The author, a senior lecturer

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 précis 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.

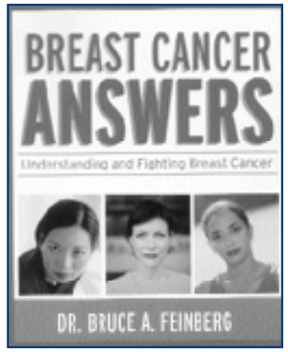
Trevor Saunders
Peter MacCallum Cancer Centre, Victoria

Bowel cancer: foundations for practice

B Borwell (ed)
Whurr Publishers 2005
ISBN: 1-86156-452-X 244 pages plus index
RRP: $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 practice, 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 potentates 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.

Michele Carey
Concord Community Nursing Service, NSW

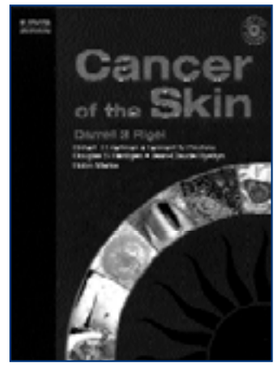
Breast Cancer Answers

Dr Bruce A. Feinberg
Jones and Bartlett (2005)
ISBN: 0-7637-3465-9 111pages plus index
RRP: $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.

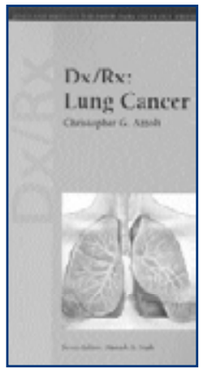
The main limitation of this book is that it has been written predominately for American women. Some of the analogies used are specific to the US. The book was also written to fill a gap identified by the author in the American market for quality information on breast cancer. Australian women have access 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

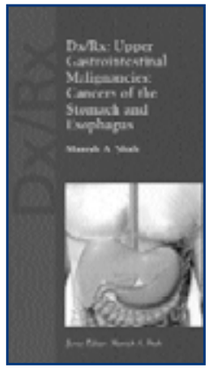
This book is targeted mostly at the practising clinician who diagnoses and treats skin cancer. It has a distinctly North American orientation, from its editorship and authorship, to its content. This will limit its relevance to many practitioners in Australia experienced in dealing with skin cancers 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.

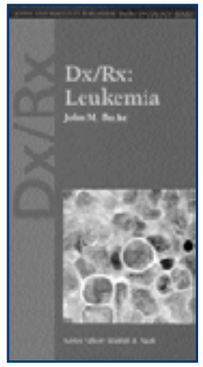
Adèle Green
Queensland Institute of Medical Research



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 critisism 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 sit 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

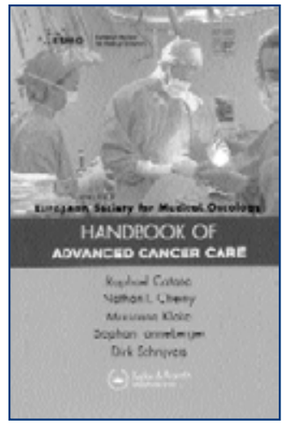
M Shah
Jones and Bartlett (2006)
ISBN: 0-7637-4743-2 160 pages plus index
RRP $56.10

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 oesophagus 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

JM 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 208 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

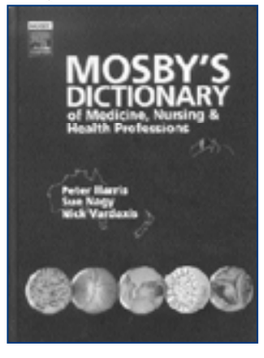
European Society for Medical Oncology: Handbook for Advanced Cancer Care

R Catane, NI Cherny, M Kloke, S Tanneberger,
D Schrijvers (eds)
Taylor and Francis (2006)
ISBN: 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 Gilchrest, C Bunker
Health Press (2005)
ISBN: 1-903734-63-0 103 pages plus index
RRP: $44.00

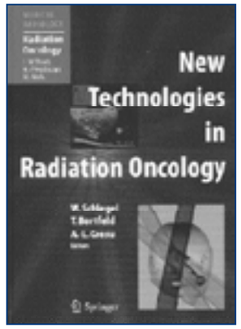
Fast Facts: Skin Cancer is suitable for a wide readership from medical students and general practitioners through to the general population.

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 dermatoscopic 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 photograph 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 on 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 lymphocintigraphy 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

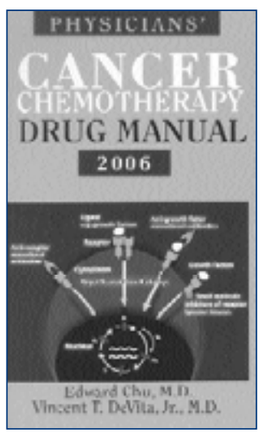
Loss, change and bereavement in palliative care

P Firth, G Luff, D Olivere (eds)
Open University press (2005)
ISBN: 0-335-21323-5
RRP: $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.

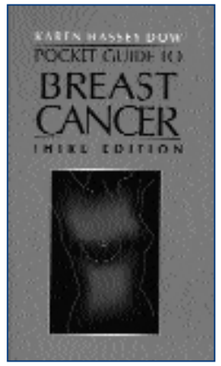


Palliative care is identified as a late comer to 'user involvement'. This is seen to be due to the fact that as a service provider palliative care already provides a strong culture of listening and thus advocating on a client's behalf. "However, offering a voice is not the same as accessing people's 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 enmeshed 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 Swetenham
Southern Adelaide Palliative Services, South Australia

Mosby's Dictionary of Medicine, Nursing & Health Professions

P Harris, S Nagy, N Vardaxis
Elsevier Australia (2005)
ISBN: 0-7295-3754-4 2134 pages
RRP:$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 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

list in the appendix.

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.

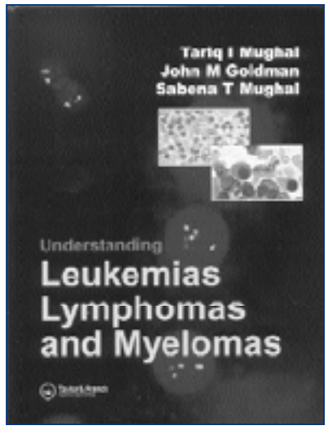
Jayne Maidens
Royal North Shore Hospital, NSW

New Technologies in Radiation Oncology

W Schlegel, T Bortfeld, AL Grosu (eds)
Springer GmbH (2006)
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 physics, such as physics registrars and research students. The text book is also an excellent tool for experienced radiation therapists to ensure they gain a more in-depth understanding of the theory behind the new technologies being implemented in their workplace. The book would also be useful for radiation oncology registrars to further consolidate their understanding of radiotherapy concepts and imaging techniques.

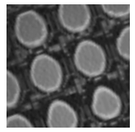


The text covers many aspects of radiation therapy: imaging, planning, treatment and questions and answers, ensuring the target audience remains informed of all aspects of the radiotherapy technology developments. Included are well researched topics such as cone beam CT, brachytherapy and image fusion/production, 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

CALENDAR OF MEETINGS


Australia and New Zealand

Date	Name of Meeting	Place	Secretariat
2006			
May			
14-17	Australasian College of Dermatologists 39th Annual Scientific Meeting	Melbourne VIC	Australasian College of Dermatologists PO Box 2065 Boronia Park NSW 2111 Tel: +61 2 9879 6177 Fax: +61 2 9816 1174 Email: admin@dermcoll.asn.au Web: www.dercoll.asn.au
July			
12-14	Royal College of Nursing Australia National Conference	Cairns QLD	Royal College of Nursing Australia PO Box 219 Deakin West ACT 2600 Tel: +61 2 6283 3400 Fax: +61 2 6282 3565 Email: nicole@rcna.org.au Web: www.rcna.org.au
14-15	Cancer Nurses Society Of Australia 9th Winter Congress	Adelaide SA	Pharma Events Tel: +61 2 9280 0577 Fax: +6 1 2 9280 0533 Email: conferences@pharmaevents.com.au Web: www.cnsa.org.au
August			
9-12	Medical Oncology Group Australia Annual Scientific Meeting	Sanctuary Cove QLD	Pharma Events Tel: +61 2 9280 0577 Fax: +61 2 9280 0533 Email: moga@pharmaevents.com.au
September			
3-9	ACCORD Workshop – A Workshop in Effective Clinical Trials Design	Sunshine Coast QLD	The Australia and Asia Pacific Clinical Oncology Research Development (ACCORD) Workshop Level 6, 52 Phillip Street Sydney NSW 2000 Tel: +61 2 8247 6207 Fax: +61 2 9247 3022 Email: mog@racp.edu.au
27-29	8th Biennial Behavioural Research in Cancer Control Conference	Brisbane QLD	Queensland Cancer Fund Email: BRCCConference@qldcancer.com.au Web: www.qldcancer.com.au/vcrcc/ psycho_oncology_research_unit.html
October			
26-29	RANZCR 57th Annual Scientific Meeting	Christchurch NZ	Royal Australian and New Zealand College of Radiologists (RANZCR) Tel: +61 2 9268 9777 Fax: +61 2 9268 9799 Web: www.ranzcr.edu.au
November			
29 Nov – 1 Dec	33rd Clinical Oncological Society of Australia Annual Scientific Meeting	Melbourne VIC	ASN Events Tel: +61 3 9863 7867 Web: www.cosa.org.au Email: congress@asnevents.net.au

INTERNATIONAL

Date	Name of Meeting	Place	Secretariat
2006			
April			
1-4	European Association for Cancer Research 19th Annual Meeting	Budapest Hungary	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: EACR19@fecs.be
1-5	American Association for Cancer Research (AACR) 97TH Annual Meeting	Washington DC United States	American Association for Cancer Research (AACR) Philadelphia, US Tel: +1 215 440 9300 Fax:+ 1 215 351 9165 Email: meetings@aacr.org Web: www.aacr.org
5-9	The American Society of Breast Surgeons 7th Annual Meeting	Baltimore United States	The American Society of Breast Surgeons Marti Boyer 10440 Little Patuxent Parkway Suite 810 21044 Columbia Tel: 410 992 5470 Fax: 410 992 5472 Email: tforte@breastsurgeons.org Web: www.breastsurgeons.org/
8-11	4th International Society of Paediatric Oncology (SIOP) Asia Conferencce	Shanghai China	Shanghai Children's Medical Center – Dept of Pediatric Hematology-Oncology Shanghai, China Tel: +86 021 5873 2020 Fax: +86 021 5839 3915 Email: siop_asia_2006@yahoo.com Web: www.siop.nl/frameset_achter.asp?p=4
20-22	5th European Oncology Nursing Society (EONS) Spring Convention	Innsbruck Austria	FECS – 5th EONS Spring Convention Brussels, Belgium Tel: +32 2 775 02 01 Fax: +32 2 775 02 00 Email: EONS5@fecs.be Web: www.fec.be/conferences/eons5
28-29	6th Annual New Strategies in the Breast Cancer Conference	Philadelphia United States	The Center for Biomedical Continuing Education Megan Ollinger 1707 Market Place Blvd., Ste. 370 75063 Irving Tel: +1 972 929 1900 Fax: +1 972 929 1901 Email: info@thecbce.com Web: www.thecbce.com/home.asp
28-30	1st Scientific Conference of Baltic Society for Pediatric Oncology and Hematology	Vilnius Lithuania	UAB CONBALTAS Renata Baublyte Jaksto g 12 LT-011 Vilnius Tel: +370 5 2120003 Fax: +370 5 2120013 Email: renata@balticconference.com Web: www.balticconference.com/bspoh2006/
May			
4-7	Oncology Nursing Society (ONS) 2006 Congress	New Orleans United States	Oncology Nursing Society (ONS) Pittsburgh, Pennsylvania, US Tel: +1 866 257 4667/ 1 412 859 6100 Fax: +1 877 369 5497 /1 412 859 6162 Email: customer.service@ons.org Web: www.ons.org

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 1N8 Toronto Tel: +1 416 596 6598 Fax: +1 416 596 1714 Email: swall@cbcra.ca Web: www.breast.cancer.ca/language/default.asp?thisUrl=%2FDefault%2Easp
6-9	NOPHO/NOBOS 2006 Nordic Conference of Paediatric Haematology and Oncology	Tampere Finland	NOPHO/NOBOS 2006 Nordic Conference Secretariat c/o Tampere Conference Service Ltd Tampere Finland Tel: + 358 3 366 4400/311 65571 Email: office@tampereconference.fi Web: www.tampereconference.fi/nopho-nobos2006/
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 Email: info@ismrm.org Web: www.ismrm.org/
14-17	11TH International Congress on Oral Cancer (ICOOC)	Grado Italy	ORL Dept. – Ospedale Civile de Udine Udine, Italy Tel: +39 432 552 801 Fax: +39 432 554 062 Email: piemonte.marco@aoud.sanita.fvg.it Web: www.icooc2006.nordestcongressi.it
16-17	Diagnostic & Interventional Radiology in Clinical Oncology	Moscow Russia	N.N. BLOKHIN RUSSIAN CANCER RESEARCH CENTER (NNBRCRC) - Office of International Affairs Dr. Somasundaram SUBRAMANIAN M.D. 24, Kashirskoye Shosse 115478 Moscow Tel: +7 095 324 1504 Fax: +7 095 323 5355 Email: 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 20123 Milan Tel: +39 02 85464527 Fax: +39 02 85464545 Email: rdemartini@esoncology.org Web: www.cancerworld.org/
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: +4 570 237 823 Fax: +4 570 237 888 Email: mammografi-symposium2006@ics.dk Web: www.mammografi-symposium.dk
24-26	XIX 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 Email: info@eso.ru Web: www.eso.ru/eng/index.htm

Date	Name of Meeting	Place	Secretariat
June			
1-2	Head and Neck Course	Hong Kong	Department of Surgery, University of Hong Kong Medical Centre, Queen Mary Hospital Sassoon Road, Pokfulam Tel: 85 22 818 0232 Fax: 85 22 818 1186 Email: HKICC05@hku.hk Web: www.hku.hk/surgery/
2-6	2006 Annual Meeting – American Society of Clinical Oncology	Atlanta United States	American Society of Clinical Oncology Annie Callender 1900 Duke St Ste 200, 22314 Denver Tel: 1 703 299 0158 Fax: 1 703 299 0255 Email: meetings@asco.org Web: www.asco.org/
7-9	European Association for Cancer Education (EACE) - 19th Annual Scientific Meeting	Enschede Netherlands	Saxion Hogescholen Inge Geerink Handelskade 75 Postbus 501, 7400AM Deventer Tel: 31 570 663 683 Fax: 31 570 663 611 Email: g.g.m.geerink@saxion.nl Web: www.eaceonline.com/
11-13	2006 Komen Foundation Mission Conference: Many Faces- One Voice (breast cancer)	Washington DC United States	Susan G. Komen Breast Cancer Foundation Dallas, Texas, US Tel: +1 972 701 2127 Fax: +1 972 855 4301 Email: drowden@komen.org Web: www.komen.org
15-16	Familial Cancer - Inside Track Conference	Madrid Spain	European School of Oncology Daniela Mengato - Francesca Marangoni Viale Beatrice d'Este, 37, 20122 Milano Tel: 39 02 8546 451 Fax: 39 02 8546 4545 Email: conferences@esoncology.org Web: www.cancerworld.org/eso/
15-17	6th International Conference on the Adjuvant Therapy of Malignant Melanoma	Stockholm Sweden	Congrex Sweden AB Britt-Marie Bohm P.O. Box 5619, Karlavägen 108, 114 85 Stockholm Tel: 0046 8 459 6600 Fax: 0046 8 661 9125 Email: britt-marie.bohm@congrex.se Web: www.congrex.com/melanoma/
15-18	11th Congress of the European Haematology Association (EHA-11)	Amsterdam Netherlands	Eurocongress Conference Management Amsterdam, Netherlands Tel: +31 20 679 3411 Fax: +31 20 673 7306 Email: eha@eurcongress.com Web: www.ehaweb.org
18-21	9th Cancer Research UK Beaston International Cancer Conference	Glasgow Scotland	Beatson Institute for Cancer Research Glasgow, United Kingdom Tel: +44 14 1942 0855 Fax: +44 14 1330 6426 Email: wheeler@beatson.gla.ac.uk Web: www.beatson.gla.ac.uk/seminars/conference.html
25-28	Tumour Vasculature: New Targets and Therapies	Cirencester United Kingdom	British Association for Cancer Research Barbara Cavilla c/o The Institute of Cancer Research, McElwain Laboratories, Cotswold Road SM2 5NG Sutton Tel: +44 20 8722 420 Fax: +44 20 8770 1395 Email: bacr@icr.ac.uk Web: www.bacr.org.uk/
28-1 Jul	3rd World Congress of the International Federation of Head & Neck Oncologic Societies (IFHNOS)	Prague Czech Republic	International Federation of Head & Neck Oncologic Societies (IFHNOS) c/o Guarant International spol.s.r.o Prague, Czech Republic Tel: +420 284 001 444 Fax: +420 284 001 448 Email: jan.klozar@lfmotol.cuni.cz Web: www.ifhnos2006.cz/

Date	Name of Meeting	Place	Secretariat
28-1 Jul	CARS 2006- Computer Assisted Radiology and Surgery	Osaka Japan	Computer Assisted Radiology and Surgery CARS Conference Office Kuessaberg, Germany Tel: +497 742 922 434 Fax: +497 742 922 438 Email: office@cars-int.org Web: www.cars-int.org
28-1 Jul	8th World Congress on Gastrointestinal Cancer	Barcelona Spain	European Society for Medical Oncology (ESMA) c/o Imedex Alpharetta, Georgia, United Sates Tel: +1 770 751 7332 Fax: +1 770 751 7334 Email: s.clemmons@imedex.com Web: www.imedex.com/calendars/gastroenterology.asp
July			
1-4	19th Meeting of the European Association for Cancer Research EACR 19	Budapest Hungary	Federation of European Cancer Societies Brussels, Belgium Tel: +32 2 755 0205 Fax: +32 2 775 0200 Email: EARC19@fecs.be Web: www.fecs.be/emc.asp?pageId=729&Type=P
8-12	UICC World Cancer Congress	Washington DC United States	American Cancer Society (ACS) Atlanta, USA Tel: +1 404 417 5998 Fax: +1 404 728 0133 Email: secretariat2006@cancer.org Web: www.worldcancercongress.org
12-13	2006 Centres for Disease Control and Prevention (CDC) Cancer Partners Summit	Washington DC United States	American Cancer Society (ACS) Atlanta, USA Tel: +1 404 417 693 3311 Web: www.cdc.gov/cancer/
12-15	13th World Conference on Tobacco OR Health	Washington DC United States	American Cancer Society (ACS) Atlanta, USA Tel: +1 404 417 5998 Fax: +1 404 728 0133 Email: secretariat2006@cancer.org Web: www.13thwctoh.org
18-28	International Summer School Oncology for Medical Students	Groningen Netherlands	World Health Orgnisation (WHO) Collaborating Centre for Cancer Education Groningen, Netherlands Tel: +31 50 3612317 Fax: +31 50 3614873 Email: summerschool@isoms.nl Web: www.isoms.nl
27-29	3rd International Breast Cancer Conference	Cancun Mexico	Miller School of Medicine- University of Miami c/o Imedex Alpharetta, Georgia, United Sates Tel: +1 770 751 7332 Fax: +1 770 751 7334 Email: s.clemmons@imedex.com Web: www.imedex.com
August			
9-12	31st World Congress of the International Society of Hematology (ISH)	San Juan Puerto Rico	International Society of Hematology (ISH) c/o Imedex Alpharetta, Georgia, United Sates Tel: +1 770 751 7332 Fax: +1 770 751 7334 Email: s.clemmons@imedex.com Web: www.imedex.com
17-20	2006 Annual Meeting & Research Workshop on Biology, Prevention and Treatment of Head & Neck Cancer	Chicago United States	American Head & Neck Society Joyce Hasper 11300 West Olympic Boulevard Suite 600 90064 Los Angeles Tel: 310 437 0559 ext. 114 Fax: 310 437 0585 Email: Joyce@ahns.info Web: www.headandneckcancer.org/

Date	Name of Meeting	Place	Secretariat
17-20	American Head & Neck Society Annual Meeting and Research Workshop on the Biology, Prevention and Treatment of Head and Neck Cancer	Chicago United States	American Head & Neck Society Joyce Hasper 11300 West Olympic Boulevard Suite 600 90064 Los Angeles Tel: 310 437 0559 ext. 114 Fax: 310 437 0585 E-mail: Joyce@ahns.info Web: www.ahns.info/meetings/index.php
24-26	4th International Conference on Gastroentroenterological Carcinogenesis	Honolulu Hawaii	The University of Texas M.D. Anderson Cancer Centre Houston, United Sates Tel: +1 713 792 2222 Fax: +1 713 794 1724 Email: register@mdanderson.org ctierney@mdanderson.org Web: www.manderson.org
September			
7-9	International Dermoscopy Course and Conference	Warsaw Poland	Dept. Dermatology CSK MSWiA Dr Lidia Rudnicka, MD, PhD Woloska 137, 02-507 Warszawa Tel: +48 22 824 22 00 Fax: +48 22 508 14 92 Email: lidiarudnicka@yahoo.com Web: www.derm.pl/index.html
13-16	Perspectives in Melanoma X	Amsterdam Netherlands	Imedex 70 Technology Drive, 30005 Alpharetta Tel: +1 770 751 7332 Fax: +1 770 751 7334 E-mail: s.clemmons@imedex.com Web: www.imedex.com
13-17	International Congress on Hormonal Steroids/Hormones and Cancer	Athens Greece	Erasmus Conferences Tours & Tracel S.A. Mrs. Penelope Mitrogianni 1, Kolofontos & Evridikis str., 161 21 Athens Tel: +30 210 725 7693 Fax: +30 210 725 7532 Email: info@erasmus.gr Web: www.erasmus.gr/web/pages.
asp?lang=2&page=1075			
21-23	2006 Gastrointestinal Oncology Conference	Arlington United States	International Society of Gastrointestinal Oncology (ISGO) Mr. Robert Ross 200 Broadhollow RD, 11747 Melville Tel: +63 1 390 8390 Fax: +63 1 393 5091 Email: email@isgio.org Web: www.isgio.org/
27-28	European School of Oncology Course (ESO): Skin Melanoma	Istanbul Turkey	European School of Oncology (ESO) Milano Italy Ph: + 39 2 8546 451 Fax: +39 2 8546 4545 Email: conferences@esoncology.org Web: www.cancerworld.org/eso
27-Oct 1	14th International Conference on Cancer Nursing	Toronto Canada	International Society of Nurses in Cancer Care (ISNCC) Cheshire, UK Tel: +44 116 270 3309 Fax: +44 116 270 3673 Email: conference@isncc.org Web: www.isncc.org
29-Oct 3	31st European Society for Medical Oncology (EMSO) Congress	Istanbul Turkey	ESMO Congress Viaganello-Lugano, Switzerland Tel: +41 91 973 1919 Fax: +41 91 973 1918 Email: congress@esmo.org Web: www.esmo.org

Date	Name of Meeting	Place	Secretariat
October			
8-11	NCRI Cancer Conference	Birmingham United Kingdom	NCRI Conference Secretariat Ms Sharon Vanloo P.O. Box 49709 61 Lincoln's Inn Fields WC2A 3 London Tel: +44 (0)20 7269 3420 Fax: +44 (0)20 7061 6004 Email: ncriconference@ncri.org.uk Web: www.ncri.org.uk/conference/
8-12	European Society for Therapeutic Radiology and Oncology (ESTRO 25)	Leipzig Germany	European Society for therapeutic Radiology and Oncology (ESTRO) Brussels, Belgium Tel: +32 2 775 9340 Fax: +32 2 779 5494 Email: info@estro.be Web: www.estro.be/estro/Index.html
8-12	International Conference of Immunogenomics and Immunomics	Budapest Hungary	Diamond Congress - International Conference of Immunogenomics and Immunomics Zoltan Prohaszka P.O.Box 48 , H-1255 Budapest Tel: +36 1 212 9351 Fax: +36 1 212 9351 Email: prohoz@kut.sote.hu Web: www.bcii2006.org/
11-14	13th Annual Conference of the International Society for Quality of Life Research (ISOQOL)	Lisbon Portugal	International Society for Quality of Life Research Email: info@isoqol.org Web: www.isoqol.org
14-16	5th European Conference: Perspectives in Breast Cancer	Amsterdam Netherlands	Imedex 70 Technology Drive 30005 Alpharetta Tel: +1 770 751 7332 Fax: +1 770 751 7334 Email: s.clemmons@imedex.com Web: www.imedex.com/
14-18 Secretariat	11th Biennial International Gynaecological Cancer Society Meeting	California United States	International Gynaecological Cancer Society Geneva, Switzerland Tel: +41 22 908 0488 Fax: +41 22 732 2850 Email: igcs-11@kenes-com Web: www.igcs.org www.kenes.com/igs-11/
18-21	8th World Congress of Psycho-Oncology	Venice Italy	International Psycho-Oncology Society Charlottesville, USA Tel: +1 434 293 5350 Fax: +1 434 977 1856 Email: info@ipos-society.org Web: www.ipos2006.it
19-21	Lymphoma & Myeloma 2006	New York United States	Imedex 70 Technology Drive 30005 Alpharetta Tel: +1 770 751 7332 Fax: +1 770 751 7334 Email: s.clemmons@imedex.com Web: www.imedex.com/
29-Nov 2	1st International Congress on Childhood Cancer (ICCC 2006)	Tehran Iran	Cancer Institute Research Center MAHAK Childhood Cancer Hospital Oshon BLVD, Darabad Tehran, I. R. of Iran 19575-566 Tehran c/o Alireza Mosavi-jarrahi Tel: +98 21 22481010 Fax: +98 21 22481011 E-mail: rmosavi@yahoo.com Web: www.crc.tums.ac.ir/En/home.as

Date	Name of Meeting	Place	Secretariat
November			
2-4 TRM	7th Meeting of the International Society of Geriatric Oncology (SIOG)	The Hague Netherlands	SIOG - International Society of Geriatric Oncology - by T. Romanyk Gevers Deynootweg 62 2586BN The Hague Tel: +31 70 3318444 Fax: +31 70 3318442 Email: tatjana.romanyk@trm-oncology.com Web: www.cancerworld.org/siog/
5-8	3rd Asian Pacific Organization for Cancer Prevention (APOCP) General Assembly Conference: "Empowering Cancer Prevention in the Asia Pacific"	Bangkok Thailand	3rd Asian Pacific Organization for Cancer Prevention (APOCP) Nagoya, Japan Tel: +66 1 809 7664 Fax: +66 2 955 9986 Email: ktajima@aichi-cc.jp Web: www.apocp.org
5-9	48th American Society for Therapeutic Radiology and Oncology (ASTRO) Annual Meeting	Philadelphia United States	American Society for Therapeutic Radiology and Oncology (ASTRO) Fairfax, Virginia, United States Tel:+ 1 703 227 0170/502 1550 Fax: +1 703 502 7852 Email: meetings@astro.org Web: www.astro.org/
5-10	XVIII FIGO World Congress of Gynecology and Obstetrics	Kuala Lumpur Malaysia	AOS Conventions and Events Sdn Bhd Kuala Lumpur, Malaysia Tel: +60 3 4252 9100 Fax: +60 3 4257 1133 Email: consec@figo2006kl.com Web: www.figo2006kl.com
7-10	18th EORTC-NCI-AARC Symposium on Molecular Targets and Cancer Therapeutics	Prague Czech Republic	Federation of European Cancer Societies (FECS) Brussels, Belgium Tel: +32 2 775 0201 Fax: +32 2 775 0200 Email: ENA2006@fecs.be Web: www.fecs.be
9	American Society for Therapeutic Radiology and Oncology (ASTRO) Annual Meeting	Philadelphia United States	American Society for Therapeutic Radiology and Oncology (ASTRO) 12500 Fair Lakes Circle Suite 375 22033 Fairfax Tel: +1 703 227 0170/502 1550 Fax: +1 703 502 7852 Email: meetings@astro.org Web: www.astro.org/
9-10	Satellite Meeting "Modeling for Detection of Environmental Carcinogens and Modifying Agents in the Asian Pacific"	Chiang Mai Thailand	Asia Pacific Organization for Cancer Prevention (APOCP) Division of Epidemiology and Prevention, Aichi Cancer Center, Research Institute 1-1 Kanokoden, Chikusa-ku, 467-86 Nagoya Tel: +66 1 809 7664 Fax: +66 2 955 9986 Email: ktajima@aichi-cc.jp Web: www.apocp.org/
9-11	2006 ONS Nurse Practitioner Conference	Pittsburgh United States	Oncology Nursing Society (ONS) 125 Enterprise Drive 15275- Pittsburgh, Pennsylvania, USA Tel: +1 866 257 4667 /+1 412 859 6100 Fax: +1 877 369 5497 /+1 412 859 6162 Email: customer.service@ons.org Web: www.ons.org/
10-12	ONS 2006 Institutes of Learning	Pittsburgh United States	Oncology Nursing Society (ONS) 125 Enterprise Drive 15275- Pittsburgh, Pennsylvania, USA Tel: +1 866 257 4667 /+1 412 859 6100 Fax: +1 877 369 5497 /+1 412 859 6162 Email: customer.service@ons.org Web: www.ons.org/

Date	Name of Meeting	Place	Secretariat
21-22	Cancer World Conference on Improving Cancer Services	Brussels Belgium	European School of Oncology Mariarita Cassese Viale Beatrice d'Este 37 20122 Milan Tel: +0039 02 8546 4522 Fax: +0039 02 8546 4545 Email: mcassese@esoncology.org Web: www.cancerworld.org/
29-Dec 2	13th Congress of the European Society of Surgical Oncology (ESSO 2006)	Venice Italy	ESSO 2006 Conference secretariat – Federation of European Cancer Societies (FECS) Brussels, Belgium Tel: +32 2 775 0205 Fax: +32 2 775 0200 Email: ESSO2006@fecs.be Web: www.fecs.be/emc.asp?pageId=719&Type=P
December			
10-14	VI International Meeting on Cancer Induced Bone Disease	Texas United States	The Cancer and Bone Society Conference Secretariat 2025 M Street, NW, Suite 800 20036 Washington Tel: +1 202 367-1138 Fax: +1 202 367-2138 Email: info@cancerandbonesociety.org Web: www.cancerandbonesociety.org/
12	The American Society of Hematology 48th Annual Meeting and Exposition	Florida United States	American Society of Haematology - ASH 1900 M Street, NW Suite 200 20036- Washington DC Tel: +1 202 857 1118 Fax: +1 202 857 1164 Email: ash@hematology.org Web: www.hematology.org/meetings/2005/index.cfm

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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Dr K White PhD

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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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)

INTEREST GROUPS

ANZ Children's Haematology and Oncology
Breast Oncology
Cancer Nurses Society of Australia
Cancer Research
Clinical Research Professionals
Epidemiological
Gastrointestinal Oncology
Gynaecological Oncology
Lung Oncology
Medical Oncology
Melanoma and Skin
Neuro-oncology
Palliative Care
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Psycho-Oncology
Radiation Oncology
Regional and Rural Oncology
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Surgical Oncology