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Current face of cancer pathology

Overview

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This edition of Cancer Forum explores the "Current face of cancer pathology". Pathology has the unfortunate reputation of being a rather traditional and static subject. The truth is that it is a vast, fascinating and constantly changing discipline.

In the late 1970s, when I was a pre-clinical medical student, university medical faculties and medical students alike understood that pathology was the basis of medicine and, as such, it occupied a major place in medical curricula. It was usual in those days for medical students to have over 240 hours of contact time with pathologists, to spend many hours studying microscope slides and bottled specimens and to witness numerous autopsies. The first edition of Robbins' Pathological Basis of Pathology, a formidably thick text, described in great detail the clinical and pathological features of all the common and important medical conditions. There is no doubt that this exposure helped develop excellent observational, descriptive and correlative skills and that these contributed substantially to the clinical acumen of the graduates. An enquiring mind, however, was left to speculate about what caused the majority of the common diseases such as cancer. These secrets still lay hidden in the tissues.

By the early 1980s diagnostic anatomical pathology was beginning to change. The routine application of immunohistochemistry to diagnostic tissue sections began to focus the pathologist's attention on the expression of individual proteins that served as markers of cell lineage. Initially, there were few antibodies available that were useful in a diagnostic setting and many only worked in frozen tissue sections. Nevertheless, the impact of immunohistochemistry was profound and it quickly replaced electron microscopy, which had revolutionised tumour classification 20 years earlier. Anatomical pathology had made its first tentative steps away from its reliance on morphological interpretation and towards functional analysis. Twenty years later most pathology laboratories now routinely perform immunohistochemistry on paraffin-embedded tissues, using over 30 highly reliable and well-characterised commercially-available antibodies. These enable the vast major categories of diagnostically-challenging tumours to be identified.

In the first article of this Forum, Leong and Leong discuss the latest generation of immunological markers that are being used in cancer pathology. These antibodies cover a wide range of uses from tumour subclassification (eg CD5 and CD23 in low grade B cell lymphomas, E-cadherin in breast cancer, and CD117 in gastrointestinal stromal tumours), predicting the primary site of a metastatic tumour (eg CK7/20, GCDFP-15, TTF-1), identification of specific somatic chromosomal alterations (eg cyclin D1, ALK, FLI-1, WT-1), germline line mutations (eg MLH1, MSH2, and MSH6 in hereditary non-polyposis colon cancer) and the identification of therapeutic targets (eg HER-2 in breast cancer).

In the second article, Cummings discusses a relatively new use of immunohistochemistry – the detection of micrometastatic disease. Studies performed by her and others have exposed some of the limitations of routine surgical pathology practice. By carefully examining axillary lymph nodes from women with breast cancer using antibodies that distinguish tumour cells from normal lymph node cells, they found that approximately 25% of cases that were reported as lymph node negative (N0) actually contain small numbers of tumour cells that were missed by routine sectioning and staining of lymph nodes. The clinical significance of these micrometastases, however, is still unclear. Do they represent passive drainage of tumour cells via the lymphatics that would have be cleared anyway by tumour immunosurveillance mechanisms or do they represent clinically aggressive disease? Should these patients be offered adjuvant therapy? The uncertainty and concern regarding these findings has recently led to a re-defining of the TMN classification for the staging of breast cancer. Pathologists are now required to examine the axillary lymph nodes in more detail and measure all lymph node tumour deposits. It will however take several more years before we will know how best to treat women with these early stage nodal metastases. These findings will also, no doubt, apply to all other types of cancer.

In the third article Field discusses another application of immunohistochemistry – the detection of a therapeutic target (HER-2) in patients with breast cancer. Since the early 1990s pathologists have become accustomed to performing immunohistochemistry for oestrogen (ER) and progesterone receptors (PR) on breast cancers as both prognostic markers and as predictive markers for treatment with tamoxifen. Although this is now part of routine practice, it is disturbing that there are still significant concerns regarding quality assurance and inter-laboratory variability in ER and PR reporting. Similar problems emerged with HER-2 immunostaining, which is now routinely performed in the larger laboratories. It took approximately 10 years from the initial discovery, in 1987, that HER-2 was over-expressed in a subset of breast cancers to the requirement for pathologists to select those patients who are eligible for treatment with the HER-2 inhibitor, Herceptin. Although we have had almost 20 years of experience with immunohistochemistry developing a reproducible HER-2 test remained a significant challenge.

Immunohistochemistry is essentially a qualitative test in which antibodies are selected and the conditions are manipulated to ensure a clear positive or negative result. HER-2 immunostaining presented a new paradigm for immunohistochemistry because

it required the test to be quantitative. Although a standardised HER-2 antibody kit (HercepTest) was commercially available it was prohibitively expensive for most diagnostic laboratories which understandably resorted to cheaper in-house tests. Most laboratories now reliably identify patients who are clearly eligible or non-eligible for treatment, however there remains a group where immunohistochemistry is less helpful. Field's laboratory is able to separate this indeterminate group by using fluorescence in situ hybdridisation (FISH) to semi-quantitate the degree of HER-2 gene amplification. This represents the first application of FISH technology to diagnostic anatomical pathology practice.

In the fourth article I discuss, from a pathologist's perspective, the recent introduction of another predictive tumour marker, c-kit (CD117). The c-kit burst onto the pathology scene about two years ago following the spectacular success of Glivec in treating patients with malignant gastrointestinal stromal cell tumours (GISTs). Within weeks our laboratory was inundated with requests to perform CD117 immunostaining on a wide range of tumour types. The requests were all initiated by oncologists who were, understandably, keen to enrol their patients onto a Glivec trial. The trial protocols required eligible patients to have tumours that showed strong staining for CD117, thus placing the onus for therapeutic decision upon the pathologists. It soon became clear that there were discrepant results between laboratories and it was a struggle to validate this test for this purpose while under intense pressure from clinicians who had patients calling them daily for the results. There are apparently several hundred similar drugs in the developmental "pipeline" and considerable effort will need to be expended to ensure that participating pathology laboratories have a reliable test in place before the clinical trials commence.

In the fifth article, Farshid describes the morphological appearance of breast cancers that occur more frequently in women who carry a germline BRCA1 mutation. Extensive phenotype-genotype correlative studies have identified a number of morphological features of particular tumours that appear to be good predictors of a germline mutation in a tumour-predisposing gene. Certain morphological features of hereditary non-polyposis colorectal cancer (HNPCC)-associated colorectal cancers (eg extensive mucinous and signet-ring areas) have already been incorporated into clinical criteria used to screen patients for the underlying mutations. It is likely that pathological criteria will soon be incorporated into the genetic screening protocols for patients with breast cancer, particularly those occurring in women under 40 years of age. These observations and protocols mean that pathologists now need to be aware of these features, and their significance, and that they have a duty of care to inform the referring clinician that the patient may require referral to a familial cancer clinic.

All of the previous major advances in pathology have been underpinned by the introduction of new technology. In the sixth article Venter et al describe the impact that microarray-related technologies are having on pathology. Whereas immunohistochemistry, FISH and genetic analysis are all based on a single gene or protein, these new technologies can analyse over 30,000 genes simultaneously. Already, there are several landmark studies that have demonstrated that genome-wide analysis has the potential to provide new insights into cancer classification and diagnosis and to generate a vast number of prognostic and predictive markers. The speed of progress at the moment is breathtaking and the amount of data that needs to be assessed and validated is already vast. Five years ago the prospect of being able to analyse the whole genome was the stuff of fantasy; now there are serious plans to begin to incorporate these technologies into diagnostic pathology practice. We are, right now, on the cusp of the genomic revolution. What will diagnostic pathology be like in five, 10 or 15 years from now? It is a daunting but exciting prospect.

Many of the advances that will be discussed in the forthcoming articles, were derived from research performed on tissue samples. Although fixed paraffin-embedded tissues are valuable for histological and DNA-based studies, unfixed-fresh tissues are usually required for major research initiatives. As the molecular revolution progressed these fresh tissues became increasingly valuable. It became common practice for researchers to obtain excess tissues, without the patient's knowledge, from pathology laboratories for their research projects. Pathologists were the gatekeepers of this process as they were responsible for determining whether the tissue was in excess to that required for diagnosis. These research projects often involved single diseases or a single gene or protein and researchers built up their personal tissue collections to support their own research.

As the genomic era dawned about five years ago, it became apparent that there was a pressing need for comprehensive well-curated collections of fresh tissue samples that were readily accessible to researchers. Tissue banks began to emerge in almost every hospital and research institution. Coincident with these developments was the emergence of widespread community concern regarding the ethical use of human tissues, particularly those obtained from autopsies, for research. Institutions with tissue collections and tissue banks responded by paying more attention to the ethical issues that related to the ownership of tissue samples; the consent to collect, store, use and transfer tissues, and the need to protect patient confidentiality. These necessary measures, however, have somewhat restricted access to tissues for research and it is a painstaking process to obtain tissues from other institutions. Presently, there are moves to improve access and streamline the process by networking existing tissue banks with common collection protocols and ethics application processes. In the last article Zeps discusses the ethics and logistics of using tissue samples in research and describes the archival tissue bank network he established in Western Australia.

The rate of change is accelerating and it is a thrilling time to be a cancer pathologist. I hope that I am still around to read the 15th edition of Robbins' Pathological Basis of Disease. What secrets will have been revealed?

Newer immunohistological markers for tumour diagnosis

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Introduction

With the rapid establishment of immunohistology as an indispensable adjunct to histological diagnosis, an ever-increasing range of antibodies has been developed to complement highly sensitive methods for demonstrating cellular antigens in fixed tissues. Space limitation restricts this coverage to those reagents that are more important for cancer diagnosis and prognostication[1] – the latter often an integral component of diagnosis. For convenience, the antibodies will be discussed in the context of specific neoplasms and markers for diagnosis of metastatic tumours will not be specifically addressed. Details of antibodies discussed are available elsewhere[2].

B-cell lymphoma

A major development in lymphoma diagnosis relates to the separation of the small cell lymphomas where newer antibodies that are immunoreactive in fixed tissue sections are now available. This group of lymphomas include small lymphocytic lymphoma/well differentiated lymphocytic lymphoma (SLL/WDL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), small cell follicle centre lymphoma (FCC) and lymphocytic/plasmacytoid lymphoma (LpL). The application of a panel of antibodies shown in table one allows the distinction of the small cell lymphomas, which have different prognoses[3].

Table 1: Antibody panel for small cell lymphomas[2]

	CD43	CD5	CD23	Cyclin D1	CD10	CD38
SLL/WDL	+	+	+	-	-	-
MCL	+	+	-	+	-	-
MZL	+/-	-	-	-	-	-
LPL	+	-	-	-	-	+
FL	-	-	-	-	+	-

SLL/BCLL = small lymphocytic lymphoma/B-cell lymphocytic leukaemia
MCL = mantle cell lymphoma
MZL = marginal zone lymphoma
LPL = lymphoplasmacytic lymphoma
FL = follicle centre cell lymphoma

The CD5 molecule is a transmembrane glycoprotein that is expressed on T and some B cells. CD5 is a marker of pre-germinal B cells. SLL/WDL (and chronic lymphocytic leukaemia) is the most common CD5+ B cell malignancy and it is thought that the small population of CD5+ B cells found in normal healthy adults and prominent in cord blood is the normal counterpart of this neoplasm. CD5 expression may be lost when large cell lymphoma of Richter's syndrome supervenes[4]. CD5 expression is also seen in MCL but not in nodal or extra-nodal MZL, the latter largely identified by the absence of most of the markers in the panel shown in table one. De novo expression of CD5 in diffuse large B cell lymphoma was shown to be an indicator of poor prognosis associated with centroblastic phenotype, interfollicular growth pattern, and intravascular or sinusoidal infiltration[5].

CD23 is invariably expressed in SLL/WDL and is an important marker for the separation of the small cell lymphomas. Activated B cells within germinal centres strongly express CD23 but mantle cells and MCL are negative. CD23 expression may be seen in a small number of other non-SLL B cell lymphomas and in Reed-Sternberg cells but staining is weak and only in a small proportion of cells.

Cyclin D1 is the most specific marker for MCL whose identification is important for prognostic and therapeutic reasons. The G1 cyclin gene (cyclin D1, PRAD-1, CCND-1), located on chromosome 11q13, exhibits characteristics of cellular oncogenes and plays an integral role in normal cell growth control. Many neoplasms including MCL, parathyroid adenomas, and a spectrum of carcinomas such as breast, supradiaphragmatic squamous cell, ovarian, endometrial and bladder transitional carcinomas, demonstrate over-expression of cyclin D1. The nuclear expression of this protein is found in over 75% of MCL and may be seen in rare cases of plasma cell myelomas, Reed-Sternberg cells and anaplastic lymphoma. It is found in hairy cell leukaemia but this over-expression is not associated with t(11;14) or bcl-1 rearrangement[6].

The bcl-6 gene product is highly expressed in germinal centre cells and their neoplastic counterparts[7]. Hence, bcl-6 immunoexpression is found in follicular lymphoma, Burkitt's lymphoma, some diffuse B cell lymphoma, nodular lymphocyte-predominant Hodgkin's lymphoma. MZL and MCL are negative.

DBA.44 recognises an unknown fixation-resistant B cell antigen expressed by mantle cells, immunoblasts, monocytoid B cells and a small proportion of low and high-grade lymphomas. It is principally employed for the identification of hairy cell leukaemia and among the node-based lymphomas, the strongest membrane staining is seen in centroblastic, immunoblastic and monocytoid B cell lymphomas[8,9].

Immunoglobulin light chain restriction was one of the earliest and most specific methods of identifying neoplastic B cell populations. Although the staining of immunoglobulin in plasma cells and immunoblasts was readily achieved, the demonstration of immunoglobulin light chain restriction in other B cell types in fixed tissue sections was beset with inconsistencies, and the technique was all but abandoned by most diagnostic laboratories. The recent description of a method that employs trypsinisation followed by antigen retrieval in 4 M urea allows consistent demonstration of light chain restriction in B cell lymphomas of small and large cell types[10].

T-cell lymphoma

The anaplastic lymphoma kinase (ALK) protein is the most important prognostic indicator in anaplastic large cell lymphoma and ALK expression is also pathognomonic for anaplastic large cell lymphoma. This chimeric protein is due to genetic alteration of the ALK locus on chromosome 2 with the most frequent alteration being a translocation involving ALK and NMP (nucleophosmin) gene on chromosome 5. Those tumours that carry the t(2;5) show localisation of the ALK protein to the nucleus and cytoplasm but variant translocations and inversions involving ALK and other partner genes on chromosomes 1, 2, 3, and 17 occur less frequently and result in different localisation of the chimeric protein to only the cytoplasm and/or cell membrane[11].

CD1 molecules are expressed in 70% of thymocytes, largely cortical thymocytes and this is reflected in the neoplastic population where precursor T-ALL/LBLs expressing cortical or immature phenotypes are CD1+, in contrast to those with prothymocyte or medullary phenotypes. Post-thymic or TDT-negative T-cell neoplasms such as T-CLL, T-PLL, cutaneous T-cell lymphoma and node-based T-cell lymphoma are CD1-. CD1a immunoexpression is thus useful for the classification of thymomas and T-cell precursor neoplasms. S100 positivity has been used as the conventional marker to distinguish Langerhans' histiocytosis and non-Langerhans' histiocytosis but it is now clearly recognised that abnormal histiocytes may also stain for S100. CD1a is an important discriminator in this context[2].

Malignant melanoma

Conventional markers for melanoma include S100 protein and HMB45[12]. S100 is not specific and is expressed in a variety of tumours whereas, HMB45, which is highly tissue selective is fixation-dependent and may not be detectable following prolonged fixation. Furthermore, HMB45 is not expressed in desmoplastic melanomas. Melan-A/Mart-1 was cloned from a human melanoma cell line and appears to show more homogenous staining of melanoma and nevus cells compared to HMB45, which stains mainly intradermal and superficial dermal cells of compound nevi. While Melan-A/Mart-1 is a useful adjunctive marker for melanomas, it too fails to label desmoplastic melanoma and is also expressed in adrenocortical and Leydig/Sertoli cell tumours. Both HMB45 and Melan-A stain an expanding group of tumours of perivascular epithelioid cells, the so-called PEComas, including angiomyolipoma, lymphangioleiomyomatosis and 'sugar' tumours.

Micropthalmia Transcription Factor (MiTF) shows high sensitivity and specificity for melanoma and appears to be equally sensitive for cutaneous nevi and metastatic melanoma[13]. The results compare favourably with HMB-45, Melan-A and tyrosinase. However, the situation is less defined in the case of desmoplastic melanoma with positivity in the range of 3-55%, allegedly inversely related to the size of the tumour[14]. MiTF is also expressed in the group of PEComas and other tumours that show melanocytic differentiation such as melanotic schwannomas and clear cell sarcomas.

Tyrosinase is an enzyme involved in the initial stages of melanin biosynthesis. Immunopositivity for tyrosinase is high in melanoma but appears to show inverse correlation with the clinical stage of the disease with homogenous staining in the early stages to a more heterogenous pattern in later stages[15]. Tyrosinase is highly expressed in epithelioid melanoma but is rarely expressed in spindle melanoma[16] and is not useful in desmoplastic melanoma and PEComas[17,18].

Soft tissue tumours

Soft tissue tumours can be difficult to diagnose and there has been a continued search for newer markers particularly as the repertoire of markers for the separation of this group of tumours is limited. Traditional markers for myogenic (skeletal and smooth muscle) differentiation include desmin, smooth muscle actin, muscle specific actin and myoglobin. These markers have varying degrees of sensitivity and a number of new antibodies have been developed to detect myogenic differentiation.

Activation of MyoD1 is an early event that commits the cell to skeletal muscle differentiation and MyoD1 nuclear immuno-expression has been shown to be inversely related to the degree of differentiation of rhabdomyosarcoma and is a useful marker, particularly in the context of the small round blue cell tumours of childhood[19]. Staining is more consistent in alveolar compared to embryonal rhabdomyosarcomas[20]. An earlier claim that the marker is highly fixation-resistant has been retracted and only as many as 35% of such tumours will stain in fixed tissue sections[21].

Myogenin is another regulatory protein essential for skeletal muscle differentiation. It is a better marker for skeletal muscle differentiation than MyoD[12,20]. Although all rhabdomyosarcomas show nuclear immunostaining, similar to MyoD1, this protein shows strongest immunoexpression in alveolar rhabdomyosacroma compared to the embryonal variant of this tumour. No reactivity has been reported in other small round blue cell tumours in children.

Calponin and caldesmon are two new markers to identify smooth muscle differentiation and are largely used in the context of distinguishing spindle cell tumours and for labelling myoepithelial cells and myofibroblasts[22,23].

Small round cell tumours of childhood

Besides MyoD1 and myogenin discussed above, two other newer markers have been added to the panel for the separation of this category of tumours[19].

Ewing's sarcoma/primitive neuroectodermal tumour (ES/PNET) is characterised by a reciprocal translocation t(11;22)(q24;q12), which results in the fusion of EWS to FLI-1. The FLI-1 protein has been demonstrated in 71% of ES/PNET and not in the other small round cell tumours with the exception of lymphoblastic lymphoma that showed 88% positivity[24]. A variety of vascular tumours also showed nuclear immunoexpression of this protein[25].

Wilms' tumour gene protein (WT1) has largely been used to identify mesothelial cells discussed below. The desmoplastic small round cell tumour is characterised by t(11;22) involving WT1 and EWS genes and has been shown to immunostains for the WT1 protein. This contrasts with no staining in ES/PNET[26]. However, there was staining of 71% of nephroblastomas.

Mesothelioma

While immunohistology has largely usurped the role of electron microscopy in the diagnosis of mesothelioma[27,28], the panel of antibodies for mesothelioma continues to expand, largely because no single marker has proven to be specific for this tumour and a panel approach is essential for accurate diagnosis.

Epithelial membrane antigen (EMA) is not a new marker but deserves revisiting because it is often not employed in the manner that we had originally described[28,29]. Cytoplasmic immunoreactivity for EMA is not a discriminator between mesothelioma and metastatic carcinoma. Both tumours are positive for EMA. However in mesothelioma, EMA localisation is not only to the cytoplasm but also to the cell membrane. Furthermore, EMA reveals the pathognomonic long microvillous processes of malignant mesothelial cells that are aberrant in location – instead of being only on the luminal surface, they are circumferential and their juxtaposition against collagen fibres is a discriminator of mesothelioma[28,29]. This pattern of immunostaining is replicated by HBME1, a more recently introduced antibody.

Calretinin is a new marker that shows the greatest promise for the identification of mesothelioma. This protein has a possible role as a calcium buffer and consistent immunoreactivity has been found in a variety of normal tissues besides both normal and neoplastic mesothelial cells. These include cutaneous eccrine glands, renal convoluted tubules, Leydig and Sertoli cells, ovarian stromal cells, adrenal cortex and neurons of the central and peripheral nervous system. It is thus a useful marker to distinguish ovarian sex cord tumours, which stain positive compared to fibrothecomas and granulosa cell tumours. Initial studies in mesothelioma suggested that cytoplasmic and nuclear localisation of the antigen was only found in about 42% of cases and also in 6% of adenocarcinomas[30] but it appears that these figures vary with the antibody clone employed. In our experience the positivity in mesothelioma is closer to 85%.

WT1 mentioned previously, has also been employed in the panel for mesothelioma and is reported to be immunoexpressed in the nuclei of 75% of cases. While nuclear immunolocalisation is not seen in pulmonary adenocarcinoma, cytoplasmic staining may occur in up to 86% of cases[31] and in the context of peritoneal tumours, 93% of ovarian serous carcinomas may show varying degrees of immunoreactivity[32].

Epithelial tumours

Breast carcinomas immunoexpress GCDFP-15 in up to 74% of cases and this marker, unlike the oestrogen receptor, serves as a relatively specific marker. Other tumours that express GCDFP-15 include those of the salivary, eccrine, apocrine and bronchial glands, seminal vesicles and prostate[2].

Amplification of HER-2/neu is a poor prognostic factor found in 20-30% of human breast cancers. The availability of trastuzumab, a recombinant monoclonal antibody against the HER-2 oncoprotein offers a novel therapeutic approach. While fluorescence in situ hybridisation (FISH) is the gold standard to assess amplification of the gene, immunostaining for HER-2 is an expedient screening method. Tumours with a HER-2 score of 3+ correspond to FISH+ and score 0 and 1+ corresponding to FISH- tumours. A proportion of tumours with score 2+ by immunostaining are FISH+ so that such cases require examination by FISH. There is controversy surrounding the method of scoring, with some laboratories taking into account the normal immunoexpression of benign mammary epithelium. Field discusses the application of HER-2 FISH in detail in this edition of Cancer Forum.

E-cadherin and the cadherin-catenin complex have been employed as markers to predict behaviour of breast cancers[33,34]. E-cadherin is not only useful for the understanding breast cancer pathobiology but has been shown to be a diagnostic discriminator between lobular and ductal carcinoma, the former showing an absence of E-cadherin immunostaining[35]. Conversely, lobular carcinomas express high molecular weight cytokeratins, whereas ductal carcinomas do not[36].

High molecular weight cytokeratin (CK5/6, 34BE12, callus keratin) immunostaining has also been used effectively to identify the basal cells in prostatic acini. Malignant prostatic acini are lined by a single layer of cells with loss of the basal cell layer a diagnostic feature that sometimes difficult to discern with immunostaining. High molecular weight cytokeratins are also expressed in mesothelial and mesothelioma cells compared to carcinoma cells, which express these proteins much less frequently.

Cytokeratin 20 (CK20) is a low molecular weight cytokeratin that is expressed in a restricted number of carcinomas, including carcinomas of the gastrointestinal tract and urinary bladder[2,37]. The combined application of CK20 and CK7 allows the separation of a number of epithelial tumours as shown in table two.

Table 2: Cytokeratin 20 (CK20) and cytokeratin 7 (CK7) immunoexpression in epithelial tumours[2]

CK7+	CK20+ Bladder Breast Colon Bile duct Ovary mucinous Pancreas Stomach	CK20- Cervical Endometrium Esophagus Breast GIT carcinoid Bile duct Pancreas Kidney Liver Lung carcinoid Neuroendocrine Lung squamous Lung small cell Mesothelioma Ovary Salivary gland Thyroid
CK7-	Merkel cell Stomach Colon	Adrenal cortex Esophagus GIT carcinoid Germ cell Kidney Liver Lung carcinoid Neuroendocrine carcinoma Lung squamous Lung small Mesothelioma Prostatic Soft tissue epithelioid sarcoma Thymus

Poorly differentiated tumours in the liver include hepatocellular, cholangio- and metastatic carcinomas. A number of markers including alpha-fetoprotein, carcinoembryonic antigen and CK19 have been purported to separate these entities but the panel is not foolproof. Hep Par 1 has been shown to be specific for hepatocytes and their neoplastic counterparts[38]. The marker is also immunoexpressed in a small number of gastric carcinomas.

Thyroid transcription factor-1 (TTF-1) was originally demonstrated in follicular thyroid cells and subsequently in respiratory epithelial cells, and has since been shown to be a useful marker of pulmonary adenocarcinoma and thyroid neoplasms, including

papillary, follicular, medullary and insular carcinomas. Anaplastic carcinomas are negative and TTF-1 has been observed in occasional gastric and endometrial carcinomas[2].

Tumour immunohistology and predictive pathology

The recent introduction of a new targeted therapy, STI-571, a receptor tyrosine kinase inhibitor that inhibits the activated KIT protein, provides effective treatment for recurrent or metastatic gastrointestinal stromal tumours (GISTs). It is now appreciated that KIT (CD117) immunoexpression in the specific context of mesenchymal lesions of the gastrointestinal tract defines a group of tumours that are collectively called GISTs so that this marker is necessary for both diagnosis and therapy. In a recent consensus meeting, it was concluded that "indeed the term 'GIST' should apply only to neoplasms displaying KIT immunoexpression with very rare exceptions"[39]. CD34, which was previously a component of the definition, is only found in 60-70% of cases. The role of c-kit in the diagnosis of GISTs is discussed further by Waring in this edition of Cancer Forum.

Tumour immunohistology and the diagnosis of familial cancer syndromes

Germline mutations of the genes responsible for mismatch repair proteins MLH1, MSH2 and MSH6 account for over 90% of mutations in hereditary nonpolyposis colorectal carcinoma (HNPCC), which makes up 1-5% of all carcinomas in the colon. Deficiency of these mismatch repair proteins leads to an increased rate of mutations in microsatellite regions and may affect crucial genes that regulate growth, differentiation and apoptosis. Patients with colorectal carcinomas showing abnormalities of one of these proteins have an increased incidence of synchronous and metachronous tumours in the colon, as well as other sites such as ovary, endometrium and urinary bladder[40].

Conclusions

By necessity this has been a brief listing of newer antibodies that are immunoreactive and applicable for routine tumour diagnosis. The continual development of increasingly sensitive antibodies contributes significantly to more accurate tissue diagnosis, better prognostication and greater individualisation of treatment in cancer.

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Occult metastases in breast cancer

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Introduction

Many patients survive breast cancer. Until newer, probably molecular, indicators are determined, axillary lymph node status remains the key parameter that determines both disease-free and overall survival in patients with breast cancer. Approximately 70% of women with operable breast cancer will have negative axillary lymph nodes[1]. Of those patients with T1N0 tumours (ie tumours less than 20mm in diameter and with negative lymph nodes) 70% will have an excellent prognosis with surgery alone[2]. Thirty percent however, will develop metastatic disease and die within 10 years. It has been suggested that this subgroup of node negative patients who do develop metastases may have clinically and pathologically 'occult' metastases in their axillary lymph nodes[3]. While certainly not the entire story, in retrospective studies of histologically negative axillary lymph nodes, up to 25% of cases have shown metastatic disease on further, more detailed assessment of the nodes[4-6]. Metastases are missed because they are not actually included in the initial haematoxylin and eosin stained section of the node, or sometimes they are present, but are not identified by the pathologist for one reason or another, such as with metastatic lobular carcinoma, when the tumour cells are scattered and resemble surrounding lymphocytes.

There have been a large number of protocols aimed at more thorough pathological examination of axillary lymph nodes for metastatic tumour deposits. These have mostly involved cutting more deeply into the nodes. This has ranged from one extra section, to taking extra sections at every 100µm right through the node, to taking one further level at 500µm or various combinations of those. A range of immunohistochemical stains for keratins and other epithelial markers has also been used to try to highlight (metastatic) epithelial cells in axillary lymph nodes to make the cells more readily seen by the pathologist. The more thoroughly a node is analysed, the more likely secondary tumours are to be found. Cutting levels through lymph nodes and performing immunohistochemical stains is time consuming and expensive and the amount of effort applied has to be proportional to the expected yield.

Size of axillary node metastases

As the natural history of breast cancer has changed – or more correctly, has been brought forward with the introduction of screening mammography – the median tumour size at diagnosis has decreased, and so too has the incidence of metastases[7].

Occult metastases have been loosely equated with micrometastases. In some of the earlier studies about hitherto occult metastases found on subsequent evaluation of lymph nodes, the metastatic deposits were not small. It is now generally accepted that lymph nodes should be sectioned at 2-3mm of thickness before embedding and so these larger 'occult' metastases are less frequently found. Many occult metastases are indeed small, but to avoid confusion it is best to give the size of the deposit found as described in the sixth edition of the TNM system[8]. Between 0.2mm and 2mm across is a useful definition of micrometastases (pNI (mi)). Those smaller than 0.2mm across should be classified as tumour-cell clusters and isolated tumour cells (ITCs). Specifying the size of the metastases in each case should enable larger series of patients to be compared and the prognostic significance of these smaller deposits to be evaluated.

There has been considerable dispute about whether occult metastases are of any prognostic significance. Studies in which a prognostic significance has been demonstrated have usually more fully evaluated the lymph nodes and found a larger proportion of involved nodes. When only one extra (close) section and possibly one further level for immunostaining have been taken, many positive nodes may have been missed, thus distorting the survival analysis. The size of the occult metastases is important, those greater than 0.5mm across giving a reduced disease-free survival both at five years and 10 years of follow-up[9]. It will be interesting to see what influence deposits less than 0.5mm across have at 15 and 20 years.

Sentinel lymph nodes

The sentinel lymph node is the first node that drains the tumour. Using radioisotopes and coloured dyes, sentinel axillary lymph nodes are being identified with increasing accuracy. As sentinel nodes are more likely to contain metastases than non-sentinel nodes, detailed and accurate assessment of these nodes is now performed routinely. Formerly-occult secondaries have been found in 12-29% of sentinel node biopsy specimens from patients with T1 tumours (those less than 20mm across)[3].

If the sentinel node is involved, should further dissection of the remainder of the axilla occur? Yes, until a lot more information is known about the significance of both sentinel nodes and axillary micrometastases. One study showed that non-sentinel lymph node involvement was significantly less for patients in whom the sentinel node metastasis measured less than 1mm across (16 vs 36%, $p = 0.02$)[10,11]. While evaluating lymph nodes from an axillary dissection specimen with deeper levels and immunohistochemistry is a relatively time consuming and expensive exercise, detailed examination of sentinel nodes is not much to ask. The only question is how to best examine them.

As a start, sentinel lymph nodes should be submitted for histology in their entirety. They should then be cut into approximately 2mm thick slices and embedded. Cutting through the node in this way often means that less sectioning will be required later at

histology[12]. Some groups recommend intraoperative assessment of sentinel lymph nodes. This is because approximately 25% of patients can then proceed to an immediate axillary dissection, thus avoiding a second operation[10]. With frozen section, the reliability has been reported to be about 65%. However, there is the not insignificant concern that substantial amounts of tissue may be lost while facing into the node, and that smaller metastases may be missed. With intraoperative imprint cytology, multiple cut surfaces can be examined quickly, without loss of tissue, but there is a significantly higher chance of indeterminant results.

Deciding how far apart to have the step sections through the node and at how many levels to have immunohistochemical stains for epithelial cells largely depends on the size of the micrometastasis that you are concerned about. If you are concerned about 2mm metastases, the sectioning would be further apart than if you were concerned about 0.2mm metastases. In a study we performed of 208 cases of breast cancer which had negative axillary lymph nodes on the initial haematoxylin and eosin assessment, occult metastases were found in 25% of cases[6]. Each block was sectioned at four levels, each separated by 100µm and each level was stained with H and E, MNF.116 an anticytokeratin antibody and the antibody BC2, reactive with MUC1 epithelial mucin core protein[13]. If only the first (at 0µm) and fourth (at 300µm) levels were analysed, which would have represented a considerable saving in labour, 96% of the metastases would have been detected. Eleven percent of the metastases were present as small, scattered deposits and a further 55% were less than 0.5mm in diameter. The remaining 34% were greater than 0.5mm in diameter.

The Australia and New Zealand guidelines for sentinel node biopsy recommend that if the initial haematoxylin and eosin stained section is negative, that four levels be cut at 500µm intervals and that an anticytokeratin antibody be used on the first level[14]. While approximately 25% of our cases would have been missed if the 0.5mm step sectioning had been used, that only occult metastases 0.5mm in diameter or greater affected survival, means that missing the smaller occult metastases may not have mattered clinically, at least in terms of 10 year survival analysis. Thorough assessment of one or two sentinel nodes, the results of which will determine whether or not subsequent surgery is performed, is certainly warranted. A prospective study of sentinel node occult metastases in 200 patients with breast cancer examined the entire lymph node at 0.25mm intervals (including with immunohistochemistry) and showed occult metastases in 25% of cases. The mean size for the largest H and E-detected metastases was 3.1mm and for immunohistochemically detected metastases was 0.75mm[15]. These values appear quite large, especially when compared with the 1mm mean size on H and E, and 0.1mm size on immunohistochemistry, as described by Turner et al[16].

Location of metastases in nodes

There has been discussion with respect to the different prognostic significance of occult metastases in various locations within the node. Carter et al[17] considered malignant cells in the extracapsular sinus of the lymph node to be an example of passive transportation and without prognostic significance, unlike so-called active migration of tumour cells into lymph node tissue proper. Hartveit et al[18] however, were more concerned about micrometastases in the capsular lymphatics than those in the substance of the node. Those in the substance of the node, they found, were associated with a better prognosis, which was similar to that of patients with node negative disease. As well as being essentially the first port of call for metastatic disease, the sentinel node, in effect, is also a gate-keeper for the tumour cells. If the tumour cells are not retained there for any length of time, the 'sentinel' function is lost. If tumour cells are 'passively transported' along lymphatics, including sentinel node subcapsular lymphatics, the opportunity for an immune attack or containment of the metastatic tumour cells in the sentinel node may be lost. Large numbers of cases would be required to clarify this issue.

Lobular carcinoma

Invasive lobular carcinoma generally shows a histological pattern of single cell invasion, rather than the glands and tubules characteristic of invasive ductal carcinoma. If invasive lobular carcinoma is associated with axillary lymph node metastases, the pattern of invasion is similar to single cells. These scattered single cells can be very hard to distinguish from surrounding lymphocytes in lymph nodes and so the false negative rate for metastatic invasive lobular cancer is quite high. In our series, 25% of invasive ductal carcinomas had occult metastases compared with 38% of invasive lobular carcinomas[6]. The lower rate (6%) for cancers of special type probably reflects their usually less aggressive clinical course. As the rate for occult metastases is so high with invasive lobular carcinomas, all histologically negative axillary nodes from such cases, whether they are sentinel nodes or not, should have as a minimum, immunohistochemical staining of at least one further section. de Mascarel[19] and Trojani[20,21] found occult metastases in 41% of 89 cases of invasive lobular cancer. However, while disease-free survival was reduced in their patients with invasive ductal carcinoma, no effect was seen in those with invasive lobular carcinoma, similar to our findings[9]. Many factors, as well as axillary lymph node status, affect long-term survival in patients with breast cancer.

Bone marrow metastases

The most common site for breast cancer metastases is bone marrow and up to 80% of patients with metastatic breast cancer will have bone marrow involvement[22]. Also, as many as 40% of patients with primary, operable breast cancer, are thought to have tumour cells present in their bone marrow[23,24]. The presence of occult metastases in the bone marrow has been shown to be unrelated to the presence of lymph node metastases[25], although that may be a reflection of how extensively the lymph nodes are examined. Bone marrow micrometastases were associated with later distant metastases ($p < 0.001$) but not with locoregional recurrence ($p = 0.77$)[25]. While further prospective studies are required, it may be prudent to consider bone marrow aspiration in patients with negative sentinel lymph nodes, to document if metastatic disease is present. However, as some clinical trials have shown, a survival advantage in women receiving adjuvant treatment, regardless of their nodal status[3] detection of occult metastases either in the axilla or the bone marrow may be less important.

Further studies

Three large prospective studies are underway which will provide further very useful information about axillary lymph node metastases. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial plans to accrue 4,000 patients with breast cancer[3,10,26]. These patients will be clinically node negative, and histopathologically, sentinel lymph node negative. If the sentinel node is positive, or is not found, axillary dissection will be performed. The study will look at the morbidity associated with sentinel lymph node biopsy, compared with axillary dissection. The clinical significance of occult metastases will also be explored. The American College of Surgeons Oncology Group (ACOSOG) protocol Z0010 will look at sentinel node and bone marrow micrometastases in patients with clinically lymph node negative breast cancer with primary tumours less than 50mm in size[15,27,28]. The Minimally Invasive Molecular Staging of Breast Cancer Study (MIMS) will study 1,130 women with breast cancer. Real-time RT-PCR analysis of sentinel nodes, axillary lymph nodes, bone marrow and peripheral blood will be examined[29].

It is hoped that in these studies, very detailed analysis of the axillary lymph nodes will be undertaken, so that the true prognostic importance of micrometastases can be determined.

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HER-2: Its molecular biology and testing by immunochemistry and fluorescent in situ hybridisation

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Introduction

The treatments available for managing breast cancer have recently been augmented by the arrival of Herceptin, a monoclonal antibody that targets a subset of breast cancers over-expressing the specific HER-2 antigen. This treatment has relatively few side-effects and has been shown to assist patients with metastatic carcinoma, and is now being trialled in earlier disease. The drug is expensive and of no use in patients whose cancers do not express the HER-2 antigen. Therefore it is essential that a reliable and as inexpensive as possible test be readily available and used to identify women who will benefit. There has been an international and Australian debate as to which test to use, when, who should perform the test, and of course, who should pay. In addition, an Australian study has addressed the question as to whether routine surgical histopathology can at least triage breast carcinomas to reduce the numbers of cases that need specialised immunoperoxidase or fluorescent in situ hybridisation testing for the HER-2 antigen.

The human epidermal growth factor receptor-2 (HER-2) has been found to be over-expressed in approximately 10-30% of breast cancers, due to gene amplification in almost all cases. HER-2 over-expression is a poor prognostic factor for patients with both axillary lymph node-negative and positive breast cancer, and predicts for a likely response to specific chemotherapy regimes. Since 1998 HER-2 assessment has become vitally important for selecting patients with metastatic breast cancer who are eligible for treatment with trastuzumab

(Herceptin). Herceptin has shown significant benefit in the treatment of patients with advanced disease whose tumours strongly over-express HER-2 and/or show HER-2 gene amplification with a response less likely in those patients whose tumours only weakly or do not over-express HER-2. Although testing is now being performed in laboratories worldwide, there remains a number of unanswered questions concerning who to test, when to perform the test, which technique to employ, which reagents to use and how to assess and express the test result?

It is essential to accurately diagnose HER-2 status to avoid false negatives that deny patients the opportunity to receive Herceptin, and to avoid false positives that waste an expensive drug and raise false hopes in the patient.

There is debate as to whether HER-2 status should be systematically evaluated in every primary carcinoma at the time of initial diagnosis, or whether testing should occur at the time of relapse, which incurs a lesser cost. Testing at the time of diagnosis allows for the selection of an appropriate adjuvant therapy such as anthracycline containing chemotherapy which may have greater efficacy in HER-2 positive tumours, or for the selection of patients for current trials which are using Herceptin in the adjuvant setting. It also maximises accuracy of immunohistochemistry (IHC) since tissue fixation and time in paraffin block are at their shortest, minimising protein denaturing and loss of antigen. There is no significant difference in the HER-2 status of primary and metastatic tumours of the breast.

There is considerable debate comparing the benefits of centralised testing for both IHC and fluorescent in situ hybridisation (FISH). Centralised testing provides economies of scale, reduced costs, standardisation of methodologies, procedures and reagents, and allows for increased experience to be gained by a group of pathologists. But local testing, as long as it is supported by quality assurance programs and training for technical and pathologist staff, avoids problems with fixation artefacts because fixation and antigen retrieval can be standardised locally.

The testing is currently performed mainly on archival material because in Australia federal government funding is only available for the treatment of metastatic disease, but increasingly some laboratories are testing all breast carcinomas at the time of initial diagnosis.

The two main methods used in the routine, clinical, diagnostic setting for HER-2 are IHC, which tests for protein production and membrane HER-2 receptor, and FISH which tests for gene amplification in the nucleus. IHC is routine technology for many laboratories and allows for rapid testing of large numbers of cases with minimal infrastructure setup costs. But there has to be rigid quality-control testing conditions and there is considerable interobserver variation in test interpretation because the HercepTest requires assessment of the intensity of staining of the cancer cells, as well as a percentage of cells that are positive. There are a large number of commercially available kits and over 20 antibodies available with varying recommended methods of antigen retrieval, tissue fixation and sensitivities and specificities, leading to varying rates of HER-2 over-expression in breast cancer of between two and 60%. This has been highlighted recently in the US in a College of American Pathology (CAP 2001) study where up to 9% of laboratories using IHC recorded a negative carcinoma as 2 or 3+, while a FISH survey by the College showed all laboratories correctly found no amplification in two breast cancers. Specific HER-2 test kits such as HercepTest minimise laboratory variables by including all reagents, detailed instructions on the specific technique and a scoring system to assess and express the results. But the reading of the test remains quantitative rather than qualitative and requires considerable training. The majority of cancers in which HER-2 over-expression is weakly positive by IHC and assessed as 2+, fail to show amplification of the HER-2 gene on FISH retesting. As a result, most authors now advocate that a score of 2+ by IHC should be regarded as an equivocal test result requiring FISH.

FISH employs fluorescence microscopy which is a complex and specialised technique not commonly available in most pathology laboratories, and it is a relatively expensive test for routine use. There are significant infrastructure costs including an immunofluorescent microscope, and each case takes considerable time to read by the skilled pathologist, who needs to recognise morphology, eg the nuclei of 60 infiltrating carcinoma cells need to be counted while avoiding intraduct carcinoma. In our Australian experience in the Roche-funded centralised laboratory, there has been a high rate of technically non-assessable tumours varying markedly between laboratories involved in the study, ranging from zero in one laboratory to 70% in another. Most of these were due to the lack of specific HER-2 hybridisation signal, reflecting poor tissue fixation possibly due to variations in time in formalin and paraffin embedding temperatures, or other adverse processing variables, such as the use of Carnoy's solution to defat specimens.

Other HER-2 testing methods such as chromogen in situ hybridisation for gene amplification and assays of 'down-stream' molecules such as tyrosine kinase are being developed, and may yet provide a more accurate, reliable and reproducible technique for routine use. In the meantime, however, if Herceptin is shown to have clinical benefit as adjuvant therapy as a result of prospective, randomised clinical trials currently underway, there will be pressure on laboratories to test all breast cancers at first presentation.

Recently in Australia, pathologists from 13 laboratories associated with the HER 2000 International Study correlated pathology features of cancers, including the size, type, histological grade and lymph node status, with the frequency of HER-2 over-expression assessed by IHC using the HercepTest and the HER-2 DNA Probe Kit to re-test the equivocal cancers by FISH. This kit includes an internal control probe to the centromere of chromosome 17 as well as the HER-2 probe, labelled with SpectrumGreen and SpectrumOrange respectively, to control for tumour ploidy and potential processing problems. Interobserver variation in assessing HER-2 over-expression on IHC was examined by a slide circulation scheme as a quality assurance measure.

Some 1,144 of the 1,536 cancers (74.5%) assessed did not over-express HER-2. Unequivocal over-expression (3+ by IHC) was seen in 186 cancers (12%) and an equivocal result (2+ by IHC) was seen in 206 cancers (13%). Of the 156 IHC 3+ cancers for which complete data was available, 149 (95.5%) were ductal NST and 152 (97%) were histological grade 2 or 3. Only one of 124 infiltrating lobular carcinomas, a pleomorphic variant (0.8%) showed HER-2 over-expression. None of the 49 'special types' of carcinoma, which are grade 1 and usually oestrogen and progestogen positive, showed HER-2 over-expression. Retesting by FISH of a proportion of the IHC 2+ cancers showed that only 25 (23%) of those assessable exhibited HER-2 gene amplification, but 46 of the 47 IHC 3+ cancers (98%) were confirmed as showing gene amplification. The highest yield of HER-2 over-expressing carcinomas is seen in the grade 3 NST subgroup in which 24% are positive by IHC.

Various testing guidelines and algorithms have been produced largely based on IHC as a first-line test with FISH as a confirmatory test to try to overcome concerns regarding the reliability of IHC. Cancers which are HER-2 2+ on IHC show no gene amplification in FISH in 77% of cases, and the 2+ category should be regarded as equivocal. The Australian study suggests that it may be possible to triage breast cancers so that HER-2 testing is only performed on carcinomas with a significant risk of HER-2 over-expression. The strong correlation between HER-2 3+ and infiltrating duct carcinoma NST, grades 2 and 3, has also been found by other groups, suggesting a predominant HER-2 positive phenotype. Triaging using grading and typing does require training pathologists and quality assurance programs.

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Predictive pathology: a pathologist's perspective

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Introduction

The history of how gastrointestinal stromal tumours (GISTs), an obscure soft tissue tumour of the bowel wall, came to occupy the center stage of oncology during 2001/2002 best illustrates the "Current face of cancer pathology in Australia", the forum subject of this edition of Cancer Forum.

GISTs arise predominantly in the stomach and small intestine, but also occur in the rectum, oeophagus and a variety of other locations including the mesentery. They are relatively rare tumours with an estimated incidence of 100 new cases per year in Australia. The majority of GISTs behave in a benign manner but larger tumours and those with a higher mitotic index can be aggressive. These malignant GISTs follow a characteristic clinical course that includes local recurrence at the site of resection, intra-abdominal spread on serosal surfaces and the development of liver metastases. Notably, radiation therapy and chemotherapy, used singly or in combination, are ineffective in the treatment of advanced disease.

For many decades GISTs were thought to be neoplasms of smooth muscle origin and were therefore classified as leiomyomas, leiomyosarcomas and leiomyoblastomas. When electron microscopy and immunohistochemistry were applied to these tumours however, there was little evidence of smooth muscle differentiation, and their histogenesis became uncertain. In the early 1990s it was discovered that most GISTs were positive for CD34, but this gave no clue to their cell of origin[1]. In 1997, Drs Seichi Hirota (Osaka University) and Lars-Gunnar Kindblom (University of Gothenburg) each independently observed that GISTs express the receptor tyrosine kinase KIT (CD117). This observation provided the clue that GISTs originate from the interstitial cell of Cajal (ICC). These inconspicuous dendritic-like cells are widely distributed throughout the muscularis propria of the GI tract where they play an important role in gut motility. Like GISTs, ICCs express CD34 and KIT. A landmark paper the following year from Hirota et al[2] transformed the field. They showed that GISTs not only express KIT but also contain mutations in the KIT gene that result in activation of the tyrosine kinase. Many laboratories have since established that KIT mutations are present in >85% of GISTs, primarily in exon 11 and less commonly in exons 9 and 13. The mutations are invariably in-frame deletions and the mutant isoforms, when cloned and expressed in vitro, have constitutive kinase activity. These mutations are thought to favour spontaneous dimerisation of KIT in the absence of its natural ligand, stem cell factor, leading to constitutive phorphoryation and activation of the tyrosine kinase.

Meanwhile, Dr Brian Druker (Oregon Health and Science University), in collaboration with Novartis Pharmaceuticals, was working on molecules that block the binding of ATP to tyrosine kinases. He discovered that STI571 (imatinib mesylate; Glivec) inhibited the kinase activity of ABL and the BRC-ABL fusion gene product of the Philadelphia chromosome. Glivec received worldwide attention in 2000 for its effectiveness against chronic myelogenous leukaemia (CML) which is driven by the constitutive activation of the BRC-ABL fusion gene. More than 85% of chronic phase CML patients taking one oral dose per day achieve a complete haematological response and many reach a complete cytogenetic remission. Glivec received FDA approval in the US for the treatment of CML in May 2001.

Glivec however, is not perfectly specific and inhibits tyrosine kinases that are closely related to ABL, including ARG (ABL-related kinase), PDGRFA and PDGRFB. Dr Michael Heinrich (Oregon Health and Science University) demonstrated that Glivec is also a potent inhibitor of KIT in vitro and Dr Jonathan Fletcher (Brigham & Women's Hospital, Boston) showed that the drug could inhibit the growth of a GIST cell line. Remarkably, Novartis declined suggestions that it would be worthwhile conducting a clinical trial to explore the effectiveness of Glivec in GISTs. The remarkable efficacy of this drug in patients with these tumours may have gone undiscovered had it not been for the persistence of the husband of a Finnish woman who had a locally advanced GIST with metastases to the liver. He, apparently, bought a large number of Novartis shares and demanded to discuss his wife's dilemma with the company's president. Compassionate use of Glivec was granted to his wife in March 2000. Within a matter of weeks the liver metastasis showed an overall reduction in size of 75% and six of 28 liver metastases were no longer detectable in CT scans after eight months of therapy. The drug was well-tolerated and the patient reported that all cancer-related symptoms had disappeared. The clinical response correlated with near complete inhibition of [18F] fluorodeoxyglucose uptake on PET scan. A post-treatment biopsy showed a marked decrease in tumour cellularity and extensive myxoid degeneration. The publication that followed[3] sent a shock wave through the oncology community around the world. The long-awaited promise of effective targeted therapy against a solid tumour had finally arrived. In it lay the hope that patients with incurable tumours could now live in long-term remission with their tumours without the need for toxic chemotherapy and radiotherapy.

This 'proof of principle' case quickly convinced Novartis to conduct multicentre clinical trials in the US and Finland (STIB2222), Europe (EORTC Soft Tissue and Sarcoma Group) and Australia (Australian Gastro Intestinal Trials Group). The rate of patient recruitment into these trials was unprecedented. The B2222 trial showed that 75% of patients had a partial response or had stable disease[4]. Most patients reported almost immediate improvement in well-being and in several cases PET activity was markedly reduced within 24 hours of commencing treatment. On the basis of these results Glivec was approved in the US by the FDA for the treatment of unresectable and metastatic GISTs in February 2001, a record eight months after the NEJM publication. Novartis also sponsored another multicentre trial (STI571B2225) to determine whether Glivec was effective in non-GIST tumours that express KIT or related tyrosine kinases. Recruitment into the B2225 trial was on the basis of a tumour being strongly KIT positive by immunohistochemistry or a likely biological rationale such as known involvement of PDGRFA or B in the biology of the tumour.

The requirement of these trials that tumours be strongly KIT positive by immunohistochemistry effectively placed the onus for deciding patient eligibility for treatment on pathologists. Several pathologists, including myself, were caught unprepared for this new role and it quickly became apparent that there was significant inter-laboratory variation in KIT immunohistochemistry reporting. With hindsight it is now apparent that most laboratories had optimised their KIT immunohistochemistry only for the purpose of diagnosing GISTs and not for identifying a therapeutic target. The optimal concentrations of the antibodies and the specificity and sensitivity of the test had not been validated against the wide range of tumours that were included in the B2225 trial. It is worth remembering that the predictive value of any test is dependent upon the prevalence of the disease. In other words, for any given sensitivity and specificity, the false-positive and negative rates of a test will vary depending upon the pre-test probability of the disease. In the context of an intra-abdominal spindle cell tumour (where there is a very high pre-test probability of the tumour being a GIST), a positive or negative KIT immunoassay result effectively confirms or excludes a GIST, respectively. Outside this context the false positive and negative rates will rise. Accordingly, several patients with KIT positive tumours were enrolled in the trial and treated with Glivec but their tumours were subsequently shown to be KIT negative by the reference laboratory that had carefully validated the assay for this purpose.

The results of the B2225 trial were interesting for several reasons. It quickly became clear that many tumours expressed KIT but almost all, except GISTs, were non-responsive to Glivec. Three tumour types however, did show a consistent clinical response, namely myelomonocytic leukaemia, dermatofibrosarcoma protuberans and hypereosinophilic syndrome. All were either known or were later found to contain chromosomal translocations or mutations that involve the PDGFRA or B genes, which result in constitutive activation of PDGFR kinase activity in the same manner as KIT and ABL. Glivec responsiveness, therefore, requires the presence of an activating mutation in a target tyrosine kinase.

Glivec is currently under consideration by the Pharmaceutical Benefits Advisory Committee for treatment of GISTs. It appears likely that patients with KIT-positive GISTs will soon be eligible for initial treatment with Glivec. Accordingly, patient eligibility will be determined routinely by pathologists on the basis of KIT immunohistochemistry. Given the cost of the drug (approximately $50,000 per patient per annum) and its effectiveness, it is important for all laboratories to carefully validate their KIT immunohistochemistry tests. In a series of 28 cases with a prior diagnosis of malignant GIST, reviewed at the Peter MacCallum Cancer Centre during the past two years, eight cases (30%) proved not to be GISTs on the basis that they were CD34 negative and had no detectable mutation in the KIT gene. Five of these cases had been previously reported as KIT positive but the staining pattern was different from the strong membranous and cytoplasmic staining typically seen in GISTs[5]. The weak cytoplasmic staining seen in the five tumours was similar to that seen in reactive fibroblasts when too high an antibody concentration is used. In addition, two of the 20 true GISTs proved to be KIT-negative and these tumours probably contain mutations in other genes such as PDGFRA. Our series was undoubtedly biased in favour of diagnostically difficult cases, but it highlights that there is a significant error rate for the diagnosis of malignant GIST. Several patients are likely to receive an ineffective treatment while others will be denied a potentially effective treatment. Clearly, as with HER-2 immunohistochemistry in metastatic breast cancer, there ought to be a second line test to help sort out the indeterminate cases. The two options are KIT and PDGFRA mutation detection (which can be performed on DNA extracted from paraffin-embedded tissues) or Western blots using anti-phosphotyrosine antibodies (which would require fresh tissue). A strong case could also be made to refer all difficult and non-responsive cases to a central referral laboratory in the same manner as HER-2 FISH.

The development of new targeted therapies is creating a new role for pathologists who increasingly will be required to identify therapeutic targets. This will necessitate the inclusion of pathologists from the earliest stages of drug development and clinical trial design to ensure that the development and evaluation of a new drug occurs in parallel with the diagnostic reagents and standardised tests required to identify the target. There are apparently several hundred drugs, such as Glivec, being developed by pharmaceutical companies. These will undoubtedly usher in a new era of predictive pathology where therapeutic target identification will be an essential tool in the patholoGIST's 'kit'.

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The clinical utility of morphologic data in the identification and care of women with BRCA1-associated breast cancer

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Introduction

We all make assumptions about the genetic composition of individuals based on their appearance. Gender, racial heritage and some genetic diseases produce recognisable outward features in individuals. Pathologists extend this activity to the microscopic appearances of tumours. The histologic diagnosis of certain tumours raises the possibility of associations with hereditary syndromes. The diagnosis of medullary carcinoma of the thyroid in young individuals, for example, requires exclusion of the familial form of this tumour and of the multiple endocrine neoplasia syndrome. For the common human malignancies, such as breast and colon cancer, there is increasing interest in whether tumour morphology may be predictive of an inherited cancer disposition. The purpose of this review is to summarise this information with regards to BRCA1-associated breast cancer and to discuss the utility of this morphological data in the current clinical context.

Breast cancer is not a single disease. As illustrated in figure one even routine histologic examination shows that the various tumours included under the rubric of 'breast cancer' appear very different from each other and follow-up studies demonstrate innate differences in the biological potential of some of these neoplasms. The classification of these seemingly disparate tumours as 'breast cancers' is a managerial decision, necessitated by the relative paucity of our present therapeutic options. Given this heterogeneity of breast cancers, are there some variants that are more frequently seen in the hereditary setting?

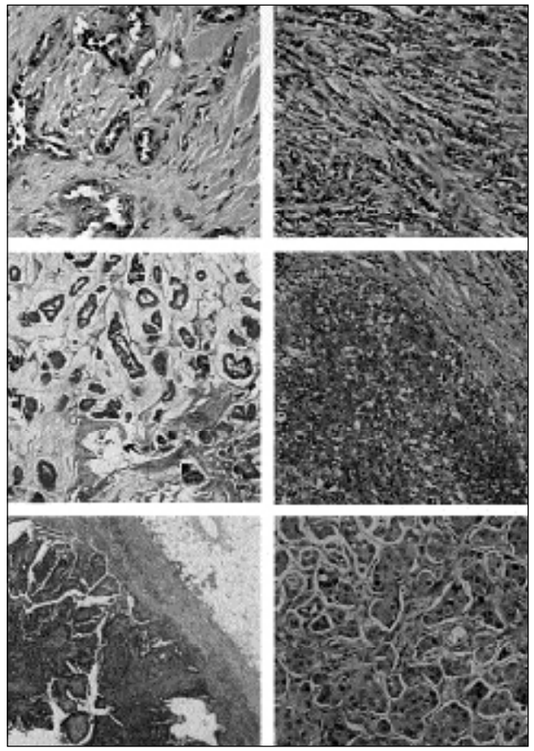

Figure 1: Heterogeneity in breast cancer morphology.
The middle panel on the right side is a high-grade BRCA1-associated carcinoma.

The phenotypic features of familial breast cancer

Table one summarises the most common histologic features of BRCA1-associated breast cancers.

Feature	Typical case
Tumour subtype	Ductal NOS in over 70%
Tumour grade	High grade in 90%
DCIS	Not extensive
ER / PR	Negative in 80-90%
Proliferation index	High
HER-2	Negative in >90%
p53	High expression

Table 1: Summary of histologic features of prototypic cases of BRCA1-associated breast cancer

Tumour subtype

Data from several studies[1-10], including those by the Breast Cancer Linkage Consortium, show that almost all types of breast cancer can occur in BRCA1 and BRCA2 mutation carriers and like sporadic cancers, ductal carcinoma of no special type is the most common variant. BRCA1 mutation carriers have been found to have an excess of medullary and atypical medullary phenotypes. In practice, the poor inter-observer concordance in the diagnosis of medullary carcinoma limits the clinical significance of this diagnosis. Some of the criteria used for the diagnosis of medullary carcinoma, such as smooth, non-infiltrative borders were however independently associated with BRCA1 mutation[1]. The presence of pushing margins was also associated with BRCA2 mutation.

Grade

High-grade cancers are over-represented among BRCA1 and 2 mutation carriers (see figure one: middle panel, right). Whereas only one-third of sporadic breast cancers are of high grade, approximately two-thirds of BRCA1 cancers are grade III. Conversely, only one in 10 BRCA1-associated cancers is of low grade.

Grade is assigned histologically by following specific rules regarding the extent of tubule formation, level of nuclear atypia and the degree of mitotic activity in a tumour. BRCA1 tumours score three out of three for each of these components of grade, whereas BRCA2 tumours score significantly higher than controls only for tubule formation.

Ductal carcinoma in situ (DCIS)

DCIS is found less often than in BRCA1-associated cancers than in sporadic cases[1,4], but when present, it is mostly of high grade[10]. No such differences are seen with BRCA2-associated cancers.

Proliferation index

The rate of proliferative activity in BRCA1-associated breast cancers is striking in some cases. This is manifested as a high mitotic rate in H&E stained sections and can also be highlighted with the use of proliferation markers, such as Mib-1 or Ki-67. This high-growth fraction is consistent with a role in regulation of cellular proliferation postulated for the BRCA1 protein.

Immunophenotype of BRCA1-associated breast cancer

Hormone receptor markers

Approximately 10% of BRCA1-associated breast cancers lack oestrogen or progesterone receptors (ER or PR). This compares to 35% of sporadic and BRCA2-associated breast cancers. This paucity of hormone receptors is a fundamental feature of BRCA1-associated cancers. It is seen even in low-grade cancers and at the earliest stages in which these cells are recognised as being malignant, that is, in their in situ component[11]. In a regression analysis ER negativity was found to be the single best predictor of BRCA1 positivity[5].

HER-2

While high grade and ER negative sporadic cancers are more likely to over-express HER-2, familial breast cancers are usually HER-2 negative when assessed by immunohistochemistry[5,9,12]. Like BRCA1, HER-2 is located on chromosome 17. It is possible that co-deletion may occur in some cases. Alternatively functional or structural suppression of the HER-2 gene may result from mutation in BRCA1.

P53

Mutations in the TP53 gene are common in breast cancers of BRCA1 and 2 mutation carriers. Some have even found high rates of mutations in the somatic cells of BRCA1 carriers. The normal p53 protein has a short half-life and is not routinely detectable by immunohistochemistry. BRCA1 is postulated to be involved in DNA repair. If faulty BRCA1 function leads to an inability to repair mutations in the TP53 gene, the resulting products may be abnormally stable and thus detectable by immunohistochemistry.

BRCA1

The use of immunohistochemical analysis of cancer associated gene and encoded proteins has become important in identifying cases of hereditary non-polyposis colon cancer (HNPCC). In this context, loss of expression of MSH2, ascertained by immunohistochemistry, is highly predictive of an underlying pathological mutation in this gene. Antibodies to the BRCA1 gene product are available and loss of nuclear staining for BRCA1 has been reported in breast cancers of mutation carriers[13] but to date very few reports have claimed success in using these reagents[14].

Clinical implications of the morphologic data

a. Morphology as a guide for the selection of individuals for genetic testing

Limitations of current means of selecting patients for genetic testing

BRCA1 and 2 are large genes. Over 200 mutations have been described in each gene and these mutations are distributed throughout the length of each gene, without mutation 'hot-spots'[15]. This necessitates full direct sequencing of both genes to exclude an obvious abnormality. Such tests are expensive. Genetic testing also raises complex ethical and legal considerations. Careful patient selection is required in order to optimise the use of these tests.

Specificity issues

Through the study of large, multi-case families, criteria have been developed to help select high-risk individuals for genetic testing. The criteria currently used are based principally on patient age and family history of cancer. There is no consensus as to the relative importance of various features of the family history, so that several different sets of selection criteria exist, including computer-generated risk calculators[15-19]. The American Society of Clinical Oncology suggests that patients whose risk of carrying a mutation exceeds 10% be considered for testing[20]. There are significant discrepancies in the risk estimates of these risk models, such that genetic testing may be advocated by one model, while others estimate the risk to be less than the threshold value of 10%[21]. Shannon et al reported 22% of routine patients attending a multidisciplinary breast cancer clinic were estimated to have a 10% probability of carrying a BRCA1/2 mutation by at least one model and should have been offered genetic counselling that included the discussion of genetic testing[22]. As expected, the specificity of the selection criteria is low with only 25-30% of families screened being found to be mutation carriers[19,23].

Sensitivity

Conversely, the current strong reliance on family history may deny some women the chance to be offered genetic testing. It has been pointed out that the families with an obvious cancer syndrome are likely to represent only a small fraction of individuals with inherited predisposition to cancer[24]. Data emerging from population-based series of early onset breast cancer suggest that a high proportion of patients with BRCA-associated cancers present as sporadic cancers[25]. Genetic risk calculators are not applicable to women from cancer-free families and even when a family history exists, the trend towards smaller family size may render it unimpressive. In Frank's study 9.5% of women with breast cancer diagnosed before age 50 and mutations in BRCA1 or BRCA2, had no family history of early breast cancer or any history of ovarian cancer[26].

1. Enhancement of current selection criteria for genetic testing

Attention to the morphologic features of an individual's breast cancer can enhance current selection criteria for genetic testing. Even using the most obvious differences in oestrogen receptor expression and grade, breast cancer patients can be stratified into risk groups for likelihood of BRCA1 mutations. Table two summarises some of the promising reports into the application of morphologic data for improved selection of at-risk women. Women with high-grade, ER negative cancers are those most likely to harbour mutations in BRCA1. Even disregarding all information regarding family history, 25% of unselected pre-menopausal women with breast cancers of this phenotype were found to carry germ line BRCA1 mutations[27]. Others have reported similar results when focusing on high-risk groups such as women 35 years or younger[28] or Ashkanazi women[29]. The combination of high-risk cancer phenotype and significant family history led to a BRCA1 mutation detection rate of 53%[30].

Criteria	BRCA1 +ve	Source
Ashkenzai woman, G3	27.10%	Karp 1997
Ashkenzai woman, other phenotype	4.10%	Karp 1997
age Š45, ER-/G3	25%	Chang 2001
age Š45, other phenotype	5.60%	Chang 2001
age Š35, ER-/G3	28.60%	Linderau 2000
age Š35, other phenotype	3.60%	Linderau 2000
high risk FH, ER-/G3	53%	Cortesi, 2000
high risk FH, other phenotype	1.30%	Cortesi, 2000

Table 2: Morphologic features as triage for genetic testing. (G3= grade III breast cancer, ER-= oestrogen receptor negative, FH= family history)

Lakhani et al have published useful tables that detail the interplay between age, tumour grade and ER status in altering the individual's likelihood of carrying a BRCA1 mutation[5]. It may well be time that such information was incorporated in the assessment of likelihood of BRCA1 mutations.

Improved sensitivity of selection criteria

It should be noted that in the above studies, a positive family history was infrequent in women who were found to be BRCA1 positive after being selected on the basis of phenotype[27,28]. Because morphologic criteria widen screening to a larger group than those with a strong family history, the sensitivity of genetic screening is enhanced, with obvious economic and ethical benefits.

Who is unlikely to carry a germ line BRCA 1 mutation?

Improved specificity

The corollary of identifying high-risk patients on the basis of morphologic data is that certain tumours are unlikely to be observed in association with BRCA1 mutations (see table two). Disregarding age and family history, a woman with an ER positive, low-grade breast cancer has less than 5% chance of being a mutation carrier[5]. Even when women with positive family histories are tested, the magnitude of the risk for this group does not exceed 10%[30]. This is lower than the threshold recommended by ASCO.

2. Genetic polymorphisms versus deleterious mutation

Some sequence variations in BRCA1 do not portend an increased propensity for cancer. Determining the significance of genetic variations is problematic. It is interesting to note that in the small number of cases studied, mutations considered non-pathogenic were found to be unassociated with the usual BRCA1 cancer phenotype[30].

3. A more targeted search

Which gene to test first?

Current criteria do not segregate risk of BRCA1 versus BRCA2 mutations with confidence[23], such that both genes have to be sequenced until a pathogenic mutation is found. An additional benefit of taking note of tumour morphology is that the phenotype may suggest one gene over the other, thereby permitting a more targeted search. This scenario may also extend to the so-called BRCAX families, in who family histories are highly suggestive of an inherited cancer predisposition, but a mutation has not been detected to date. If morphology is strongly suggestive of BRCA1 mutation in some of these patients, a closer analysis of that gene may be attempted, since it is known that some abnormalities, for example large genomic alterations, are undetected by direct sequencing[23]. Alternatively, morphologic sub-groups may be found among the breast cancers of BRCAX families, potentially leading to the discovery of presently unknown genetic factors. Some early reports suggest heterogeneity among this group, but with a preponderance of low-grade cancers[31].

4. More precise hereditary risk assessment

Until now, for the purposes of estimating risk of familial breast cancer, a history of DCIS has not been distinguished from a history of invasive breast cancer. Frank's data demonstrate the importance of maintaining such a distinction[26]. While a history of DCIS represents some increased likelihood of mutations in BRCA1 and BRCA2, the magnitude of this risk is lower than for invasive cancer. They suggest that a history of DCIS at a particular age be given as much merit as that of an invasive cancer diagnosed 10 years later.

b. Implications for the management of affected women

Breast cancer patients who are carriers of BRCA1 mutations have a propensity for recurrence and are at risk for further primaries in both breasts[32]. In this setting the prevention and early detection of future breast cancers is a worthy aim. Yet certain features of these tumours pose formidable challenges in the achievement of this goal.

1. Biological perspective on the likely value of anti-oestrogens in treatment of BRCA1-associated breast cancer and in cancer risk reduction

The use of tamoxifen has been shown to halve the incidence of breast cancer among women who are at increased risk for developing breast cancer[33]. This includes women who have already experienced breast cancer. At first glance, women with a genetic predisposition to breast cancer would be expected to benefit from this therapy. Unfortunately, the efficacy of tamoxifen in cancer prevention is largely limited to patients whose tumours express ER. Little or no benefit is documented for the smaller proportion of sporadic patients who have ER negative tumours.

An estimated 80-90% of breast cancers in women with BRCA1 mutations are ER negative. In this setting even DCIS lacks ER[11]. On the basis of this fundamental ER-resistant phenotype, from a biological standpoint, one would predict that most breast cancers in BRCA1 mutation carriers would be relatively resistant to such hormonal therapy. Also, the use of tamoxifen for prevention of future cancers in cancer-free mutation carriers would be anticipated to be limited to the minority of these women who develop ER positive tumours.

The limited data available on the value of tamoxifen for cancer-free mutation carriers need to be read carefully to distinguish the outcome between BRCA1 and BRCA2 mutation carriers. This distinction is important because whereas up to 90% of BRCA1-associated cancers are ER negative, BRCA2 mutation carriers have similar rates of ER positivity to sporadic cancers, and would be expected to draw similar benefits from this medication. Some incongruous data have been presented in this regard. King performed a subset analysis of BRCA1 mutation carriers participating in the NSABP- P1 trial and found no evidence that the use of tamoxifen beginning at age 35 years or older reduced the incidence of breast cancer in those patients[34]. However Rebbeck[35] reported a 50% reduction in the incidence of breast cancer in BRCA1 mutation carriers who underwent prophylactic oophorectomy. It is possible that earlier use of tamoxifen in cancer-free women may duplicate the effectiveness of oophorectomy. The finding of risk lesions in mastectomy specimens of these patients, would support this notion, since it raises the possibility of a pre-invasive phase for some BRCA1-associated tumours[36,37].

Until results of primary prevention trials in women with BRCA1 are available, the use of anti-oestrogens in these women should be considered carefully and be accompanied by disclosure that such drugs may not be effective in reducing the risk of breast cancer.

2. Surveillance for early detection of hereditary breast cancer

Attempts at chemoprevention aside, even the early detection of these tumours poses formidable challenges. Morphologic studies of BRCA1-associated breast cancers reveal significantly lower incidence of an in situ component in these tumours. The paucity of a significant in situ component, and the high proliferation rate of these tumours, implies rapid carcinonogenesis. These observations would suggest that BRCA1 mutation carriers might not be optimal candidates for routine screening mammography. The young age of the at-risk population and the increased density of breast tissue in young women further compound the obstacles to screening mammography. These morphologic predictions are unfortunately borne out by the limited data available.

Surveillance programs in BRCA1 mutation carriers have shown that only approximately 50% of their breast cancers are detected by annual screening mammography[37,38]. The remaining tumours were radiologically occult a few months before, or even at presentation. Of more concern is the observation that these were not all 'early cancers'. At least some, and in one report over half, of the interval cancers, were node positive[38]. Self-breast examination and clinical examination were the most common methods of detection in this cohort of women. These data suggest that the transition from a radiologically undetectable stage to clinically detectable mass is too rapid for annual screening mammography to be reliable.

These sobering data call into question the reliance on annual screening mammography for the detection of cancers in these women. Reducing the interval between screening episodes and the addition of frequent breast examinations and magnetic resonance imaging (MRI) are worthy of investigation, but at least in one of the above-mentioned surveillance programs annual mammograms and MRI were combined[39]. Other reports are more encouraging[40,41].

3. Prophylactic surgery

Given the high risks for the development of breast cancer among BRCA1 mutation carriers, estimated to be between 50-80% for BRCA1, and the unproven efficacy of attempts at prevention or early detection of these tumours, bilateral prophylactic mastectomy is a difficult choice that should be discussed with these women. Intuitively, this procedure would be expected to be effective in cancer reduction and the limited data available suggest that this is indeed the case[39,42].

Incidentally, a small proportion of women who undergo prophylactic mastectomy are found to have significant lesions, including occult DCIS in the mastectomy specimen, further underscoring the high level of risk faced by these patients[36,37].

Prophylactic salpingo-oophorectomy is also being advocated in BRCA1 mutation carriers[43] since not only does it offer protection against ovarian cancer, to which these women are predisposed, it has also been found to reduce the risk of subsequent breast cancer among BRCA1 mutation carriers by approximately 50%[35].

Conclusions

Differences exist between BRCA1-associated breast cancers and BRCA2-associated and sporadic cancers. Attention to even the most rudimentary of these features opens new avenues for the identification of possible mutation carriers and offers perspectives towards more effective care of those individuals who are known to carry these mutations.

Failure to take note of these biological differences would represent a regrettable loss of opportunity for the families involved. The challenge for pathologists is to demonstrate the reproducibility and clinical validity of these distinctions. It is also hoped that highlighting the discriminative clinical value of an increasingly sophisticated array of phenotypic features can extend these benefits. This task requires study of larger numbers of cases and access to relevant tissue is currently limited. The prospective collection and proper storage of normal and tumour tissue from all appropriately consented individuals would represent a valuable resource for further investigation. In Australia we are fortunate to have already in existence organisations such as kConFab that serve these families and the scientific community by documenting important aspects of the pedigree, environmental and psychological influences in these patients. Closer involvement of pathologists in these efforts is to be encouraged.

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The use of gene expression profiling in tumour classification and management

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Introduction

Microarray-based transcript profiling is a technique used to measure the steady-state levels of gene expression on a genome-wide scale in a cell or tissue. The technology essentially involves making a collection of labelled probes from all the genes expressed in a cell, and then defining the gene and its level of expression – by hybridising them to a target of sequences representing thousands of genes, which have been previously immobilised on a solid substrate. This snapshot of the gene expression reflects the degree to which genes are switched on or off in the cell, a process that is tightly controlled for each individual cell and tissue type. Given that the total cellular composition of the mRNA species encoded by the active genes largely will determine which proteins are expressed in that cell, and thus much of its biology, the ability to profile gene expression at the genomic level can provide major insights into the molecular mechanisms driving the function of normal tissues and of cancers. The uniqueness of a gene expression profile seen in individual tissues can also extend to different subgroups of cancer.

This technology is therefore useful in the field of cancer management in the context of improving our ability for accurate diagnosis, prognosis, choice of therapy and monitoring of therapeutic response. Further, global gene expression profiling can give us valuable insights into the molecular pathogenesis of individual cancer types, which can in turn, provide a basis for more rational management.

This review will highlight several advances in the application of microarray profiling to the clinical management of various cancer types. In addition, it will touch upon potential novel applications that could result from ongoing research.

Haematolymphoid malignancies

It is now apparent that microarray expression analysis will substantially augment the established diagnostic protocols of morphology, immunophenotype and cytogenetic analysis in the diagnosis of leukaemia and lymphoma. The dysregulated genes involved in the translocation breakpoints defined by cytogenetic analysis appear to be integrally involved in the genesis of these tumours. However, the diversity of clinical response observed within the translocation-defined categories of leukaemia and lymphoma indicates that other, accompanying molecular events can be equally important in determining the outcome of these malignancies. Global gene expression signatures have been identified that correlate extremely strongly with several of these chromosomal translocations, and may thus in future replace the need to perform cytogenetic and immunophenotypic analysis. Moreover, gene expression profiling has now begun to identify many of the additional key-molecular abnormalities related to outcome, and these insights into molecular pathogenesis have begun to facilitate novel therapeutic options for the management of these tumour types.

Leukaemias

Paediatric acute myeloid leukaemias (AML) are a group of malignancies displaying heterogeneity at the clinical and molecular pathogenic levels. It is difficult to accurately predict the likely therapeutic outcome, and thus to select the optimal, risk-adjusted treatment protocols for AML using the current morphological, cytogenetic and immunophenotypic diagnostic approaches. The implementation of risk-adjusted therapies for AML is based partly on the likelihood of failure to induce remission, or on the chances of relapse. In the case of paediatric AML, several genes associated with prognosis have now been identified by gene expression profiling, thus facilitating an improved classification based on the likely risk of relapse, which is not dependent on cytogenetics or morphology. In addition these microrarray-based analyses have identified molecular pathways which are not associated with conventional classification systems, and which may constitute novel targets for therapy, eg dysregulation of the NF-kappa B signalling pathway[1].

There is a similar need to assign a patient to an individual risk of recurrence group for tailoring therapy in the paediatric acute lymphoblastic leukaemias (ALL). Gene expression profiling has now been used in several studies to classify the known prognostic subtypes of ALL (such as T-ALL, E2A-PBX1, TEL-AML1, MLL rearrangements, BCR-ABL and hyperdiploid >50 chromosomes). In one study, a small number of genes differentially expressed between these subtypes were able to accurately distinguish between these different classes of ALL with an overall 97% success rate. This achievement makes the evaluation of a diagnostic array containing relatively few genes feasible[2].

A new insight into T-cell ALL leukaemogenesis resulted from the demonstration of activation of five T-cell oncogenes encoding the developmentally-important transcription factors HOX11, TAL1, LYL1, LMO1 and LMO2, in the absence of chromosomal translocations[3]. Over-expression of LYL1, HOX11 and TAL1 were each in turn associated with the abnormal expression of other groups of genes, which together indicated developmental arrest of the leukaemic cells at the pro-T (LYL1 signature), early cortical thymocyte (HOX11 signature) and late cortical thymocyte (TAL1 signature) stages. This study was therefore able to classify the leukaemias according to these various newly-identified oncogenic pathways, and was also able to highlight cases with a more favourable prognosis (eg HOX11 signature) versus those with a worse prognosis (eg TAL1 and LYL1 signatures).

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia encountered in humans. Microarray-based profiling has supported the view that this disease has a distinct gene expression profile, when compared with similar analyses of other lymphoid malignancies. It now appears that the distinct subgroups of CLL, namely the slowly-progressive form in which the cells have somatic mutations of the immunoglobulin genes, and the more aggressive form in which the cells lack immunoglobulin gene mutations (and for which patients require immediate therapy), each have a distinct pattern of altered gene expression. Interestingly, one gene (ZAP-70) was found to be strongly differentially expressed in the aggressive form of the disease, and this gene alone was able to identify this aggressive form of CLL with over 90% accuracy. If this finding is confirmed in further studies, it would be an example of microarray analysis advancing knowledge of the molecular basis of a disease at a genome level, followed by the identification of a single gene as a discriminator between disease subtypes in the clinical setting[4].

Non-Hodgkin's lymphomas

The molecular alterations driving lymphoma tumourigenesis are frequently linked to fundamental events occurring during the ontogeny of lymphoid cells. It is now accepted that the cells giving rise to the majority of non-Hodgkin's lymphomas (NHL) are derived from germinal centre cell (GCC). The propensity for these GCCs to develop malignancy is presumed to result partly from the genetic instability, which exists during the B-cell developmental phases of immunoglobulin gene recombination, somatic hypermutation and class switching. This transient genetic instability predisposes towards the development of oncogenic chromosomal translocations, resulting in dysregulation of genes controlling cellular proliferation, apoptotic and differentiation pathways.

Diffuse large B-cell lymphoma (DLBCL) is a common adult lymphoma showing a variable response to conventional chemotherapy, and thus may constitute a collection of distinct disease types, all with a similar histological appearance. Hierarchical clustering of global gene expression data has supported this hypothesis, by identifying at least three distinct clinical subgroups of DLBCL. One of these, the germinal centre B-cell-like subgroup (in which all the commonly-encountered oncogenic changes of bcl-2 translocation and c-rel amplification were encountered) had a far greater likelihood of response to anthracycline-based chemotherapy than the other groups – an activated B-cell like group, and a group designated as DLBCL type 3. When these three tumour categories were further analysed to identify the individual genes that influenced outcome, four functional groups of genes were highlighted. The worst outcome was associated with the increased expression of genes associated with cellular proliferation, and the best outcome was seen in the tumours that had high expression of genes, which might reflect a competent immune response to the tumour cell, including MHC class II genes. The gene expression-based prognosis was superior to the currently used international prognostic index in predicting treatment response, and is likely to be of great utility in stratifying patients for future clinical trials[4].

Mantle cell lymphoma (MCL) is a form of NHL which is presently incurable, and which displays a diverse clinical course, with survival ranging from one to 10 years after diagnosis. Information resulting from genome scale expression profiling has now begun to elucidate the molecular drivers of these tumours, including the determinants of the observed clinical heterogeneity. Insights into the microanatomical location of tumour formation include the normal expression level of the CC motif chemokine receptor, CCR7 (involved in homing of B-cell subsets to primary lymphoid follicles) by tumour cells, and the abnormal expression of other B-cell trafficking receptors such as CCR5 and CCR6[5]. In a different study, two subtypes of MCL were identified, one of which carried the commonly-encountered cyclin D1 over-expression, (usually resulting from the t(11;14)), and a cyclin D1-negative cohort. Within the cyclin D1 positive cohort, a signature of over-expression of several genes associated with cellular proliferation was an extremely powerful prognostic indicator, and was able to define cohorts of tumour cases with widely variable outcomes. The importance of this prognostic signature in predicting outcome argues for stratification of future clinical trials based on this predictor, and for the development of novel therapies directed at the altered G1/S checkpoint function believed to result from abnormal cyclin D1 activity[4].

Brain tumours

A number of studies have employed global gene expression analysis in an attempt to improve on the limitations of the histological classification systems as a basis for therapeutic decision making for malignant gliomas. A gene expression-based prediction model proved far superior than histological assessment in distinguishing between tumours with atypical histology which were more likely to behave as glioblastomas (and which were chemoresistant) than those more likely to behave as anaplastic oligodendrogliomas (which were chemosensitive)[6]. Further evidence regarding the possible utility of gene expression-based diagnostic algorithms was revealed

in a study on the heterogeneous group of malignancies of the CNS known as embryonal tumours. This analysis was able to distinguish between medulloblastomas and other tumour types such as primitive neuroectodermal tumours and rhabdoid tumours, and indicated that medulloblastomas might arise due to dysregulation of the Sonic Hedgehog (SHH) pathway in cerebellar granular cells. The gene expression profile also proved much more successful at predicting clinical outcome than the widely-used morphological criteria[7].

Breast carcinoma

Breast cancer patients with localised disease that are deemed by conventional clinicopathological criteria to have a high risk of distant metastases are frequently treated with hormonal or chemotherapy. However, only approximately one-third of these cases would have gone on to develop distant metastasis, and therefore the remainder of patients would have received this therapy unnecessarily. A gene expression-based signature utilising 70 genes has now been defined that acts independently of other prognostic systems to accurately predict the likelihood of distant metastasis and the prognosis of breast carcinomas. It is hoped that, if reproducible, such signatures might assist in the optimal choice of therapy for this disease. In the context of the management of individuals with a potential inherited mutation in the breast and ovarian cancer predisposition gene BRCA1, a gene expression signature has now been defined that appears to identify tumours arising on the basis of BRCA1 protein dysfunction. The ability to accurately identify BRCA1 associated tumours is useful in guiding decision relating to the diagnosis of the underlying germline mutation[8].

Future outlook

The tumour types highlighted above constitute a snapshot of the possible applications of gene expression signatures to enhance our comprehension of the molecular basis of cancer, and to improve our ability to make decisions in the clinical context. Numerous additional studies have been performed, on tumours ranging from paediatric sarcomas to gastric carcinomas. Together with this revolution in our understanding of cancer pathobiology, there is a concomitant technological revolution represented by efforts to produce a 'lab-on-a-chip'. This concept involves the coordinated endeavours of experts in fields as diverse as nanotechnology (eg narrow-bore capillaries), microfluidics and microimaging, to make the tools of gene expression profiling available to the deliverers of primary medical care in a time frame which will be useful to these practitioners.

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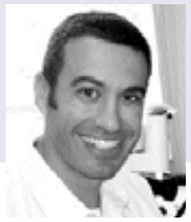
Ethics and logistics of using archival pathology material



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It seems that almost every day heralds a new 'breakthrough' in our understanding of, or ability to treat, diseases such as cancer. However history has shown us that the majority of these are in reality relatively minor incremental advances in our knowledge, with few emerging as significant in improving healthcare. Much of this is due to overzealous reporting and overstatement for funding purposes, and it is clear that there is much to be done to make good on the promises of rapid advances in medicine through molecular biology.

Most recently, alongside the preliminary completion of the Human Genome Project, DNA array technology has been predicted to revolutionise our understanding of the natural history of disease by providing a means to examine several thousand genes in any individual at a single time. However, it is already clear that any practical applications of data from microarrays will utilise only a handful of the several thousand genes present on such arrays. Moreover, many gene array studies have been limited in using small numbers of samples and are biased towards cases from which spare tissue, excess to that required for a diagnosis, may be obtained. The potential for limited application of any findings is a real concern and therefore attention is already turning to validation of any such gene candidates in larger and broader patient series. This translational research may be carried out using archival pathology material and the following outlines some pressing issues with using this, as well as how this is currently being carried out in Perth.

Pathology archives

The supply of quality human tissue for validation of new prognostic and predictive markers is dependent on pathology services whose primary objective is to provide diagnoses and not to provide a suitable archive for research. Moreover, access to these archives is limited by stringent ethical considerations, there are issues regarding the number of cases available and how representative these are of a general population, and great care has to be taken to ensure some element of consistency in the handling of the tissue. As important as access to the pathological material itself is the breadth and quality of associated clinical information such as staging, treatment and outcome.

In recent years there has been some debate on who 'owns' archival pathology material. The various State and Territory Human Tissue and Transplant Acts do not extend to tissue taken as part of elective surgery and in the WA Act (1982) section 32 (1) (a) goes so far as to say:

> "Nothing in this Ordinance applies to or in relation to:
>
> (a) the removal of tissue from the body of a living person in the course of a procedure or operation carried out, in the interests of the health of the person, by a medical practitioner with the consent, express or implied, given by or on behalf of the person or in circumstances necessary for the preservation of the life of the person;
>
> (b) the use of tissue so removed;"

This has led to the adoption of the common law principle of ownership such that those who have done 'work' on the samples 'own' them, ie tissues fixed and processed become the property of the pathology service. The recent Australian Law Reform Commission (ALRC) and Australian Human Ethics Committee (AHEC) Discussion Paper 66 (DP66) entitled Protection of Human Genetic Information[1] re-affirms this and states in proposal 17-1 that:

> "The common law right to possession of preserved samples, which is currently enjoyed by hospitals and others, should continue to be upheld, but full property rights in genetic samples should not be granted"

This recommendation ensures the continued use of this material for medical research and for teaching.

Consent for using archival material

It is important to understand that consent for use of archival pathology material is almost never obtained. However, the NHMRC National Statement on Ethical Conduct in Research Involving Humans —June 1999[2], provides specific guidelines on "where the requirement for consent could be waived" under sections 15.8 (tissue) and 16.13 (genetic samples). The decision to allow consent to be waived is given to a Human Research Ethics Committee (HREC) and requires that they carefully consider items such as the difficulty or obtrusive nature of obtaining consent, as well as the likely risk to benefit ratio of permitting a restricted and carefully monitored invasion of an individuals privacy. Although it is commonly ignored, the National Statement goes on under section 16.14 to recommend that institutes permitting waiver of consent put in place some formal system of prospective consent. It would seem sensible to follow this guideline.

Privacy

Beginning in 2001 the Australian Law Reform Commission (ALRC) together with the Australian Human Ethics Committee (AHEC) undertook a joint program to obtain submissions on the issue of protecting human genetic privacy. In their document, DP66, they make two key recommendations. The first, proposal 7.1 identifies that the current Privacy Act (Commonwealth and Private Sector) permits great inconsistency in the way in which privacy is protected across state/federal or public/private domains, and so seeks the harmonisation of health privacy legislation as it relates to human genetic information to provide nationally consistent rules. It then goes on under proposal 7.2 to amend the privacy act expressly to "a) define bodily samples as personal information, b) define a record to include a bodily sample". This follows then that tissue and blood samples become legislatively covered by the Privacy Act.

This is, in substance, similar to some legal interpretations made in the UK in regard to the Data Protection Act (1998), which stated that "Human tissue contains DNA, and DNA represents data". However, whereas legal interpretation of the UK Act demands consent from the individual for each and every use of this "data", there are several provisions within the Australian Privacy Act (1988, 2001) that permit waiver of consent. In the section 95a guidelines on the Privacy Act published by the NHMRC, section 10.3 outlines ways in which non-consented secondary uses of health information, other than the original purpose to which they were collected, are permitted, such as if the subsequent research is relevant to public health or public safety, and it is impracticable for the organisation to seek the individual's consent to the collection.

As one can see this not only covers the use of existing health information about the person from whom the sample was obtained, but also the potential for tissue samples to come under the privacy act as recommended by DP66, and avoids the devastating effect such provisions have had in the UK and US.

Tissue microarrays

The chronic shortage of archival pathology material and the difficulties with abiding by ethical and privacy guidelines requires optimal management of existing samples and tissue microarrays (TMAs). Containing hundreds of tissue samples on a single glass slide represent the means to achieve this. The advantages include speed of analysis, throughput, standardisation and conservation of material. Their use is analogous to the use of DNA microarrays and already there are 300-400 academic groups worldwide who are working with TMAs. Like their DNA cousins, TMAs have a 'garbage in: garbage out' principle and many of the current groups are working with widely heterogenous collections that cannot be used for systematic evaluation of disease.

The National Cancer Institute has a Tissue Array program[3] that makes available breast, prostate, ovary, lung, colon and brain specimens with 600 samples per slide at a cost of US$20 each. A limit of 10 slides per investigator is levied and there is limited clinical information made available, with many samples not having information on sex of the patient or any pathological diagnosis. This is similar for the multi-tumour tissue microarrays[4] made available by the National Human Genome Research Institute's Tissue Array Research Program (TARP)[5].

Within WA we have established, under the WA Research Tissue Network (WARTN)[6], a program of accessing archived pathology material from all pathology services, both public and private, that provides a unique population-based collection of samples. Ethics approval has been sought and obtained at each hospital individually for the construction of the TMAs, as well as linkage to health information. Each project requesting sections will need to go through only one ethics application in WA, and reciprocal approval will be sought from other Perth institutes by the WARTN. The existence of the WA Health Data Linkage Unit (DLU) has enabled us to create a TMA relational database of all cases put into TMAs that can then search the DLU databases electronically for treatment and outcome data and produce this as anonymised output for researchers. Moreover, this provides a means to carry out quality assurance between databases as a quid pro quo. For instance, the WA

State Cancer Registry provides mortality data to the TMA colorectal database, which in turn provides staging data on all its cases. This exchange is facilitated by the WARTN being governed and wholly owned by the WA Government.

To identify cases in WA is relatively simple involving either the creation of a list of all cases from the WA State Cancer Registry or a search by ICD0 code (WHO) of the respective pathology database (pathology records are in electronic form from 1995 onward in most institutes in Perth). A data extract is made of all cases into the TMA database. This database has been developed alongside the Data Linkage Unit and existing clinical databases to ensure it is compliant for data exchanges. Blocks and slides are retrieved from the pathology archives using a system that includes card labelling for facilitated tracking and return of these items.

A pathologist reviews slides and marks areas of normal and malignant tissue for punching on the H&E section. A consultant histopathologist can mark up to 12 cases per hour, or approximately 500 cases per week full-time. However, finding a willing pathologist is less difficult than finding one with sufficient time available over and above diagnostic demands to do such work. It is likely that pathology review will provide the rate-limiting step in TMA production. Marked slides are matched to their paraffin block and cores taken. Two malignant and one normal core of tissue is taken wherever possible, and at least two replica blocks are made for each tissue type.

The precise location of each sample is entered into a database during TMA manufacture. Once completed, sections may be cut from TMAs in the routine way on a microtome and depending on core depth up to 200 5mm section may be cut from one TMA. Blocks so created are constructed separately for each institution so that not only is there internal quality assurance and consistency of all cases on any single TMA, but also so that each stakeholder retains ownership of their own blocks. Sections can then be processed for techniques such as immunohistochemistry to look for protein expression patterns associated with specific disease processes, and the resulting data extrapolated back to the database. We are collaborating with the Burnham Institute in San Diego for high throughput automated scanning of slides using robotic techniques. As with DNA arrays, bioinformatics and the ability to handle large data sets is likely to demand high-level computational and statistical support.

Conclusion

Pathology archives represent a valuable resource for translational oncology but the real challenge will be to establish prospective collections of samples from all patients with their informed consent, both from clinical trial and otherwise, in order that these may be used for molecular analysis. In a recent paper, Betensky et al[7] have clearly illustrated that a major confounder in any clinical trial is molecular heterogeneity, and point toward the necessity of obtaining appropriate samples from clinical trials in order to evaluate these potential confounders. Moreover, moves to establish national networks of biospecimen banks such as the Australian Biospecimen Network, will be vital in increasing the attractiveness of conducting Australian oncology trials for both industry and trials groups.

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Cancer nursing education: An editorial comment

During a time of global nursing shortages, cancer nursing has been identified by the Australian Institute of Health and Welfare[1] and in the report Optimising Cancer Care in Australia[2] as one of the specialties particularly affected by workforce deficits. A complex range of issues has contributed to the nursing shortage and include, but are not limited to, expanding career opportunities for women, an ageing nursing workforce with consequent family commitments, inadequate remuneration, unsociable hours, poor social status and a perceived lack of support and recognition for the work undertaken. At the same time the shift in the delivery of cancer care from inpatient to outpatient, and increasingly community-based services, has placed demands upon nurses (particularly those working in rural and remote areas) to be the providers of care for which they may have minimal or sub-optimal training. These factors have an obvious impact upon the provision of quality care to people with cancer.

A study of 67 nurses administering chemotherapy in rural and remote areas of Queensland, published last year by McCarthy et al[3], alarmingly found that 6% of respondents had received no training or minimal training in the administration of chemotherapy, 28% had not received training in the management of nausea and vomiting and 34% had not received training in the management of neutropenia. Furthermore, 36% of respondents indicated that no form of employer supported training was available to them either within their facility or offsite and 52% believed that they had been inadequately prepared for chemotherapy practice.

The following paper by Dewar et al identifies a range of training and educational needs of cancer nurses working in rural and remote areas and describes an innovative scholarship program implemented by the Queensland Cancer Fund that attempts to address those needs. Creative approaches such as this help facilitate a greater understanding of cancer care and hopefully an increased satisfaction in the work that cancer nurses perform. The beneficiaries are not only the course participants, but also workplace colleagues, employers and, ultimately, patients.

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Delivering cancer-nursing education to regional, rural and remote area nurses in Queensland

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Abstract

Purpose: To evaluate nurses' perceptions of an intensive mode post-graduate cancer nursing education program targeting regional and rural registered and enrolled nurses.

Design: Cross-sectional

Setting: Urban non-government cancer control agency.

Sample: 147 nurses, of who 95% were female, with a mean age of 45 years and a mean of 13 years experience in oncology nursing, 40% of nurses worked in highly accessible areas, and 57% in accessible to very remote areas.

Method: Nurses were surveyed using self-report measures assessing recalled impact of the education program on nursing practice, effectiveness in meeting nurses educational needs and perceived need for further training in cancer care.

Findings: Participants rated the cancer-nursing program as highly effective in improving their knowledge about cancer, professional networking, information about support/referral sources and knowledge of other health facilities. Other benefits described included increased confidence in cancer nursing skills and improved community referral skills. Barriers to implementing new skills were lack of interest, motivation or cooperation from work colleagues, organisational structure or procedural policies and financial or time constraints. Respondents requested further training in pain and symptom management, palliative care, psychosocial aspects of cancer, and communication skills with Brisbane-based Queensland Cancer Fund courses and seminars in their local area as a preferred delivery method.

Conclusions: Results suggest that intensive mode cancer nursing education programs are a preferred and effective learning mode for regional and rural nurses.

The role of the cancer nurse is evolving. For example, the emerging requirement for cancer care to include psychosocial care has led to an expansion in the role of the cancer nurse[1,2]. Similarly, the shift to outpatient or home-based care in Australia has added complexity, particularly evident in the case of chemotherapy administration[3-5]. To assist nurses, continuing nursing education programs that are delivered in a variety of modes including distance education, online learning, university based courses, joint university-health agency programs and vocational programs have emerged. However, there are barriers preventing or deterring nurses in the cancer workforce undertaking ongoing education. These barriers include a lack of awareness of continuing education opportunities, accessibility and the clinical relevance of educational courses[6].

Rural and remote nurses have specific needs that relate to a broad nursing role encompassing knowledge and skills in a range of medical contexts, including cancer and palliative care[7]. Due to the scarcity of health resources in remote areas, these nurses often provide health services that in larger centres

are undertaken by medical or allied health professionals[8,9]. Geographical isolation limits opportunities for regional and rural nurses to extend their knowledge and interact with their peers[10]. Specific barriers to ongoing education reported by Queensland regional and rural nurses include family constraints, physical distance from nursing programs, lack of access to resource personnel for education on site, lack of resources for external consultants, and inadequate funding to support travel to education programs and to replace staff absent for educational support[11,6]. Regional and rural nurses are a priority group for ongoing education programs sensitive to the context in which they work.

Accordingly, the Queensland Cancer Fund cancer nursing education scholarship program was developed to specifically target rural and remote nurses, a group that accounts for 27% of the Australian nursing workforce[12]. Scholarships address issues of access by providing participants from all areas of Queensland with travel, accommodation, course registration and materials. Intensive mode course time-tabling, delivered over a five-day period, assists with time constraints. Finally, locating the program in a major centre facilitates professional networking. In terms of uptake by nurses in Queensland, these programs have been particularly successful. For example, since 1997, 305 nurses have attended fully-funded residential nursing education programs offered by the Queensland Cancer Fund. Of this group, 81% were from regional and rural Queensland.

The present study investigated participants' recalled impact of attending the cancer nursing education program between 1997 and 2001. This included impact on nursing practice, effectiveness in meeting nurses educational needs, perceived need for further training in cancer care, and barriers to the implementation of new skills and learning.

Method

Participants and procedure

One hundred and forty-seven participants who had attended a Queensland Cancer Fund Cancer nursing education program between 1997 and 2001 inclusive (55% response rate) were surveyed by mail. The programs attended by respondents were Cancer Nursing for Enrolled Nurses (25%), followed by Palliative Care for Registered Nurses (23%), Introduction to Cancer Nursing for Registered Nurses (21%), Breast Cancer Nursing for Registered Nurses (16%), and Chemotherapy Awareness for Registered Nurses (14%) programs. In all, 91% of participants resided outside of the Brisbane metropolitan area, with 22% residing in south-west Queensland, 25% from the Gold and Sunshine Coasts, 15% from central Queensland and 29% from north and far-north Queensland.

Demographic data was provided by 144 respondents, with a mean age of 45 years (SD=8.66, range of 23 to 69 years). Most participants were female (95%) and had been working as registered or enrolled nurses for an average of 19 years (range = 1 to 41 years). The mean duration of time for participants providing nursing care to people with cancer was 13 years (range = 1 to 34). With respect to nursing qualifications, 81% of respondents reported that they had obtained a hospital certificate, 27% had been awarded bachelor degrees, 23% had completed post-registration certificates, and 11% held either post-graduate qualifications or TAFE diplomas or certificates. A further 9% of participants reported that they had obtained other forms of nursing qualifications, 6% held post-graduate degrees specifically in the area of oncology and 4% had been awarded undergraduate diplomas. Finally, 88 participants (61%) reported that they were members of the Oncology Nurses Group of the Queensland Cancer Fund. The demographic of the participants was consistent with the demographic of other studies investigating rural and remote area nurses[8].

A questionnaire was developed to assess study aims. Seven items assessed the impact of the program on cancer nursing knowledge, knowledge about community cancer care services, professional networks, confidence and skills in providing care for cancer patients, overall program benefit and fit with learning needs. For each item participants were asked to indicate how helpful/effective the program was on a scale of one, not at all helpful/effective, to five, very helpful/effective. The second section of the questionnaire asked about the nurses' use of community cancer support services. The third section of the questionnaire assessed participants' preferences for further ongoing education in cancer care.

Course description

The program consists of five-day residential courses for nurses working with people with cancer on four topic areas: palliative care, breast cancer, chemotherapy awareness and introduction to cancer nursing. By providing specific cancer-related training and information to nurses currently working in health care settings, the program aims to improve the supportive care of people with cancer across the state of Queensland. Participants are selected on the basis of written application with two participants selected from seven geographical regions across the state. Selection criteria include demonstrated involvement in the care of people with cancer, professional development activities and leadership qualities. Clinical experts deliver course content using didactic instruction, clinical visits, small group work and interactive workshops. Course materials include journal articles and an oncology text with participants mailed course 'pre-readings' two weeks prior to the course. On completion participants are required to submit an assignment and achieve a passing grade to fulfil assessment requirements. Assessment aims to reflect integration of theoretical knowledge into clinical practice.

Results

Geographic location and work history

The ARIA coding system was used to ascertain respondents' geographic accessibility/remoteness. Forty percent of nurses were employed in highly accessible regions, with excellent access to goods and services and opportunities for social interaction. An additional 48% reported that their workplace was in an accessible or moderately accessible location (27% and 21% respectively), with only 13 participants working in remote (6%) or very remote (4%) regions. Six nurses (4%) reported that they were not working at the time of the study.

In all, 87% of nurses were providing nursing care to people with cancer at the time of the study. Of these, 27% were employed in combined clinical settings that included a specialist oncology or palliative care component. A further 15% of nurses were caring for people with cancer through domiciliary nursing services or in other clinical settings (15%) and oncology/haematology units (9%). The remainder (34%) were employed in varied clinical settings (for example, medical units, surgical units, palliative care units, and nursing homes). In all, 35% of nurses reported that between 50% and 100% of their work each month was in cancer nursing, with the remainder reporting that caring for cancer patients comprised less than 50% of their work.

Course effectiveness

Nurses indicated their perceptions of course effectiveness across seven domains relating to improvements in their knowledge and skills, and how well the program met their learning needs. Scores for assessment of the effectiveness of the course were uniformly high indicating high levels of satisfaction with these aspects of the program (see table one). Nurses were also given the opportunity to comment on:

1. strengths and weaknesses of the program;
2. suggested changes in order to improve learning outcomes; and
3. aspects of their work that changed as a result of their participation in a bursary program.

The most commonly reported benefits from attending the program were: gaining knowledge about cancer, diagnosis and treatment; professional networking; obtaining information about support/referral sources; and site visits to observe other health facilities. Most nurses (75%) felt that there were no unhelpful aspects of the program, while 20% described theoretical components as unhelpful. Three nurses felt more practical exercises would have been helpful and other aspects described as unhelpful indicated by two or less individuals included items such as having to travel for the course. The most common suggestion for improving the program was to include more practical exercises, indicated by 19% of respondents.

Table 1: Ratings of effectiveness of education program

Item	Mean	Median
Did you feel that your knowledge about cancer treatments was increased?	4.31	5
Did you feel that your knowledge about community and cancer care services increased?	4.26	5
Did you feel more confident in caring for people with cancer?	4.38	4
How helpful was the program in improving your ability to care effectively for cancer patients?	4.18	4
How beneficial was the program in helping you network with nurses working in cancer care?	4.14	4
How helpful was the program for you as a nurse working with people with cancer?	4.50	5
How well did this program meet your educational and learning needs?	4.48	5

Note: Scales for all items ranged from one to five with higher scores indicating greater effectiveness.

The most common changes nurses reported making in their nursing practice as a result of attending the program were providing staff or patient education, increased confidence in their cancer nursing skills, and knowing how to refer patients to support services in the community. Twenty-two percent of nurses reported that they experienced barriers at work that affected their ability to implement the skills that they had acquired as a result of participating in the program. Of these, just over half maintained that a lack of interest, motivation or cooperation from work colleagues was the primary barrier. However, other responses included organisational structure or procedural policies and financial or time constraints.

Need for further education

In relation to further education, 93% of nurses reported that they would like further training or education in cancer care. The most preferred topics were: pain and symptom management; palliative care; psychosocial aspects of cancer; and communication skills (see table two). The methods most preferred by nurses for the delivery of future educational programs were Brisbane-based Queensland Cancer Fund courses and seminars in their local area (see table three). The majority of nurses (65%) indicated that the Queensland Cancer Fund was the preferred provider for education programs, followed by universities (11%) and health care employers (10%). Most nurses reported that it was not important that education programs provide credit toward university study, with only 20% indicating that this was an important issue. Only 3% of nurses reported that they had used the Queensland Cancer Fund nursing program as credit for a university-based course.

Table 2: Preferred topics of education or training

Topic	Number of respondents	Percentage of respondents
Most preferred		
Pain and symptom management	96	81
Palliative care	76	64
Psychosocial aspects of cancer	64	54
Communication skills	60	50
Less preferred		
Oncological emergencies	38	32
Chemotherapy nursing	36	30
Nursing care associated with specific cancers	34	29
Surgical management of cancer	27	23
Radiotherapy nursing	23	19
Other training	11	9

Note: Percentages do not add up to 100 as respondents were asked to indicate four preferred topics. All mentions are listed in the table above.

Table 3: Preferred method of training delivery

Method of training delivery	Percentage of respondents who elected as most preferred
Seminars in my local area	35
Queensland Cancer Fund Brisbane-based nursing education program	33
Distance education	16
Video conferencing	8
Teleconferencing	6
Internet course	3

Referral to Queensland Cancer Fund cancer support services

Of all participants who were currently working in cancer nursing, 94% reported that they referred cancer patients and their families to Queensland Cancer Fund cancer support services, with 79% of these nurses referring patients to the Cancer Helpline. Other services referred to by more than half of nurses were volunteer peer support programs and accommodation facilities for country patients travelling for cancer treatment. Finally, 43% of nurses referred patients to the Living with Cancer Program and Wig Service. With regard to nurses who did not make referrals to cancer support services were: other professionals arranging referrals (63%); and patients already being aware of Queensland Cancer Fund services (37%). Finally, 94% of nurses reported that they provided Queensland Cancer Fund patient education material to their patients. Those that did not provide this information, reported that the information was provided to the patient by

someone else.

Discussion

The delivery of appropriately targeted and accessible educational programs for nurses working in cancer care is a priority both nationally, and in terms of regional, rural and remote health service delivery[6,14]. Given that the demographic profile and identified needs of this cohort is consistent with the profile of regional, rural and remote nurses interstate, and the similar national trend towards referral of chemotherapy to these areas, it is reasonable to generalise these Queensland results to nurses working in other rural and remote areas of Australia[6,8,14].

The current study suggests that for regional, rural and remote area nurses, the Queensland Cancer Fund cancer nursing education programs were effective in meeting these nurses' educational needs and were a preferred mode of education. It is important to note that the nurses who accessed this program were, for the most part, already experienced in cancer nursing and working in cancer nursing in the field. Thus, this model may have broader potential in terms of its contribution to cancer care services given that nursing education has been identified as an important strategy for increasing the retention of experienced nurses in the cancer workforce[13].

Nurses expressed a strong interest in further nursing education, with supportive care topics most preferred. As outlined earlier, recent documents regarding cancer care have emphasised the role of the nurse in psychosocial care[1,13]. Accessible nursing education programs addressing these areas, in particular communication skills and psychosocial aspects of cancer care, will be needed if such proposals are to operationalised.

The impetus for this program has largely been to positively influence cancer care by educating and supporting cancer nurses, in line with the overall mission of the Queensland Cancer Fund. In this regard, it is pleasing to note the high level of referral by nurses who attended these programs to community-based cancer support services, and in particular the Cancer Helpline. Cancer Councils generally utilise a number of strategies to inform patients and their families of the support services they provide, often relying on professional networking. The present study suggests that close interaction with nurses through the provision of nursing education programs is an effective way to promote referral and use of Cancer Council services and patient education materials.

A limitation of this study is the cross-sectional design and reliance on retrospective recall. As a consequence, a further study utilising a prospective design has been undertaken. However, the consistency of nurses' responses supports the positive nature of the results. It is also important to acknowledge that these nurses were a specific subgroup, in so far as they resided regionally. Nurses from major metropolitan centres who have easier access to nursing education programs may have different preferences. This may also explain in part the low preference for tertiary-based education programs that may be less accessible for geographically isolated nurses. Future research should address this question by assessing the needs and preferences of nurses from a broader more representative sample, and including nurses from tertiary treatment centres.

In conclusion, we believe that the key aspects of this program that differentiate it from other educational initiatives and suggest it may have a wider application outside of Queensland, are the intensive mode time-tabling, emphasis on building professional networks, use of small-group learning in a face-to-face setting, the focus on current nursing practice and targeting of nurse participants within the current cancer care workforce. Both nurses and ultimately patients benefit from this approach, and in the face of current concerns nationally about nursing workforce shortages this model may be of interest to others.

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The Cochrane Collaboration: Building a global network of systematic reviews in cancer

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Abstract

Busy clinicians, policy makers and consumers faced with having to make important decisions about cancer health care need to be able to identify evidence that is relevant, reliable and up-to-date. The Cochrane Collaboration prepares, maintains and promotes the accessibility of systematic reviews of the effects of healthcare interventions. Cochrane reviews are designed to minimise bias and follow a strictly scientific format. Fourteen Cochrane Collaborative review groups are currently preparing and maintaining systematic reviews relating to cancer, covering nearly ninety per cent of cancers. Over 120 Cochrane reviews relating to cancer have been published on The Cochrane Library, now regarded as the best single source of information on the effects of healthcare. A national subscription has been negotiated by the National Institute of Clinical Studies (NICS), enabling all residents of Australia with access to the Internet to have free access to The Cochrane Library. NICS Cochrane Users Awards totalling $11,000 have been established to identify examples of best use. It is important that the needs and perspectives of Australian clinicians and consumers are properly represented in the preparation of Cochrane systematic reviews. Opportunities for clinicians and consumers to become contributors to the Cochrane systematic review process are described.

Introduction

Cancer remains the leading cause of death in Australia with an annual mortality of around 34,700 people. More than 82,000 new cases of cancer are diagnosed each year. One in three men and one in four women can expect to be directly affected by cancer before the age of 75[1].

Every year tens of millions of dollars are spent worldwide on randomised controlled trials (RCTs) in cancer, investigating the comparative effectiveness of different interventions. But gaining access to the results remains a problem. With over 20,000 biomedical journals being published globally reports of cancer RCTs are easily lost in the flood of information, making it difficult for busy health care professionals to identify the relevant studies, much less make use of the evidence they contain to make daily clinical practice more effective. Despite excellent electronic databases such as Medline and Embase, only a part of the published literature is covered[2]. The Internet has not proved as helpful as we had hoped in organising the literature; keying in 'cancer' on a search engine like Google currently produces over 16 million 'hits', often containing unreliable or biased information.

The need for evidence-based care

In order to make well-informed decisions, clinicians, policy makers and consumers need to be able to identify relevant evidence and they need to know whether the evidence underlying the advice they give is valid and up-to-date. This is not news. UK epidemiologist Archie Cochrane drew attention to our great collective ignorance about the effects of health care more than 30 years ago. In his influential book, Effectiveness and efficiency: Random reflections on health services published in 1972[3], he explained how evidence from RCTs could help us to use resources more rationally. The principles he set out were straightforward: because resources in health care would always be limited, they should be used to provide equitably those forms of health care which had been shown in properly designed evaluations to be effective. Recognising that people who wanted to make more informed decisions about health care did not have ready access to reliable reviews of the available evidence, he argued that priority should be given to finding out which treatments are effective and then ensuring that these treatments are efficiently given to all who need them. In particular, he stressed the importance of using evidence from RCTs because these were likely to provide much more reliable information than other sources of evidence. Writing in 1979, Cochrane commented: "It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials"[4].

The Cochrane Collaboration

Archie Cochrane died in 1988 but his encouragement, and the endorsement of his views by others, led to the opening of the first Cochrane Centre (in Oxford, UK) in 1992 and ultimately to the founding of The Cochrane Collaboration in 1993. The Cochrane Collaboration is an international not-for-profit organisation that aims to help people make well-informed decisions about health care by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of healthcare interventions. With 81 bases around the world the Cochrane Collaboration operates as a global network and plays a leading role in the international effort to review and synthesise data from intervention studies asking similar questions in health care (using meta-analysis where possible). Cochrane systematic reviews are designed to minimise bias and follow a strictly scientific format. They are published quarterly on The Cochrane Library, and updated at least every two years in order to include the evidence from new trials.

Cochrane reviews are produced by close to 50 Collaborative Review Groups, within which the reviews are prepared and maintained. The members of these Groups – healthcare professionals, researchers, consumers and others – have come together because they share an interest in generating reliable, up-to-date evidence relevant to the prevention, treatment and rehabilitation of particular health problems or groups of problems. Fourteen of these Collaborative Review Groups are responsible for preparing reviews relating to cancer and cover nearly 90 per cent of cancers. Some of these Groups are concerned predominately with cancer (eg the Lung Cancer Review Group based in Barcelona or the Breast Cancer Review Group based in Sydney) while others are concerned with various diseases in an organ system that could include cancer (eg the Hepato-biliary Review Group based in Copenhagen or the Ear, Nose and Throat Disorders Review Group based in Oxford, UK). The scope of Cochrane reviews reflect the clinical need for unbiased information at every stage of the cancer journey. All types of available interventions are reviewed, including:

- biological therapy;
- chemotherapy;
- complementary therapies;
- delivery of care;
- gene therapy;
- hormonal therapy;
- immunotherapy;
- radiotherapy;
- surgery;

and combinations of the above. A list of Cochrane Collaborative Review Groups concerned with cancer is presented in table one. Support is currently being sought for the establishment of a Cochrane Collaborative Review Group in childhood cancer. Reviews in areas where there are no review groups or where the review involves many different types of cancer are overseen by the Gynaecological Cancer Review Group supported by a grant from the UK NHS Research and Development Program.

The work of these Collaborative Review Groups is facilitated and supported by a network of 12 Cochrane Centres spread around the world. They are responsible for coordinating and supporting members of the Collaboration in areas such as training, and for promoting the objectives of the Collaboration at national and regional level. The Australasian Cochrane Centre (www.cochrane.org.au) was established with funding from the Commonwealth Department of Health and Ageing at Flinders University, Adelaide in early 1994 under the directorship of Chris Silagy. In March 1999 the Centre relocated to Monash University, Melbourne. Chris Silagy died on 13 December 2001 after a long battle with non-Hodgkin's

Area of cancer care	Cochrane CRG
Bowel/colorectal cancers	Colorectal Cancer CRG www.cccg.dk
Breast cancer	Breast Cancer CRG www.ctc.usyd.edu.au/cochrane/
Prostate, kidney, bladder, and penis cancers	Prostatic Diseases & Urological cancers CRG roderick.macdonald@med.va.gov
Skin cancers	Skin CRG www.nottingham.ac.uk/~muzd
Lung cancer	Lung Cancer CRG www.cochrane.es/LCG/
Ovary, cervix, uterine, vulval and fallopian tube cancers	Gynaecological cancer CRG www.cochrane-gyncan.org
Leukaemias, lymphomas, and myeloma	Haematological malignancies CRG www.chmg.de
Oesophageal, stomach and and pancreatic cancers	Upper Gastrointestinal and Pancreatic Diseases CRG cochrane@lrf.leeds.ac.uk
Liver cancer (primary and secondary)	Hepato-biliary CRG http://inet.uni2.dk/~ctucph/chbg
Head and neck cancers	Ear, Nose and Throat Disorders CRG www.entgroup.demon.co.uk/
Oral cancers	Oral Health CRG www.cochrane-oral.man.ac.uk
Ocular cancers	Eyes and Vision CRG www.cochraneeyes.org
Supportive care and palliation	Pain, Palliative and Supportive Care CRG www.jr2.ox.ac.uk/Cochrane/
Smoking prevention	Tobacco Addiction Group CRG www.dphpc.ox.ac.uk/cochrane_tobacco

Table 1: Common areas of cancer care and associated Cochrane Collaborative Review Groups (CRG)

lymphoma. His successor Sally Green continues the Centre's mission: to train and support reviewers and contributors to the Cochrane Collaboration in Australasia; to conduct research to improve the quality of Cochrane systematic reviews; and to work to inform healthcare decisions through the uptake of Cochrane systematic reviews. Core funding for the Centre comes from the Australian Commonwealth Department of Health and Ageing.

Cochrane systematic reviews

In 1987 Cynthia Mulrow revealed the poor state of the contemporary medical review article showing it to be all too often subjective, scientifically unsound and inefficient. She proposed criteria by which trials might be systematically reviewed[5]. Ten years later Viv Bramwell and Chris Williams showed that there had been little improvement in the field of cancer. Using Mulrow's criteria, they evaluated the methodological quality of review articles including meta-analyses published over a 12-year period in a major cancer journal. They found that, with the exception of the meta-analyses, the majority of authors had not used systematic methods to identify, assess and synthesise information[6].

There are currently over 1,500 Cochrane systematic reviews published on The Cochrane Library[7]. Prepared by experienced health care professionals and peer reviewed at both the protocol stage and at pre-publication, these independent, high-quality reviews are presented in a systematic, unbiased way and are updated regularly to include evidence from the latest trials. Readers are provided with the opportunity to offer their comments or criticisms online, thereby improving the quality of the systematic reviews. Over 120 of these reviews relate to cancer. Although this represents a good starting point, more needs to be done to encourage the production of systematic reviews in cancer, particularly relating to more common cancers. Authors of good quality non-Cochrane reviews and meta-analyses are being approached by the Cochrane Cancer Network (www.canet.org) and invited to turn their papers into Cochrane reviews. Based at the Institute of Health Sciences in Oxford, UK, the Cochrane Cancer Network (Director: Chris Williams) is developing a list of high priority questions ('hot topics') for systematic review or new trials in cancer. Following discussions with the UK's National Cancer Research Network it has issued an international standing invitation to individuals (clinicians, cancer nurses, patients and researchers) and organisations (cancer charities, funding bodies and support groups, research institutes) to suggest five questions that they would most like to see addressed in a Cochrane systematic review. Its current list of 'hot topics' (www.canet.org/hot.html) covers a broad spectrum of cancer care interventions including:

- cancer prevention;
- screening for cancer;
- treatment;
- the control of treatment side effects;
- rehabilitation;
- palliative care;
- symptom control;
- psychosocial effect of cancer; and
- organisation of cancer care.

One critical area of cancer care – diagnosis – has so far been omitted from the Cochrane canon due to the methodological difficulties such reviews present. At its meeting in Melbourne earlier this year the Cochrane Collaboration Steering Group agreed to take forward a program of work to extend the definition of Cochrane systematic reviews to include systematic reviews of diagnostic test accuracy. Clearly, this will not happen overnight. There is much work to be done before systematic reviews of diagnostic test accuracy can be included in The Cochrane Library, but success in this area promises tremendous benefits to both cancer health care professionals and their patients.

Building an evidence-based research agenda

As Cochrane emphasised, reviews of research evidence must not only be prepared systematically, they must be kept up-to-date in order to take account of new evidence. If systematic reviews are not properly maintained, important effects of health care (good and bad) will not be identified promptly, and people using the health services will be ill-served as a result. In addition, without systematic, up-to-date reviews of previous research, plans for new research cannot be well informed. Researchers and funding bodies may miss promising leads or embark on studies asking questions that have already been answered[8]. It is this capacity to prevent duplication of effort and place proposed or completed trials within the context of existing research that is leading to the systematic review's gradual replacement of the RCT at the top of the hierarchy of evidence when determining the comparative effectiveness of health care interventions. As Mulrow observed in 1994: "The hundreds of hours spent conducting a scientific study ultimately contribute only a piece of an enormous puzzle. The value of any single study is derived from how it fits with and expands previous work, as well as from the study's intrinsic properties. Through systematic review the puzzle's intricacies may be disentangled"[9].

Supporting the preparation and maintenance of systematic reviews, even at its current level, represents a phenomenal effort by the Cochrane Collaboration's 8,000 contributors. Identifying as many relevant studies as possible is a prerequisite for preparing high quality systematic reviews. Of its 81 bases located around the world, 54 either are conducting, or have conducted, manual searches of journals publishing reports of controlled trials relating to cancer. The Cochrane Cancer Network maintains an overview of these searches. By February 2003, 334 journals were either being or had been retrospectively searched and 201 were being prospectively searched, representing approximately 5,600 years of journal publication. From a baseline of around 8,000 reports identified on Medline in 1996 (when the Cochrane Cancer Network was established), the number of trials identified by the Cochrane Collaboration had grown to over 26,000 by February 2003.

Dissemination

The Cochrane Collaboration provides and promotes access to its systematic reviews through The Cochrane Library. Updated quarterly and distributed on an annual subscription basis on disk, CD-ROM and via the Internet The Cochrane Library is the main output of the Cochrane Collaboration and is now regarded as the best single source of information on the effects of health care. It currently includes the following databases:

The Cochrane Database of Systematic Reviews containing systematic reviews and protocols of upcoming systematic reviews of healthcare interventions, prepared and maintained by Collaborative Review Groups.

The Database of Abstracts of Reviews of Effects assembled and maintained by the NHS Centre for Reviews and Dissemination in York, England, containing critical assessments and structured abstracts of other systematic reviews, conforming to explicit quality criteria.

The Cochrane Central Register of Controlled Trials (CENTRAL) containing bibliographic information on hundreds of thousands of controlled trials, including reports published in conference proceedings and many other sources not currently listed in other bibliographic databases.

The Cochrane Database of Methodology Reviews containing Cochrane methodology reviews and protocols of methodological studies prepared by the Methodology Review Group.

The Cochrane Methodology Register containing references to articles and books on the science of reviewing research. The Cochrane Library also contains a Handbook on how to conduct a systematic review, and a glossary of terms.

The Cochrane Collaboration section in The Cochrane Library contains contact details and other information about Collaborative Review Groups and the other contributing entities within the Cochrane Collaboration.

In October 2002 Australia obtained a national subscription to The Cochrane Library negotiated by the National Institute of Clinical Studies (NICS) on behalf of the Commonwealth Government of Australia. This subscription enables all residents of Australia with access to the Internet to have free access to The Cochrane Library. The NICS Cochrane Users Award was launched at the same time, designed to recognise and reward the best use of research evidence contained in The Cochrane Library for enhancing patient care. A total of $11,000 will be awarded to seven individuals, or groups, who can demonstrate excellent use of The Cochrane Library to improve clinical care. The winning entry will receive $5,000; five runners-up will receive $1,000 each and an additional award of $1,000 will also be made for improvements in maternal and perinatal health. Applicants for all awards categories must submit a publication-ready, 500-word abstract explaining how evidence they found in The Cochrane Library contributed to the improvement of health care for Australians. (See www.nicsl.com.au for further information about using The Cochrane Library and the Users award.)

The Cochrane Library will eventually be joined by a new Cochrane product designed especially for the cancer community. The Cochrane Cancer Network is currently discussing with John Wiley & Sons (who have recently taken on the role of publishing The Cochrane Library) the publication of The Cochrane Library: a specialised database of evidence-based information relating to cancer including both Cochrane and non-Cochrane systematic reviews as well as a maintained register of controlled trials in cancer.

Good decisions about health care

Reliable evidence about the effects of specific interventions in cancer is only part of what is needed for good decisions about health care. The results of Cochrane reviews should be integrated with the dual expertise of the clinician (which has been acquired through experience and practice) and of the patient (which derives from their knowledge of their condition, the treatments on offer and their preferences, and the likelihood of success and treatment side-effects). Similar qualifications

are appropriate when considering the relevance of Cochrane reviews in decisions taken in respect of whole communities. Local disease burdens and barriers to implementation vary widely from country to country and from place to place within countries. Local attention to these issues will help to ensure that the evidence will help those who can best benefit from it. It is important that the needs and perspectives of Australian clinicians and consumers are properly represented in the preparation of Cochrane systematic reviews.

Existing opportunities for contribution

A number of opportunities exist for clinicians and consumers to become contributors to the Cochrane systematic review process:

- as a reviewer or by collaborating with other health professionals, consumers or researchers on a Cochrane systematic review;
- as a consumer, offering valuable insights to reviews;
- as a peer-reviewer of protocols and reviews relating to cancer prior to their publication on The Cochrane Library;
- as an advisor on methodological issues;
- as a volunteer, helping to search for the evidence by hand-searching journals, conference proceedings etc, particularly in languages other than English; and
- as a funder, providing financial support to the review process.

The Cochrane Cancer Network provides a useful liaison point for cancer health care specialists around the world interested in contributing to the work of the Collaboration. It supplies information about the progress of Cochrane reviews in cancer and offers a forum for networking among cancer Collaborative Review Groups within the Collaboration. The Australasian Cochrane Centre holds regular training workshops designed to meet the needs of both new and more experienced reviewers.

Conclusion

Daily, clinicians and others confront questions about the effectiveness of preventive and therapeutic interventions in cancer, the interpretation of diagnostic tests, the harm associated with exposure to a particular agent, the course of disease and the cost-effectiveness of what they do. Health professionals and their patients need to be able to make sense of all the research going on around the world. Healthcare decision-making throughout the world will be informed by high quality, timely research evidence. The Cochrane Collaboration is playing a pivotal role in the production and dissemination of this evidence across all areas of cancer.

Useful websites

Australian Cochrane Centre
www.cochrane.org.au

Cochrane Cancer Network
www.canet.org

Cochrane Collaboration
www.cochrane.org

The Cochrane Library
www.update-software.com/clibng/cliblogon.htm

Hot Topics List
www.canet.org/hot.html

NICS Cochrane Users Award
www.nicsl.com.au

National Health & Medical Research Council
www.health.gov.au/nhmrc

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REPORTS

Cancer and programmed cell death: A report on the 15th Lorne Cancer Conference, 13–16 February 2003

The unifying theme of the 2003 Lorne cancer conference was set by Nobel Laureate, H Robert Horvitz (Howard Hughes Medical Institute and Massachusetts Institute of Technology, Cambridge, USA), in the plenary address describing his seminal work on the genetic control of programmed cell death in Caenorhabditis elegans. Apoptosis, as he pointed out, is a major feature of normal development, and disruption of this process results in a variety of human disorders, including cancer.

Cell death

The Nobel prize in physiology or medicine for 2002 was awarded to Sydney Brenner (The Salk Institute, La Jolla, USA), John Sulston (University of Cambridge, UK) and Horvitz for their combined work in establishing Caenorhabditis elegans as an experimental model organism and elucidating the genetic pathway for programmed cell death. Horvitz extended the work of Brenner and Sulston by identifying the central genes in the cell death (ced) pathway, including egl-1, ced-3, ced-4 and ced-9. Loss of function mutations in egl-1, ced-3 and ced-4 mutants cause the 131 cells normally fated to die by programmed cell death to survive in the adult hermaphrodite. Current work in the Horvitz lab centers on understanding the signals between cells undergoing programmed cell death and the cells that will engulf them. In a typically simple yet powerful screen, ced-3 hypomorphic mutant worms have been made transgenic for a reporter construct comprising green fluorescent protein (GFP) under the lin11 promoter (lin11::GFP), which marks ventral cord cells that are fated to undergo programmed cell death. A combination of mutagenesis and direct observation of GFP fluorescence in live worms has led to the identification of a number of mutations in known and novel genes that act in this pathway. Two mutations disrupting the engulfment process have been mapped in mutant strains, n3380 and n3376, identifying the dpl1 and MCD-1 genes respectively.

Two major pathways control the caspase-dependent apoptosis of a cell, namely the extrinsic and intrinsic pathways. The dogma in the field has suggested that initiation of the intrinsic pathway of apoptosis, which can be activated in response to cytotoxic stress such as DNA damage, requires permeabilization of the mitochondria and subsequent formation of the apoptosome, a protein complex made up of cytochrome c, Apaf-1 and caspase-9. Given that cytochrome c release in C elegans and Drosophila is not required for apoptosis, however, several groups have hypothesised that some apoptotic pathways are independent of the mitochondria and the apoptosome, and that the mitochondria serve to amplify but not to initiate the apoptotic caspase cascade.

Yuri Lazebnik (Cold Spring Harbor Laboratory, USA) described the use of the increasingly popular technology of small interfering RNA (siRNA) to inhibit the production of caspase-2. Using siRNA avoids the need to produce gene knockouts and does not appear to produce the anti-viral responses that are triggered by traditional antisense RNA methods. He and his coworkers have demonstrated that inhibition of caspase-2 production using siRNA can inhibit the translocation of the proapoptotic protein, Bax, from the cytoplasm to the mitochondria following induction of DNA damage with the drug etoposide. When translocated to the mitochondria, Bax is involved in mitochondrial permeabilization and release of cytochrome c. Thus, caspase-2 activation precedes activation of the well-characterized apoptosome cell death machinery. One obvious implication of this work is that a detailed study of caspase-2 activation in human tumours may provide insight into the failure of apoptosis in vivo and lead to the discovery of new therapeutic targets. Further evidence that caspase activation occurs upstream of the mitochondria and that the apoptosome functions to amplify the caspase cascade was presented by Vanessa Marsden (The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia). In order to study the requirement of Apaf-1 and caspase-9 in apoptosis, where Apaf-1 and caspase-9 deficiency is embryonic lethal, Marsden and colleagues reconstituted normal mice with foetal liver cells deficient in Apaf-1 and caspase-9. They found that lymphocyte apoptosis was largely unaffected by the loss of Apaf-1 and caspase-9 in response to growth factor withdrawal and stress.

One of the most interesting observations made by Lazebnik was that the field of apoptosis research is afflicted with an overwhelming productivity. This is manifest in the more than 10,000 papers that have been published yearly in this field for the past few years. How, Lazebnik asks, are we to assimilate and conceptualise all this information? To answer his own question, he created an analogy of a broken transistor radio. The functional properties of cellular signal transduction can be likened to those of a transistor radio; both are made up of many components which function together to receive, transduce and transmit specific signals. Could we as biologists, fix a broken radio? Firstly, we might obtain working examples of the radio and sooner or later find that we could remove the back to see inside. We would study it carefully and describe and categorise the size, morphology and colouring of all the components. Next, some scientists might begin a functional analysis by removing specific parts or cutting their connections to other parts. Finally we could arrive at a working model that might help us in diagnosing the problem with the original radio. If the radio is not working due to the lack of one component or a broken connection, or perhaps a fused and discolored component, no problem. We can replace the part and fix the radio. But what if the radio does not work as a result of a number of small changes in several tunable components not apparent in our analysis? We need an electrical engineer with a circuit diagram that describes the precise physical and functional relationships between the components that make up the transistor radio. Likewise, in order to understand cellular signal transduction, perhaps we need to develop a formal language to describe these relationships.

Cytokine signaling

In the signaling and cancer session, John O'Shea (National Institutes of Health, Maryland, USA) described finding patients with mutations in the cold autoinflammatory syndrome 1 (CIAS1) gene. Such mutations (of which 20 have been reported) result in a spectrum of diseases including neonatal-onset multisystem inflammatory disease (NOMID; also known as chronic infantile neurologic, cutaneous, articular, or CINCA, syndrome). O'Shea found that patients with CIAS1 mutations resulting in NOMID syndrome produce markedly elevated levels of IL-3, IL-5, IL-6, IL-1 and the IL-1 receptor antagonist, IL-1Ra. Interestingly, mutations in CIAS1, which encodes the protein cryopyrin, a regulator of NF-kB and the processing of IL-1, were found only in approximately 50% of the cases clinically identified as NOMID/CINCA syndrome. O'Shea proposed that heterogeneity in the promoter or intron regions of cryopyrin or cryopyrin homologs may explain the spectrum of diseases in humans with this genetic abnormality. Furthermore, he suggested that it may be possible to alleviate some of the symptoms of this disease using drugs that block IL-1 signaling.

Dendritic cells are specialised antigen presenting cells that coordinate immune responses to bacterial and viral pathogens. The development of dendritic cells is controlled both by interactions with the stromal environment, including T lymphocytes, and by cytokines, including those that signal through receptors bearing the signal-transducing gamma common (gamma c) chain, which is shared by receptors for IL-2, IL-4, IL-7, IL-9 and IL-15. Jak3 is an essential signalling component immediately downstream of the gamma c chain. Mice deficient in Jak3 are deficient in responses to IL-2, IL-4, IL-7 and IL-15. Morgan Wallace and collaborators have shown that Jak3 deficient mice display a three-fold decrease in CD8a+ splenic DC whereas CD11b+ splenic DC numbers were normal. CD11b+ cells are normally found in the marginal zone of the spleen and are responsible for Th2 T-helper cell responses, whereas CD8a+ dendritic cells are found in T-cell areas of the spleen and are probably the only dendritic cells capable of crosspriming CD8a+ T cells. To test whether the decrease in CD8a+ dendritic cells was a haematopoietic-specific defect, bone-marrow chimeras were generated using Jak3-deficient cells. The CD8a+ dendritic cells isolated from these chimeric mice showed a decrease in number and an increase in the expression of the CD40, B7.1 and B7.2 activation markers. Several possibilities have been suggested to account for the observed alterations in dendritic cell populations: activated Jak3-deficient T cells may kill CD8a+ dendritic cells or may provide inappropriate dendritic cell maturation signals; and disrupted splenic architecture may also prevent normal maturation. An alternative hypothesis revealed at the conference is that Jak3-deficient T cells produce a three- to five-fold increase in levels of IL-10, providing a possible negative feedback signal for CD8a+ dendritic cell development.

Cancer therapeutics

The conference included a number of notable presentations on current research into cancer therapeutics. The applications of combinatorial library technology were outlined by Kit Lam (University of California, Davis, USA) in a talk that focused on anti-cancer drug development and cancer proteomics. Combinatorial peptide chemistry is a blossoming field that is increasingly being utilised for the identification of cell-surface ligands and lymphocyte epitopes, and for studies of peptides binding to the major histocompatability complex (MHC), as well as vaccine development. The one-bead one-compound library method was first described by Lam in 1991: each 80-100µm bead expresses approximately 1013 copies of a unique peptide (of which there are up to 10^9 permutations). These peptide-coated beads are capable of binding a desired target, such as an antibody, protein, cell-surface receptor, tumour cell, virus or bacteria. Individual beads bearing a particular peptide can be isolated and sequenced by Edman degradation. This year, Lam described a peptide library screen designed to identify specific peptides that bind to tumour cells but not to normal cells. It is envisaged that these peptide agents could be used to target drugs to tumour cells. Tumour-specific peptides prepared using D-amino acids would be less likely to be rapidly degraded in vivo or to induce immune responses and might therefore be optimal as therapeutics.

The conference was the occasion of the inaugural Ashley Dunn oration. For the past decade, the Lorne Cancer Conference has been chaired by Ashley Dunn (Ludwig Institute for Cancer Research, Melbourne, Australia). The success of the conference during this time is undoubtedly a reflection of the patience, commitment and grace under pressure that has been a characteristic of Ashley's tenure. The Ashley Dunn oration acknowledges the contribution Ashley has made not only to the Lorne Cancer Conference but to fostering research excellence within the Australian research community. Mary-Claire King (Department of Medicine and Genome Science, Seattle, USA) delivered the inaugural Ashley Dunn oration for 2003. The genetic analysis of breast and ovarian cancer, past, present and future was the subject of her lecture. The first BRCA1 mutations in families with inherited breast cancer were described by King and others in the early 1990s. They have continued to define the spectrum of mutations present in the BRCA1 and BRCA2 genes in familial breast and ovarian cancer and to search for other genes linked to this disease. Recently, King and co-workers observed that most of the BRCA1 mutations cause truncation and loss of the carboxy terminal transactivation domain. They have identified a number of direct transcriptional targets of BRCA1, including MYC and cyclinD1 which are frequently overexpressed in breast tumours.

In his concluding remarks, Douglas Hilton (The Walter and Eliza Hall Institute of Medical Research, Australia) noted that the 2003 Lorne Cancer Conference had brought together a group of leading scientists in a beautiful beachside location with anticipated results. Local and international speakers had outlined the central role of apoptosis and the cell death machinery in cancer. The importance of cytokine signalling regulation and cell cycle control in tumourigenesis was highlighted and several developments in tumour diagnosis and therapeutic strategies were revealed. In summary, the 15th annual Lorne conference confirmed that breakthroughs in the cancer problem can be achieved by utilising the power of diverse yet complementary approaches.

Acknowledgements

We acknowledge Douglas Hilton and Warren Alexander for their roles as joint chairmen of the Lorne Cancer Conference organising committee, and Helene Martin for her role as meeting co-ordinator.

B Croker and A Hart
The Walter and Eliza Hall Institute of Medical Research, VIC

Historic global tobacco control treaty welcomed
And now the real work begins …

Framework Convention on Tobacco Control

> Tobacco use is estimated to have killed 100 million people in the 20th century and is expected to claim the lives of ten times that number – one billion people – in this century, based on current trends. The burden of death and disease caused by tobacco is shifting rapidly to low income nations as most high income nations are implementing effective tobacco control policies. J MacKay, M Eriksen "The Tobacco Atlas", WHO, 2002

Health and medical organisations and governments throughout the world hailed the adoption of the Framework Convention on Tobacco Control (FCTC) by the World Health Assembly (WHA) on 21 May 2003. The world's first-ever public health treaty, it represents an important global response to the tobacco epidemic.

Created under the auspices of the World Health Organisation (WHO), the treaty sets down a comprehensive range of

measures for reducing the harm caused by tobacco.

Key obligations under the treaty include:

- Price and tax measures: Governments shall implement tax policies, and where appropriate, price policies "so as to contribute to the health objectives aimed at reducing tobacco consumption", and prohibit or restrict duty-free sales to international travellers.
- Exposure to tobacco smoke: Recognising that "scientific evidence has unequivocally established that exposure to tobacco smoke causes death, disease and disability", governments shall take measures "providing protection from exposure to tobacco smoke in indoor workplaces, public transport, indoor public planes, and, as appropriate, other public places."
- Regulation of the contents of tobacco: Governments shall implement "effective legislative, executive and administrative or other measures" for testing and measuring the contents and emissions of tobacco products following the development of guidelines by competent international bodies.
- Regulation of tobacco product disclosures: Governments shall require manufacturers and importers of tobacco products to disclose information about the contents and emissions of tobacco products. Governments shall implement effective measures for public disclosure of information about the toxic constituents of the products and their emissions.
- Packaging and labelling: Within three years of entry into force of the convention, signatories shall adopt national measures to ensure that product packaging and labelling "do not promote a tobacco product by any means that are false, misleading, deceptive" or give the impression that a particular product is less harmful than others. "These may include terms such as 'low-tar', 'light', 'ultra-light', or 'mild'" – although there is no total ban on such terms. Each pack must carry health warnings that should ideally be 50% – but no less than 30% – of the principal display areas and may include pictures or pictograms.
- Advertising, promotion, and sponsorship: "Each party shall, in accordance with its constitution or constitutional principles, undertake a comprehensive ban of all tobacco advertising, promotion, and sponsorship". This should be within five years and include sponsorship of international events and – subject to technical constraints – cross-border advertising. Radio, television, print media, and as appropriate, other media such as the Internet, should be covered. Countries unable to impose a ban for constitutional reasons (including the US) shall apply restrictions.
- Demand reduction: Governments shall increase public awareness and education activities and develop effective cessation and counselling programs.
- Illicit trade: Governments shall implement measures to ensure that all unit packets and outside packaging are marked to help determine the origin of the product and carry wording such as "sales only allowed in xx country". There should be more international exchange of information between tax and customs authorities and cooperation between enforcement agencies.
- Sales to minors: Governments shall prohibit the sale of cigarettes to minors, require vendors to place prominent signs and ask for proof of age; ban sales from accessible store shelves; ban the manufacture and sale of sweets, snacks, toys or other objects in the form of tobacco products which appeal to minors; and restrict the sale of individual or small quantities of cigarettes. Governments shall restrict the placement and display of vending machines, but may implement a total ban on vending machines as a codicil to the treaty.
- Liability: "For the purpose of tobacco control, the Parties shall consider taking legislative action or promoting their existing laws, where necessary, to deal with criminal and civil liability, including compensation where appropriate." This

is the first time an international treaty has introduced the concept of manufacturer liability, although the provisions are deliberately vague.

Tobacco smoking remains the single largest preventable cause of premature death and disease. Worldwide each year, five million people die prematurely as a result of tobacco-caused diseases. Many of the factors affecting tobacco consumption – such as tobacco smuggling, and the portrayal of smoking and promotion of tobacco through films and other popular forms of entertainment – are international in nature and need to be

tackled at a global level. It is also disturbing that the developing countries are being increasingly targeted by the tobacco industry in its quest for new and less regulated markets for its deadly products.

Current trends indicate that by 2020, tobacco use will cause 10 million deaths per annum worldwide. This makes it particularly critical that the international community supports global and comprehensive approaches to tobacco control.

Adoption of the FCTC was an historic moment for tobacco control, and brought to an end over four years of protracted and taxing negotiations with the tobacco industry an all-pervasive, undermining presence. It also sent a clear signal to the tobacco industry that the world stands united in the fight to curb the human toll of death, disease and suffering caused by tobacco. Adoption of the treaty, however, is but the start to even greater challenges: the ratification and effective implementation of the treaty by all nations. Much will depend on political will and the might and vigilance of civil society.

Both the Australian government and civil society have important and ongoing roles to play in ensuring that the treaty comes into force. It is vital that the Australian government ratify the treaty, and that this is done soon. As a community we should be urging the Government's early ratification of the treaty. It should also be recognised that the treaty outlines minimum standards in some areas, but encourages countries to go further. We need to call for the strongest interpretation possible of obligations under the treaty, and continuing progress.

Australia has been a lead nation in tobacco control, and its ratification of the treaty offers the prospect of revitalising tobacco control policy in this country. While we have come a long way in tobacco control in this country, over 19,000 Australians die each year from diseases caused by smoking, and the social costs of smoking to the community have blown out to over $21 billion. Clearly, there is still much work to be done.

The Government continues to reaffirm its commitment to tobacco control, but there has been a noticeable complacency in more recent times that is reflected in low investment in tobacco control and a lack of action in terms of legislative reforms. The treaty provides an opportunity to lift tobacco control on the Government's health agenda and to leverage increased funds and resources for tobacco control.

As well as stepping up domestic tobacco control activity, we should urge the Australian government to support developing countries who are trying to boost their tobacco control efforts. Around 70 per cent of the worldwide tobacco-related deaths occur in developing countries, where education campaigns about smoking are almost non-existent. Developed countries,

such as Australia, have a moral obligation to help those countries that are facing the biggest challenges in tobacco control, and which are really just starting to address the tobacco epidemic. We should be encouraging the Australian government's support of developing countries within the Western Pacific region in building capacity in tobacco control in particular.

The FCTC will be open for signature at the UN headquarters (New York) from 30 June 2003 to 29 June 2004. The treaty becomes a legal document once 40 nations have ratified it. The FCTC will result in unprecedented global action by countries to reduce tobacco use, but we all share responsibility for ensuring that it truly delivers on all that it promises.

The treaty can be viewed online at http://tobacco.who.int/

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D Sullivan

History of the Framework Convention on Tobacco Control

May 1996: WHA resolution formally endorses plans for a global tobacco control treaty.

October 1999: WHO holds first working group meeting, which agrees on basic elements of planned FCTC.

August 2000: WHO report says that Big Tobacco systematically tried to infiltrate the organisation and undermine its antismoking strategies.

October 2000: WHO hosts unprecedented public hearings on tobacco. First formal Intergovernmental Negotiating Body (INB) meets, bringing in representatives of finance and agriculture ministries for the first time.

April 2001: INB2 discusses text by then chairman Celso Amorim of Brazil, which would ban advertising and sponsorship aimed at under-18s.

November 2001: INB3 discusses text filled with brackets with competing options.

March 2002: Luis Felipe de Seixas Correa takes over as chairman at INB4 after heading off a challenge from South Africa, one of the strongest proponents of strict tobacco control.

July 2002: Seixas Correa publishes draft of treaty, proposing that countries "reduce, with a view to gradually eliminating" advertising, promotion, and sponsorship.

October 2002: Momentum grows at INB5 in favour of much stronger restrictions on advertising and sponsorship.

January 2003: Seixas Correa produces a watered-down text, which is endorsed by Bruntdland. But antismoking groups and African nations denounce it as too feeble.

17 February 2003: INB6 opens with Brundtland appealing to countries to agree to a draft treaty that can command broad support.

1 March 2003: Negotiators from over 170 countries approve the language of the draft FCTC and agree that it should be forwarded to WHA for adoption.

21 May 2003: The WHA unanimously adopts the FCTC at its 56th meeting in Geneva, Switzerland.

16 June 2003: The treaty is opened for signature and ratification by member states of the World Health Assembly.

Australian Behavioural Research in Cancer

This is a regular feature in Cancer Forum describing behavioural applications in cancer prevention.

Australia has five behavioural research centres: the Cancer Prevention Research Centre (CPRC) of the University of Queensland, the Centre for Health Research and Psycho-oncology (CHeRP) of The Cancer Council New South Wales, the Centre for Behavioural Research in Cancer (CBRC) of The Cancer Council Victoria, the Centre for Behavioural Research in Cancer Control (CBRCC) at Curtin University of Technology Perth, and the Centre for Cancer Control Research (CCCR) of The Cancer Council South Australia.

This report has been edited by N Mills (CHeRP).

New results

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

Improving psychosocial well-being in an outpatient oncology clinic

Although people with cancer suffer considerable psychosocial morbidity, much of it goes undetected and untreated by health care providers. While there are many valid and reliable self-report tools measuring cancer patients' psychosocial issues, the feasibility of using them routinely in clinical practice has often been questioned. There is growing evidence that computer-based methods of survey administration are fast, robust, acceptable to cancer patients and feasible to implement in oncology clinics. They also enable patient self-report data to be collected, scored and fed back to health care providers in real time to enable issues of concern to be addressed during the consultation.

Allison Boyes, Afaf Girgis and colleagues undertook a pilot study to evaluate whether providing medical oncologists with regular printed feedback about their patients' self-reported psychosocial well-being resulted in lower levels of patient anxiety, depression, perceived needs and fewer debilitating physical symptoms. Patients visiting the medical oncology outpatient department at one hospital completed a 15-20 minute touchscreen computer survey at their first four visits to the clinic. Each person was allocated to either the intervention or control group after completing the initial survey. For each patient in the intervention group, the oncologist received a printed feedback sheet prior to each consultation which summarised the individual's responses to the most recently completed survey and recommended strategies for dealing with the issues identified. Results of the study indicated that patients in the intervention group were significantly more likely to report fewer debilitating symptoms and levels of anxiety, depression and perceived needs also decreased (non-significant) from the initial consultation to final follow-up. Providing medical oncologists with summarised information about patients' self-reported well-being via a touchscreen computer survey in the waiting room may be an effective strategy for improving patient outcomes.

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

Respiratory symptoms and staff exposure to second hand smoke in hospitality industries

The aim of this study was to assess the relationship between exposure to second-hand smoke (SHS) in the workplace and respiratory and sensory symptoms. This formed part of a study in which data were gathered by a telephone survey of 1,078 members (77% response rate) of the Australian Liquor, Hospitality and Miscellaneous Workers Union (Victoria). Data were gathered from 382 respondents who worked at least 35 hours per week, indoors or in a vehicle, and were never smokers or ex-smokers who had quit over one year ago. Exposure to SHS at work was measured by the number of hours in the same room as someone who was smoking. After controlling for potential confounders, exposure to SHS at work for part of the day was significantly associated with an increased risk of wheeze (OR=4.26), frequent cough (OR=2.26), sore eyes (OR=3.77) and sore throat (OR=2.70). When we stratified the analysis according to whether workers had experienced a cold in the past four weeks, the risk of symptoms disappeared for those who had, and strengthened for those who had not. Among workers who had not experienced a cold, we found strong and dose response relationships between increasing levels of exposure to SHS at work and morning cough, frequent cough, sore eyes and sore throat, and a positive relationship for wheeze. These findings provide compelling evidence that Victorian indoor workers are adversely affected by exposure to SHS at work and underline the importance of workplace smoke-free policies in protecting the health of workers. This study, which was funded by VicHealth was conducted by CBRC researchers Melanie Wakefield, Melissa Cameron, Lisa Trotter, Tessa Letcher, Graeme Inglis and David Hill, plus Alistair Woodward (University of Otago), and is in press in the Journal of Occupational and Environmental Medicine.

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

Progress in tobacco control 2002: Health omnibus survey

This report by TCRE used data from the health omnibus survey. The health omnibus survey is a state-wide annual survey of more than 3,000 respondents. The results revealed that smoking prevalence for the South Australian population was 24.1% in 2002 (unstandardised; all smokers). Smoking rates remained consistently higher for men than women. Most smokers made a quit attempt at some point and almost one-third of smokers made a quit attempt in the past year. Passive smoking remains a major public health concern, with a majority of the population being concerned about passive smoking, and a similar proportion reported being exposed to someone else's cigarette smoke in the previous two weeks. Exposure was the highest in hotels and bars, where there are still little or no restrictions on smoking.

Analysis presented a detailed picture of the socio-economic predictors of smoking in South Australia using population trend data. A draft report, "Smoking and social inequalities in South Australia", demonstrated that social inequalities are evident in the prevalence of smoking and involuntary exposure to tobacco smoke. Evidence about whether the difference between the groups is widening over time is mixed but warrants close monitoring.

Lung cancer trends in South Australia

CCCR assisted the Epidemiology Branch of the Department of Human Services to assess lung cancer trends in South Australia by histological type, as a means of evaluating cancer control initiatives. A three-fold increase in age-standardised lung cancer mortality had occurred in males between the 1950s and 1970s, followed by a decrease of approximately a quarter by the year 2000. This reduction was consistent with the decrease in smoking prevalence in Australian males in the latter part of the century. In females, an approximate three-fold increase in lung cancer mortality presented between the 1960s and 1980s, followed by a plateau in the 1990s. These trends also are consistent with historic trends in cigarette smoking in Australian women.

In both males and females, the ratio of adenocarcinomas to squamous carcinomas increased, potentially due at least in part, to changes in cigarette choice to varieties with a lower tar and nicotine yield. Compensatory smoking practices have been reported when these varieties are used, including deeper inhalation. Higher ratios of adenocarcinomas to squamous cell cancers were observed in females, younger patients, and residents of upper socio-economic areas. Notably, data from a South Australian household survey in 2002 pointed to a greater use of low-tar as opposed to high-tar cigarettes by residents with this socio-demographic profile. More favourable trends in lung cancer rates generally were observed in younger age groups, which hopefully will transfer to the older age groups, as these younger cohorts get older.

An audit of nutrition and cancer information in popular magazines

This audit of nine popular general or health-focussed magazines identified a total of 204 cancer related articles from 88 individual issues in press between February 2002 and January 2003. Of these, 39% related to cancer in general, 25% focussed on breast cancer, 18% on colorectal cancer, 14% on skin cancer, 13% on prostate cancer, 7% on lung cancer and the remainder on other less common cancers. Forty-seven per cent of all cancer related articles made some mention of nutrition. (The quality and accuracy of this information was not assessed.) Specific dietary recommendations (eg increasing vegetable consumption) were mentioned infrequently and advice was generally not specific to the type of cancer being discussed. Other cancer related lifestyle factors (obesity, sedentariness, and excess alcohol consumption) were rarely mentioned.

Given that popular magazines are a major source of health-related information for many people, more attention needs to be paid to working with the media to enhance communication about nutrition and cancer risk. Acknowledgments to Catherine Easterbrook who worked on this project during a student placement at The Cancer Council Australia South Australia.

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

Analysis of Western Australian and national data resulting from a population survey of 2,501 subjects concerning various attitudes towards cancer proceeds with aplomb. Papers continue to be prepared for submission to various peer-reviewed journals. Two recently prepared articles include one entitled "Metropolitan Australians' perception of genetic testing for cancer". The paper outlines results to suggest that the majority of metropolitan Australians are aware of genetic screening for cancers, are quite accepting of them and appear willing to subject themselves to genetic screening tests.

The second paper is entitled "Changes in Western Australians' beliefs about cancer: 1964 to 2001". The results suggest that Western Australians in 2001 are much better informed about cancer than they were in 1964. Some interesting results include a four-fold increase in the rates of people who have ever had a cancer check-up, and the virtual disappearance of a previously commonly held belief that cancer could be caused by receiving a physical 'knock'.

Research in the pipeline

n CHeRP

Art psychotherapy: its effect on the immunological and psychosocial functioning of cancer patients

Art therapy, the use of patient-created visual images and the exploratory conversations that ensue as a result of their creation, as the primary focus in emotional healing, has been used since before World War II. There has also been much interest in the impact of emotional state on immunological function and the positive impact of emotional support on psychological health and adjustment to cancer.

Christina Virago, under the supervision of Afaf Girgis and Margaret Dunkley, is undertaking an innovative project as part of her PhD, to assess the effects of art psychotherapy on the psychological and social coping skills and immune function of a group of people with non-metastatic malignant melanoma. The research will be a randomised controlled trial, with those in the intervention group taking part in weekly art psychotherapy sessions over a period of six months. Those in the control group will also meet on a weekly basis for informal conversation. At the beginning and end of the trial, and also at 12 months follow-up, all participants will complete a series of self-administered psychosocial questionnaires. Participants' IgA levels and T-cell activity will also be tested at various intervals as a measure of their immune response. It is anticipated that participants taking part in art psychotherapy will have better psychosocial and immunological functioning post-intervention when compared to the control group. To date, most art therapy research has relied upon anecdotal evidence or case studies. It is hoped that this research will provide the scientific rigour research to establish the discipline within an acceptable medical paradigm.

n CBRC

Youth appraisal of anti-smoking advertisements: A comparative study in the United States, Australia and Britain

Melanie Wakefield is leading a study with Russil Durrant in CBRC and colleagues in the United States and Britain (funded by the US National Cancer Institute with support from VicHealth) to compare the similarity in how youth in the United States, Australia and Britain appraise anti-smoking advertisements with different characteristics. The study involved each participant viewing and evaluating a set of 10 anti-smoking ads (for an overall total of 50 ads) in a controlled experimental context using an audience response methodology. A structured telephone interview was completed one week after viewing the ads, in which recall and engagement with the ads by participants was evaluated. Overall 615 grade eight, 10 or 12 youths from the US, Australia and Britain completed the protocol. The study has collected measures of ad appraisal (% of youth who rated the ad as a very good anti-smoking ad; % of youth who nominated the ad as the one that most stands out) and engagement (% of youth who recalled the ad at follow-up; % who discussed the ad with someone outside of the rating session; % who thought more about something in the ad between session and follow-up). Analyses are being undertaken to contrast the potential effectiveness of different advertising themes (health effects of smoking, secondhand smoke, industry manipulation, etc), executional styles (personal testimonial, negative visceral element) and target audiences (youth or general). The findings will be discussed with regard to the possibility of sharing anti-smoking ads among broadly similar cultures.

Unintended effects of advertising for nicotine replacement therapy and Zyban

Funded by NHMRC, this study is investigating whether youth exposure to television advertising for nicotine replacement therapy (NRT) and Zyban might result in increased perceptions of the ease of quitting smoking or decreased perceptions of addiction, leading youth to conclude that there is less of a problem with taking up smoking. This is consistent with research which found that optimism about quitting is a major predictor of trial and subsequent progression to heavier smoking among young people.

The study is premised on the fact that television advertising of NRT and Zyban will ipso facto reach more than its intended primary target group of smokers, so it is important to consider the responses of those at risk of taking up smoking, namely teenagers, to the advertising. The study will employ an audience response methodology where 495 youth who meet eligibility criteria are randomised within stage of quitting/stage of uptake to either 1. a control group, where they will view three ads promoting non-pharmacological methods of quitting, such as the Quitline; 2. an Experimental NRT condition, where they will view three ads promoting the gum and patch, or 3. an Experimental Zyban condition, where they will view three ads promoting Zyban (from New Zealand and USA). One-page rating forms will be completed by participants after viewing each ad twice, and at the end of the session, participants will complete a questionnaire which asks questions about perceptions of addiction; smoking health risks; perceived confidence in, and difficulty of quitting smoking; intention to smoke in future; and perceived need for help to quit smoking. By comparing responses to these questions between the groups, this study will furnish information to help assess potential risks of advertising for NRT and Zyban, alongside the established benefits.

Evaluation of the impact of a peer support program for cancer patients on adjustment to a cancer diagnosis

The Cancer Connect Program puts people in touch by telephone with a trained volunteer who has been through a similar cancer and treatment experience. This study aims to determine if cancer patients who participate in Cancer Connect are satisfied with the program they received. It will also examine what effect, if any, participation in Cancer Connect has on the experience of cancer treatment for program participants compared to those who did not take part.

This is a prospective quasi-experimental trial comprising two research arms: a Cancer Connect Group (newly diagnosed patients participating in the Cancer Connect program), and a Usual Care Control Group (newly diagnosed patients in Western Australia accessing an established professional cancer information and support telephone help line). Patients are recruited into the study by nurse counsellors and are interviewed by telephone, after the initial contact with the Cancer Information and Support Service (CISS), three months after initial CISS contact, using the Computer-Assisted Telephone Interviewing (CATI) program, by experienced interviewers blinded to the study group. Patients are currently being recruited and interviewed for this study which is being conducted by Victoria White and Trish Livingston.

A pilot test of shade intervention for secondary schools

Adolescents have a high knowledge of the risk of sun exposure in relation to skin cancer and appear resistant to traditional approaches to promoting sun protection. Further research is urgently needed to explore innovative approaches to intervening with this group. Suzanne Dobbinson and Melanie Wakefield recently conducted a pilot study exploring the feasibility of developing a shade intervention for secondary schools. VicHealth provided funds to test the development of shade-sail structures for two areas in a high-activity and relaxation area at one school. In January 2003 a school with suitable areas for shade development was recruited. A pre-test over two weeks in late February used photographic observation to assess students' use of the pre-defined areas prior to the shade development. A number of delays and difficulties were experienced with the installation of the shade structures, which took until early April to complete. Nonetheless, the weather remained moderately warm and six days of post-test observations were completed prior to the end of term one. A complete analysis of the results is underway with some anecdotal evidence that students will utilise the shade under these purpose-built shade structures at least while weather is warm and for passive activities. The results of this study are invaluable to refining this intervention study and in seeking funding for a larger study to test efficacy.

n CCCR & TCRE

Quit Media Campaign Evaluation: Jenny

The new Quit campaign, originally from WA, started in March this year featuring Jenny, a woman with lung cancer. The campaign was targeted primarily at younger women (18-24 years). The secondary target was older women in the 25-39 age group. An evaluation is currently underway, using the Morgan Natural Exposure Advertising Research methodology.

Community perceptions about tobacco control and the tobacco industry

Also under investigation are community opinions and attitudes about a range of (potential) tobacco control policies and the tobacco industry. Of specific interest is whether community attitudes have undergone any change in the period 1999 to 2002.

Review of cancer research outcomes in SA

The Cancer Council Australia South Australia has provided research funds totalling over $20m since 1989, mainly for project grants and fellowships with smaller amounts going to scholarships, data managers in hospitals, travel grants and the like. In order to provide feedback to the community who provides the funds and to inform development of research policy, we propose to review the returns on this investment in terms of impact on cancer control and possibly identify gaps. Citation analysis and journal impact factors will be considered, as will post-fellowship career paths and changes to policy, practice or curriculum resulting from research. Contacts, advice, references to similar work, etc would be very welcome, to kkirke@cancersa.org.au.

n CPRC

The Cancer Prevention Research Centre has recently obtained funding from Health Promotion Queensland for an eight-month project which aims to investigate factors that influence young Queensland women to initiate, maintain or stop smoking tobacco. The project involves a number of interrelated components which will provide information that will be triangulated to develop specific, evidence-based recommendations for strategies to reduce cigarette smoking among young women in Queensland. These components include:

- a review of the scientific literature, specifically relating to young women and smoking;
- review of relevant state, national and international tobacco control initiatives;
- focus group discussions and in-depth interviews with young women to examine personal and social influences relating to smoking behaviour;
- analysis of factors influencing young Queensland women's smoking behaviour, using existing data from several national and state sources, including the Australian Longitudinal Study on Women's Health;
- web-based survey of knowledge and attitudes toward anti-smoking and smoking cessation messages among young women;
- semi-structured telephone interviews with young women conducted through Women's Health Queensland Wide's Health Information Line, to explore knowledge and attitudes toward anti-smoking and smoking cessation messages; and
- semi-structured telephone interviews with key service providers and key informants to investigate dissemination

and implementation of anti-smoking and smoking cessation initiatives.

The resulting report will have specific, practical recommendations for ways to significantly reduce smoking among young Queensland women.

n CBRCC

The Centre is currently participating in the Consumer Participation Project at the Cancer Foundation of Western Australia. Breast, colorectal and prostate cancer guidelines booklets so far have been evaluated in terms of consumer awareness, utilisation and perceptions of usefulness. The methodology has involved telephone interviews, postal surveys and focus groups with consumers who have been diagnosed with either breast, colorectal or prostate cancer. Consumers are also being invited to critique the guidelines and identify aspects that may not be meeting consumer needs. The research aims to inform the improvement of the various guidelines to make them more available and relevant to consumers' needs.

News

n CHeRP

Congratulations to Dilhani Bandaranayake who was awarded her PhD for her research entitled "Why do some non-melanocytic skin cancers reach an advanced stage before they are treated? The effect of delay and predictors of delay in presentation, referral and treatment of NMSC".

In March, CHeRP hosted a workshop of national and international statisticians and methodologists to develop scoring, analyses and interpretation recommendations for the Supportive Care Needs Survey (SCNS). This was a follow-on from the workshop held in November 2002 on the practical aspects of needs assessment in oncology. The recommendations have been incorporated into a SCNS users' manual.

CHeRP has had a number of recent grant successes. Afaf Girgis, Chris Paul and Claire Johnson were awarded a seeding grant from Effective Healthcare Australia to conduct research into the attitudes and barriers to appropriate and timely referral of cancer patients to palliative care. Afaf Girgis, Paul Glare, Amanda Neil and Sibilah Breen were awarded a grant from the MBF Health Research Awards to conduct a trial of supportive care strategies for advanced cancer patients in NSW.

CHeRP staff presented three papers at the 2nd Australian Tobacco Control Conference, held in Melbourne on 9-11 April. Paul presented 'Smoking care provision in NSW public hospitals'; Wiggers, Paul and Walsh presented 'Pro-active delivery of smoking cessation strategies to smokers in the community: Feasibility and acceptability'; and Walsh presented 'Community attitudes towards environmental tobacco smoke in New South Wales bars and other licensed premises'.

Afaf Girgis and Allison Boyes attended the 6th World Congress of Psycho-oncology in Banff, Canada, and presented a poster on CHeRP's population-based studies of cancer survivors' physical and psychosocial well-being and another poster promoting the various applications of the SCNS.

Allison Boyes visited the American Cancer Society's Behavioural Research Centre in Atlanta, USA, and gave an invited presentation on CHeRP's research in cancer survivorship.

n CBRC

CBRC staff presented nine papers at the 2nd Australian Tobacco Control Conference: Wakefield presented 'The cigarette pack as an image: Implications for tobacco control policy', 'Relation between anti-smoking advertising and youth smoking in the United States' and 'Youth appraisal of anti-smoking advertisements: a comparative study in Australia, the United States and Britain'; Cameron presented 'Exposure to secondhand smoke (SHS) at work: a survey of members of the Australian Liquor, Hospitality and Miscellaneous Worker's Union'; Dixon presented 'Smoking in movies: Does it matter who does the smoking?' and 'Is on-screen smoking by teenagers' favourite actors and actresses associated with teenagers' beliefs and behaviour toward smoking?'; Durrant presented 'Tobacco in the News: an analysis of newspaper coverage of tobacco issues in Australia, 2001'; Letcher presented 'Adaptation to mandated restrictions on smoking in dining areas: Results of an internet survey'; and, Letcher presented, 'Bans on tobacco advertising at point of sale'.

Helen Dixon gave two presentations at the International Communications Conference in San Diego in May. Dixon, Borland and Paxton presented 'Smoking in movies: does it matter who does the smoking?' and Dixon, Hill, Karoly, Jolley and Aden presented 'Solar UV forecasts: an evaluation of their impact on adults' sun protection behaviour'.

n CCCR & TCRE

TCRE has undergone some staff changes in the last few months. Sophie Kriven has left the team to travel extensively through the US, Canada and Europe. She has been replaced by Sinéad Quinn. Sinéad comes to the team from an academic background, with specific experience in the area of psychology.

n CPRC

Neville Owen attended the American College of Sports Medicine Conference in San Francisco, 38-31 May 2003. Neville has also been invited to speak at the Conference of the European College of Sports Science in Salzburg, 9-12 July 2003 and the Second Conference of the International Society for Behavioural Nutrition and Physical Activity in Quebec City, Canada, 17-20 July 2003.

Congratulations to Liane McDermott. Formerly the Senior Research Officer with the Centre, Liane began her PhD candidacy in March this year with 'Reducing cigarette smoking among young women', and as if this is not enough of a challenge, Liane will be adding motherhood to her busy life in October.

The Centre is currently advertising for two research fellow positions for a fixed-term of two years: a Research Fellow – Behavioural Studies of Physical Activity; and a Research Officer/ Fellow – Behavioural Studies of Cancer Prevention. Successful applicants will commence in late June.

Welcome to Alexia Lennon. Alexia joined the Centre in early May as the Project Co-ordinator for the Centre's new Young Women and Smoking Project.

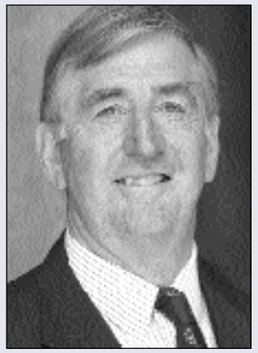
n CBRCC

Rob Donovan and Narelle Weller presented at the 2nd Australian Tobacco Control Conference. Donovan's presentation was entitled 'Developing effective communication strategies in mass media'. Discussed was recent progress the Centre had made on the early formative research techniques for "getting the right message and getting the message right" in relation to successful health awareness media campaigns. Weller presented a paper entitled 'Incidental smoking in the media'. It described the results of research over the past year to identify the frequency and characteristics of smoking incidences at media targeted to the 18 to 30 year old age group. Outlined were the methodologies used to investigate various media including newspapers, magazines, movies, television programs, televised sporting events, music videos, music lyrics and websites.

Thanks to Anne Gibbs, Melanie Wakefield, Owen Carter, Cathy

NEWS & ANNOUNCEMENTS

Farewell Lawrie Wright



On the occasion of his retirement, much is likely to be said or written on the various roles that Lawrie Wright has played in the evolution of The Cancer Council Australia and the Clinical Oncological Society of Australia (COSA). This editorial is prompted by Lawrie's role as Managing Editor of Cancer Forum, a role he has played from the time of his appointment to the then Australian Cancer Society. My own involvement with the publication dates from about that time in the mid-70s: a time when the Editorial Board consisted of Lawrie, the late Fred Gunz and me. Our meetings were at the then King and Castlereagh Street offices of the Society. And I think it's fair to say that both Lawrie and I learned the business of scientific publishing from Fred who was then, among other things, editor of Pathology. 'Learning the business' involved everything from Fred's meticulous review of any manuscript through to the basis of creative and productive contact with those who saw fit to provide us with manuscripts.

As all present readers are doubtless aware, a professional journal lives or dies largely on the quality of material it is able to publish. And extracting (for want of a better word) that material from authors who invariably have a range of professional commitments that rank ahead of their obligation to a local journal is something that requires tact and persistence. And more tact and persistence. Though the close attention he pays to manuscripts remains one aspect of Lawrie's contribution to Cancer Forum, his crucial role has been to maintain a creative relationship with those who (for the most part) gave an initial obligation to contribute and have to be 'followed up'.

Since Lawrie has been at the helm Cancer Forum has changed. The layout has evolved to match current publishing practice. And, of equal importance, the adoption of particular themes (as 'Forums') has been so successful that we have the benefit of distinguished and authoritative professional contributors on a regular basis. I'm sure that much of this evolution has involved detail of which I and the other members of the Editorial Board have been oblivious. But it has all been under the one Managing Editor. Cancer Forum and Australian professionals in the field of cancer – for whom the journal exists – are in Lawrie's debt.

BW Stewart
on behalf of the Editorial Board

Awards

The Cancer Council Australia's Vice-President, Mrs Judith Roberts, and the Medical Director of the Australian Cancer Network, Professor Bruce Barraclough, were made Officers in the General Division in this year's Queen's Birthday Honours.

Mrs Roberts received her award in recognition of her service to the community – particularly through leadership roles in a range of women's health, social service, family and multicultural organisations and boards; and to education through Flinders University, the Senior Secondary Board of SA and the Helpmann Academy.

Professor Barraclough's award was in honour of his service to medicine as a surgeon; to medical education, particularly the development of high-level surgical training facilities; and to the community through fostering improvements in the delivery of safe, quality healthcare in Australia.

And the winner is…

Every year, the World Health Organisation's Collaborating Centre for Cancer Education runs the international summer school 'Oncology for Medical Students'. This year, The Cancer Council Australia held a cancer-related essay competition for one Australian medical student to attend the summer school in Vienna.

From 24 entries, the winner of The Cancer Council Australia's essay competition is Troy Keith. Mr Keith is a final year medical student at the University of Tasmania, Hobart. His essay, "Gastrointestinal stromal tumour prognostic parameters: case report and literature review", has won Mr Keith tuition at the summer school from 28 August to 6 September 2003. He also wins an airfare, accommodation and living allowance.

The summer school aims to help students become familiar with cancer care in general practice, reduce fear for patients with cancer, understand cancer-related problems in other countries and interact with other future medical doctors.

A copy of Mr Keith's abstract follows.

Abstract

This paper is a critical review of the evaluation of malignancy and prognostic parameters used in gastrointestinal stromal tumours (GIST). Incorporated is a case report of a duodenal GIST identified and treated at our institution. GIST represents a spectrum of mesenchymal tumours that include benign and malignant variants, which can arise from anywhere in the gastrointestinal tract. A central pathogenetic event recognised in most GISTs is KIT activation (a tyrosine kinase receptor) believed to be the result of oncogenic mutations. Imatinib mesylate, highly effective in vitro in reducing KIT tyrosine activity, has revolutionised the treatment of metastatic GIST, and is discussed along with other treatment options. Traditionally three key prognostic factors used in GIST have been mitotic rate, tumour size, and anatomic location. However, the unpredictable behaviour of GIST has led to development of immunohistochemical differentiation markers including CD117 (detecting KIT protein). In addition genetic markers have been used as prognostic parameters, including KIT activating mutations, cytogentic aberrations and telomerase activity.

Australia's Biggest Morning Tea

The Cancer Council Australia's second largest national fundraising event, Australia's Biggest Morning Tea, celebrated its tenth birthday in May. More than 38,000 people hosted morning teas throughout the month, and The Cancer Council is confident that its fundraising target of $6.5 million will be met.

An estimated 1.4 million hot beverages were consumed as people around Australia took part in the event during May. While many held a simple morning tea at home or work, others hosted an event for hundreds, incorporating fashion parades, bake-offs, raffles and other activities.

The tenth year of the event was also a great opportunity to introduce a new television and radio campaign. Sydney-based advertising agency Singleton developed a new ad pro-bono, which highlights the social essence of Australia's Biggest Morning Tea.

Patenting human genes – Australian Law Reform Commission inquiry

The Cancer Council Australia has urged exemptions from patent law for the genuine, not-for-profit use of human gene sequences for research and testing.

In a submission to the current Australian Law Reform Commission inquiry into the patenting of genes, The Cancer Council said while recognising the need to respect and reward intellectual property, patent law reform should also take into account the public health good of the community.

Its preliminary submission to the inquiry also stated that consideration should be given to reviewing the patentability of naturally-occurring substances such as genetic sequences.

"While we recognise it is important that individuals and organisations should be rewarded for the ingenuity, time and funding they put into scientific research, we have grave concerns about a system that allows exclusive rights to a naturally-occurring substance if such rights are to the detriment of public health," the submission states. "We also seriously question the ethics of patenting such a discovery."

The Cancer Council strongly believes that, pending the outcomes of the Commission's inquiry, the publicly-funded genetic testing being performed at specialist clinics around Australia and not-for-profit genetic research should be allowed to continue, without penalty.

In February this year, more than 40 stakeholders attended a workshop on the patenting of genes and implications for cancer control, convened by The Cancer Council.

The Commission is due to release an issues paper – outlining the key issues it will cover in its inquiry – in July, and formal submissions will then be invited. Further information is available at www.alrc.gov.au.

Prostate cancer

A bi-partisan call for measures to improve understanding of the most common form of cancer in Australian men was welcomed by The Cancer Council Australia last month.

A Private Member's Motion on prostate cancer was moved in the House of Representatives on 2 June by Liberal MP Jim Lloyd, and seconded by Labor MP Wayne Swan. Ten MPs spoke to the motion.

The President of The Cancer Council Australia, Professor Ray Lowenthal, said The Cancer Council recognised the need for better education about the disease, as well as continued research to improve diagnosis and treatment.

"The issues around diagnosis and treatment of the disease are not straightforward, and men deserve the best possible information and advice to help them make important decisions such as whether to be tested," he said.

The Cancer Council believes that in the absence of strong medical proof that testing for prostate cancer saves lives, it is up to individual men to decide whether to be tested. Before they make this decision, they need to be fully aware of the pros and cons.

"We would support a balanced education campaign to help men reach an informed decision about whether or not to be tested," Professor Lowenthal said.

Daffodil Day

Two million fresh daffodils will be in full bloom to help The Cancer Council Australia spread the message of hope for all touched by cancer on Daffodil Day – Friday 22 August.

By purchasing a daffodil in memory of a loved one, to celebrate a survivor, or in the hope of creating a cancer-free future, supporters will help The Cancer Council Australia reach its fundraising target of $9.5 million.

Funds raised in August support research into the causes and potential cures for cancer, and fund support programs for patients and their families, a Cancer Helpline, and education programs aimed at preventing cancer.

To order merchandise or fresh daffodils to sell to friends, colleagues or customers during August, or to register as a Daffodil Day volunteer, call 1300 65 65 85 or visit www.

Find a specialist

Three more professional bodies are joining with The Cancer Council Australia to help people with cancer "find a specialist".

Members of the Medical Oncology Group of Australia and the Royal Australian and New Zealand College of Radiologists are now listed online through The Cancer Council's website: www.cancer.org.au/specialist.

The site also will soon have a link to a list of members of the Australian Society of Gynaecologic Oncologists.

These three additions join links that direct consumers to membership lists of the Colorectal Surgical Society of Australia, the Australian and New Zealand Head and Neck Society, Australasian Chapter of Palliative Medicine, the Thoracic Society of Australia and New Zealand and the Urological Society of Australasia.

CEO profiles

In each edition of Cancer Forum this year we will be profiling the CEOs of The Cancer Council Australia's member organisations.

The Cancer Council South Australia

Associate Professor Brenda Wilson

The Cancer Council South Australia appointed Associate Professor Brenda Wilson as Chief Executive Officer in February 2003.

Associate Professor Wilson has worked in the health industry for 33 years, mostly in large teaching hospitals in South Australia and also overseas. She trained as a nurse at the Royal Adelaide Hospital and has worked in a range of clinical, management and executive positions. Her most recent appointments include Executive Director of the Flinders Medical Centre, Executive Director of the Lyell McEwin Health Service, and Chief Executive and Director of Nursing at the Hampstead Rehabilitation Centre.

Associate Professor Wilson holds a Master of Business Administration (MBA), a Bachelor of Business (Health) and a Diploma of Applied Science (Nursing). She is a Fellow of the College of Health Service Executives and a Fellow of the Royal College of Nursing Australia. She is also a surveyor for the Australian Council on Health Care Standards (ACHS).

She was the recipient of the Telstra SA Business Women's Award for the Corporate and Government Sector 2000 and the Johnson & Johnson Wharton Fellow 1999, which enabled her to attend the Wharton School of Management in Philadelphia.

Associate Professor Wilson's appointment followed the resignation of Associate Professor Kerry Kirke, who had held the position of Executive Director since 1998.

The Cancer Council
Northern Territory
Helen Smith

Helen Smith was appointed as Director of Cancer Services for The Cancer Council Northern Territory in February 2003.

A Registered Nurse and Registered Midwife, Mrs Smith also holds a Diploma in Nursing Education. She has a wide range of management experience in the private sector including sports administration, but her background is mostly in nursing in Victoria and the Northern Territory, including a position as Assistant Director of Nursing of Sacred Heart Hospital in Moreland, Victoria (now called John Fawkner Private Hospital).

Before joining The Cancer Council NT, Mrs Smith was unit manager of the Medical Surgical Unit at Darwin Private Hospital. This encompassed both the chemotherapy and palliative care units.

Mrs Smith's appointment follows the resignation of Brian McCarthy.

The Cancer Council NSW
Dr Andrew Penman

A Graduate of the University of Queensland Medical School, Dr Andrew Penman subsequently pursued training in internal medicine and public health in the US. Between 1978 and 1982, as Director of the MEDEX program at the University of Washington in Seattle, his major interests were in the development and training of physician assistants and nurse practitioners and in health services research. During this period he acted as a consultant to US AID and the World Health Organisation on primary health care development projects.

Dr Penman returned to Australia in 1983 and for 13 years held a succession of positions with the Health Department of Western Australia – as Medical Officer in Halls Creek, Director of Public Health in the Pilbara Health Region and then on the Executive of the Health Department as Assistant Commissioner for Country Operations, Assistant Commissioner for Public Health, General Manager Public Health Services and Chief Health Officer.

In 1996 Dr Penman moved to New South Wales to take up the appointment as Director, Disease Prevention and Health Promotion for the NSW Health Department, and subsequently as Deputy Chief Health Officer.

In June of 1998, Dr Penman took up his appointment as Chief Executive Officer of the (then) NSW Cancer Council.

Dr Penman's interests in health have been wide-ranging. In public health and disease prevention he has had strong interest in sexually transmitted disease control, especially in remote rural areas, and has been instrumental in developing environmental health maintenance programs for Aboriginal communities, establishing community-based education programs, in diabetes, injury control and in alcohol, tobacco and other drug issues.

In clinical care, he has played a role in bringing a public health perspective to the development and evaluation of clinical services, exemplified most clearly by his authorship of the goals and targets for clinical services in Western Australia and The Cancer Council's role in getting commitment to improving cancer care. In mental health, Dr Penman has an interest in early interventions to prevent the subsequent development of mental disorders, and in cancer control Dr Penman's key interests are tobacco control, screening and adoption of best treatment practice.

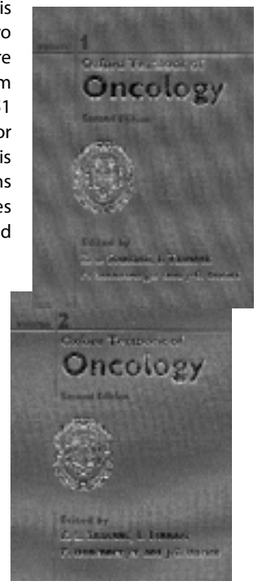
The November edition of Cancer Forum will profile The Cancer Council Tasmania's Executive Director, Lawson Ride; The Cancer Council ACT's Executive Officer, Joan Bartlett; and Professor Alan Coates AM, CEO of The Cancer Council Australia.

BOOK REVIEWS

OXFORD TEXTBOOK OF ONCOLOGY, VOLS 1 AND 2 (2nd ED)

RL Souhami, I Tannock, J-C Horiot (eds)

Published by Oxford University Press (2002)
ISBN: 0-1926-2926-3. 2,851 pages plus index.
RRP: A$1,200.00



The Oxford Textbook of Oncology is a massive work. It is split into two volumes that together measure 283mm by 224mm by 129mm and weigh 8kg. There are 2,851 pages and the index stretches for 64 pages. The list of authors is eight pages long and contains many well-respected authorities predominantly from the UK and Europe.

Like its main competitors, the Oxford Textbook of Oncology is exhaustively comprehensive in its coverage of cancer. There are 20 sections. The first seven cover the basic and clinical sciences of oncology including molecular biology, epidemiology and the scientific basis of cancer treatments. A number of special topics such as cancer in the elderly and long-term follow-up are most welcome. There is also the obligatory section on clinical trial methodology and the interpretation of evidence. The section on quality of life and psychosocial issues has a lucid and useful chapter on complementary medicine. The majority of the work covers the traditional anatomical tumour sites in the remaining 13 sections.

Clearly it is unlikely that any reviewer could thoroughly assess such a work before the next edition was published. I have taken the approach of considering a variety of topics, both familiar and unfamiliar, in an attempt to determine the depth and accuracy of reporting of well-known subjects and the didactic quality of unfamiliar subjects.

Any work of such size and with such diversity of authorship runs the risk of being uneven and fragmented. The editors and publishers have done an excellent job in selecting authors who write well and informatively. The clinical chapters appear to be well-written and thorough but cannot of course, have the depth or scope of texts devoted to a single tumour site. The quality of illustration is uniformly good. All diagrams and graphs have been re-drawn in a clear and accessible manner.

What then is the place of such a massive omnibus? Despite its size, oncologists may find the depth of coverage in some areas less than they need when dealing with unfamiliar problems. The vast complexity of modern oncology means that no practitioner can have up-to-date knowledge in every area. The Oxford Textbook of Oncology provides a ready and accessible reference (as long as you don't want to carry it too far). All oncology specialist trainees will need to work through a text of this size and scope. Trainees will find it a daunting prospect to read and absorb the large body of knowledge that the Oxford Textbook of Oncology contains. However if a trainee was familiar with a majority of its contents there is no doubt they would have enough knowledge for much of daily clinical practice.

The major competitors to the Oxford Textbook of Oncology are the tomes of similar size, De Vita and Holland's textbooks from North America. The choice between them is difficult. This reviewer does not wish to do a detailed comparison of a further 16kg and 6,000 pages and such a task is beyond all but the most obsessive purchasers. The decision will have to be made on content, range style and availability.

M Barton
Collaboration for Cancer Outcomes Research and Evaluation
Liverpool Health Service
Liverpool, NSW

100 QUESTIONS AND ANSWERS ABOUT LEUKEMIA

E Ball and G Lelek

Published by Jones & Bartlett (2003)
ISBN: 0-7637-2038-0. 130 pages plus index.
RRP: A$39.95

100 Questions and Answers about Leukemia is a book written specifically for patients, families, carers, and consumers. An American haematologist and one of his patients, a CML and bone marrow transplant survivor, authored the book.

The content is based around 100 questions and is set out in seven parts: the basics of leukemias; facts about leukemia; treatment; blood and marrow stem cell transplantation; side-effects and complications of treatment; treatment facilities and healthcare providers; and living with leukemia. It has a good glossary of terms to help people understand complex haematology jargon.

The book, at 130 pages, is clearly more detailed than the average patient education booklet generally available in Australia, and is more typical of the complex literature that people educated at higher levels require these days. Patients or carers with lower levels of literacy would struggle with the details in this book. Therein is the main benefit to clinicians who are challenged to find materials that their patients and families are able to understand. This book could help build on more basic education.

The beauty of this book is that the authors have posed the sort of questions that people do not tend to ask as they think they might be silly ones, but will wish they had asked, and are not normally covered in other patient education materials. The book manages to include succinct information that generally suits all the different sub-types of leukaemias and their different treatments – information that patients can then build upon in discussions with their own specialist.

Given the rapid advances in knowledge and treatment practices in the malignant haematology arena, this book makes a good attempt at trying to cover the bases. It proactively discusses clinical trials, study drugs and protocols.

As a book for consumers, the discussion on treatment facilities and healthcare providers is interesting. While set in an American context, the principles remain pertinent to the Australian scene: concerns about the skills and experience of the treating team; being a patient in accredited facilities; and the role and importance of family members as advocates/decision makers when ill.

The last section is rightly entitled 'living with leukemia' and addresses common rehabilitation and survivorship concerns of relapse of disease, uncertainty of full recovery of life roles and functioning and getting back into life and work.

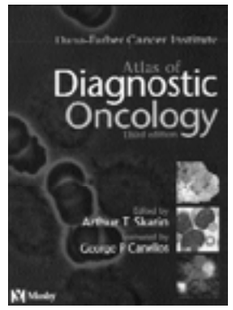
Anyone who works with patients and families would appreciate having this book to refer them to, if they need information that is more detailed. It would also provide a useful perspective for all health professional students engaged in the care of people with haematological malignancies.

G Prest
Leukaemia Foundation of NSW
Cremorne, NSW

ATLAS OF DIAGNOSTIC ONCOLOGY (3RD EDITION)

A Skarin

Published by Mosby (2002)
Distributed in Australia by Elsevier
ISBN: 0-7234-3206-6. 610 pages plus index.
RRP: A$421.69



This is the third edition of the Atlas of Diagnostic Oncology, probably the best oncology 'picture book'. It comes from the Harvard Medical School and associated hospitals but in a book like this the lack of geographical spread of the authors is of no problem.

In essence this is a series of photo-essays with colour pictures covering the entire spectrum of oncology. There are pictures of patients demonstrating physical signs. There are pictures of CTs, MRIs and imaging. There are pictures of surgical specimens and anatomical pathology and cytology. There are pictures of radiotherapy machines, scanners and other toys. And there are tables of many colours listing staging criteria and basic epidemiology and molecular information for all types of cancer.

The book is quite up-to-date and contains pictures of PET scans as staging investigations and pictures of sentinel node biopsy surgery for primary therapy. There are chapters on molecular biology, paediatric tumours, haematologic malignancies, AIDs-related malignancies, and a chapter of pictures showing all the skin reactions and other visible complications of chemotherapy. The text deals briefly with presenting symptoms and signs, diagnostic workup and the basics of treatment. For a medical oncologist these are not sufficient for a textbook, and I suspect a radiologist or pathologist will find the pictures inadequate for a textbook on cancer imaging or pathology. However for a medical oncologist or medical oncology trainee who enjoys looking at pictures then this book is ideal. As well as the book the purchase price includes a CD-ROM with all the colour slides that it is claimed (I haven't tried this yet) can easily be imported into other software such as powerpoint to help give lectures or other presentations. At roughly $400 the book and CD-ROM can be recommended to all medical oncology departments and I suspect many individuals would want their own copy.

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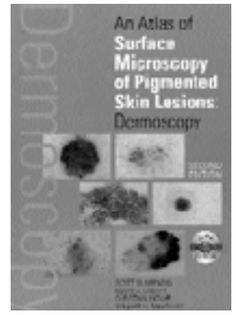
ATLAS OF SURFACE MICROSCOPY OF PIGMENTED SKIN LESIONS: DERMOSCOPY (2ND EDITION)

SW Menzies et al

Published by The McGraw-Hill Companies Inc (2003)
ISBN: 0-0747-1102-4. 171 pages plus index.
RRP: A$79.90



This atlas is an expert review of surface microscopy of pigmented skin lesions, designed to be of use to the novice as well as those experienced in regularly examining the skin. The second edition has been substantially rewritten and expanded from the first edition (published in 1996). It comes with a CD-ROM containing a quiz of 217 lesions. It is set out into eight chapters, each of which begins with a succinct description of the important features in the chapter. The greatest strength of the atlas is the clinical and histopathological correlation with the dermatoscopic features. All but three benign lesions in the book were biopsied and reviewed for histological diagnosis. The clarity of the photographs throughout the book are excellent, as are the images on the CD attached to the atlas.

As well as comprehensively defining the important individual diagnostic features used in surface microscopy, Menzies et al describe a (two-step) surface microscopy method for the diagnosis of pigmented skin lesions, which the newcomer to surface microscopy will find very useful. Initially the lesion is identified as melanocytic or non-melanocytic. If the lesion is identified as melanocytic, then a second step procedure is used to differentiate between benign melanocytic lesions and melanoma. At least one of nine positive features must be found and both negative features (symmetrical pigmentation pattern and the presence of only a single colour) must be absent. Although there are a number of other diagnostic algorithms that can be used, this system is simple and easily learned. This algorithm can then be applied to identifying images on the CD-ROM. The 'help' page very clearly describes the method and how it is used to work through the quiz images. These can be looked at in random, diagnostic or features order, depending on the requirement of the user.

The last chapter briefly discusses the use of digital (computerised) surface microscopy systems. This is a very topical issue and perhaps could have been covered in more detail. Some may disagree with the idea of short-term monitoring of atypical or changing melanocytic lesions, but the authors do include strict criteria for excising such lesions over a three-month period.

Skin surface microscopy is a tool which has been shown to improve the diagnosis of pigmented lesions and this publication will be an invaluable aid to all those clinicians who are presented with skin lesions for diagnosis.

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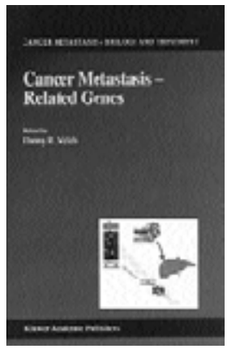
Cancer metastasis: related genes

DR Welch (ed)

Kluwer Academic Publishers (2002)
ISBN: 1-4020-0229. 265 pages plus index.
RRP: US$115.00



As stated in the preface, "relatively little is known about the control of the metastatic process at the molecular level". This book explores current knowledge of factors that control the metastatic phenotype. To date, only a limited number of genes have been shown to functionally regulate the metastatic cascade, required for the spread of cells from the primary tumour to secondary sites. To be mentioned in this book, genes thought to be involved in the metastatic process are those that have been validated in vivo. They include a series of metastasis-promoting genes involved in tumor progression, including components of the MAP kinase signalling cascade, and metastasis-suppressor genes, including AP2, KiSS1, BRMS1, MKK4, KAI-1, NM23 and others.

Mechanisms through which the expression of these genes is regulated are discussed. These include the roles potentially played by transcription factors (and their identification), growth factors and their receptors (eg autocrine motility factor and its receptor), diet and restriction of specific amino acids, members of the stress-activated MAP kinase family, and heterochromatin associated protein. Interactions of the cell surface with other cells, or with the surrounding matrix, through surface adhesion molecules, integrins, selectins, cadherins, Ig superfamily proteins, tetraspan molecules, proteolytic enzymes and their receptors, and other cooperative molecules, are discussed.

As this area is relatively young, each chapter is written in the style of a summary work-in-progress, with future plans for further experimentation. The book is generally well-written and easy-to-read, despite its complexity. Unfortunately, the figures and tables have been omitted from chapter four, though reference is made to them.

The whole area of factors involved in the metastatic cascade and its genetic background, together with the array of potential interactions between the multiple factors, is tantalizing. It is not yet clear whether metastasis-suppressor genes are specific to particular types of cells or have a general role in cancer.

The book is suitable for researchers in the field, and for students, rather than for clinicians, as most of the work is at the preclinical evaluation stage.

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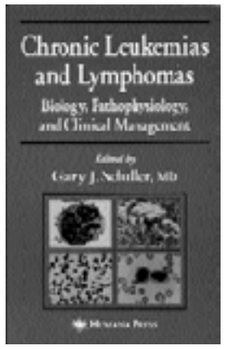
Chronic leukemias and lymphomas

GJ Schiller (ed)

Published by Humana Press (2003)
ISBN: 0-8960-3907-2. 327 pages plus index.
RRP: US$135.00



This compact volume is one of the Current Clinical Oncology series and is edited by Gary Schiller from the UCLA School of Medicine. It consists of 12 chapters written by a total of 22 authors. The majority of contributors are haematologists from American institutions and include such authoratative figures as KR Rai. Each chapter is individually referenced and the format is that of a collection of up-to-date review articles, rather than a classical textbook.

Chronic Leukemias and Lymphomas addresses the aetiology, clinical features, pathology, prognosis and management of the chronic haematological neoplasms. Chapter one is an interesting summary of the history, epidemiology and risk factors relating to chronic leukaemias. Subsequent chapters cover each of the chronic leukaemias, including chronic lymphocytic, hairy cell, prolymphocytic and chronic myeloid types, lymphomas (low-grade, aggressive large-cell and Hodgkin's disease), the myeloproliferative syndromes and multiple myeloma. Two less common disorders, Sézary syndrome and the Large Granular Lymphocyte proliferative diseases, have a chapter each and over 20% of the total text devoted to them. Despite the apparent overemphasis of epidemiologically rarer disorders, these two chapters review in comprehensive detail topics that may not be so well-covered elsewhere.

The preface to the book states that its purpose is to focus on the biological features of the diseases. The best example of this aim is found in chapter nine, in which there is a very detailed description of immunophenotypes, cytokines, HHV-8 and chromosomal and genetic abnormalities in relation to multiple myeloma. The use of multiple sub-headings in this section helps maintain clarity and readability, as it does throughout the book.

As a trainee in Haematology, I found the thorough sections on clinical management in each of the chapters especially useful. Currently accepted regimens, and the evidence for them, are well-outlined, as are the relevant studies referenced to enable further reading. Recent advances and concepts, as well as ongoing trials, are also described. The emphasis on current treatment options also makes this text a useful resource for clinical haematologists and oncologists managing patients with the disorders described.

At a cost of US$135 this book is unlikely to be purchased by individual trainees, however it would be an excellent reference in a Haematology department's collection or hospital library.

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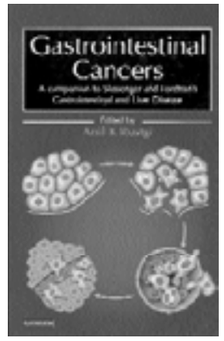
Gastrointestinal cancers

A Rustgi (ed)

Published by Sanders (2003)
Distributed in Australia by Elsevier
ISBN: 0-7216-8963-9. 732 pages plus index.
RRP: A$324.50



This large textbook of gastrointestinal cancer has 81 contributing multidisciplinary authors who are mainly from the US although 11 contributors are international. It combines a review of the molecular and cellular biology, physiology and pathology of gastrointestinal malignancies with clinical aspects of diagnosis, evaluation and management. The book is designed for both clinicians as well as basic science researchers.

The book is divided into two parts. The first covers the fundamentals of gastrointestinal oncology, with sections on principles of oncogenesis, pathology of gastrointestinal cancers, diagnostic and therapeutic approaches and principles of patient care. The oncogenesis chapter begins from first principles with the cell cycle progressing through the role of cyclin dependent kinases, signal transduction, oncogenes, proto-oncogenes, tumour suppressor genes and peptide growth factors. Mechanisms of tumour invasion and metastasis including the role of angiogenic factors, adhesion molecules and proteinases are covered. The second part of the book is on organ-based oncology and builds on the fundamentals of the first part. It covers in great detail the epidemiology, risk factors, molecular genetics, screening, clinical presentation, diagnosis, therapy and future directions for each tumour type.

The book has been edited to make it relevant to an international multidisciplinary audience. For example data regarding incidence of each malignancy include figures from a range of Western and underdeveloped countries to compare and contrast geographical variations. Comparisons are made of Japanese and US staging systems for gastric cancer. There is a chapter on iaparoscopy discussing its role, oesophagastric, colon, pancreatic and liver cancers. Another good chapter analyses the issues of the strength of evidence on efficacy and cost effectiveness of colorectal screening, surveillance of ulcerative colitis and Barrett's oesophagus.

The chapters are in general up-to-date (circa 2001) and cover the role of new drugs such as oxaliplatin and irinotecan in colorectal cancer and imatinib mesylate in gastrointestinal stromal tumours. Mention is made of the rationale behind novel agents undergoing evaluation such as the monoclonal antibody C225, farnesyl transferase inhibitors, matrix metaloproteinase inhibitors, COX-2 inhibitors and gene therapy techniques using adenoviral vectors. Some chapters suffer from an American bias where important European studies have not been mentioned.

In summary this is a comprehensive GI oncology text that would be a good reference for gastroenterologists, surgeons, oncologists and scientists alike.

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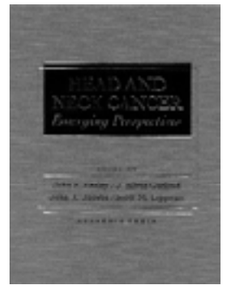
Head and neck cancer: emerging perspectives

J Ensley et al

Published by Academic Press (2003)
ISBN: 0-1223-9990-0. 591 pages plus index.
RRP: A$585.73



As an up-to-date reference text designed for clinicians and researchers in the field, this book presents North American evidence-based expert opinion on the management of head and neck cancers. It summarises pathogenesis, epidemiology, investigation and treatment as well as the current molecular knowledge and some of the more promising scientific research.

Perhaps more than any other cancer, the treatment of head and neck cancer involves a team approach. John Ensley of Detroit, Michigan and his co-editors have collaborated with a pre-eminent team of North American surgeons, radiation and chemotherapy oncologists, pathologists, epidemiologists and scientists to write this reference text.

The book is divided into five parts. A short introduction includes precancerous lesions and staging, and is suitable for oncologists or surgeons. The detailed second part covers the genetic, molecular and cellular pathogenesis of head and neck cancer. The up-to-date summaries of scientific results would more than suffice as reference for surgeons or oncologists and would be useful background reading for scientists proposing research in this field.

A substantial third part discusses the North American epidemiology as well as ongoing trials into head and neck cancer prevention including a chapter on statistical analysis and molecular detection. This is a detailed discussion about current developments that may form the basis of future treatments.

As a clinician I feel the fourth part is the highlight. In under 200 pages, some of the foremost experts in North American surgery, radiation and chemotherapy, discuss their treatment of common head and neck cancers. The less common tumours such as parotid and sinonasal tumours are omitted with more detailed discussion on difficult management problems in the more common tumours, such as a chapter on management of the carotid artery.

My one criticism of the treatment section is the under-representation of non-North American literature in the references. Like many areas of medicine, North American treatment of head and neck cancer is of a high standard but may underplay important developments outside North America. The current Australian head and neck cancer management, for

instance, has been revolutionised by Steiner and others in Germany who have used laser instead of chemoradiotherapy for voice preservation in laryngeal tumours. This is barely mentioned in the text.

Finally, the fifth part outlines the more promising developments in head and neck cancer research including gene therapy, immunology and molecular assessment of surgical margins.

I would recommend this text to libraries as a reference for researchers, surgeons and oncologists involved in head and neck cancer. It is well-written, very up-to-date and well-researched. It would help inform each member of the treating team about the others' field. Its major drawback is that North American practice is not exactly Australian practice but we are certainly very similar and have much to learn from one another.

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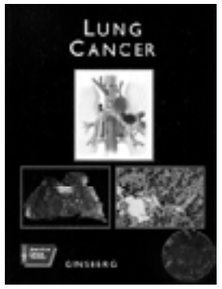
Lung cancer



RJ Ginsberg (ed)

Published by B C Dekker (2002)
Distributed in Australia by Elsevier
ISBN: 1-5500-9099-2. 175 pages
plus index.
RRP: A$210.48

This book on lung cancer is one of the Atlas series by the American Cancer Society. This volume is edited by Robert J Ginsberg, a well-known and leading clinician researcher in the field of lung cancer.

The book is divided into 13 chapters ranging from the epidemiology of lung cancer to clinical features, work-up and selected chapters on the therapy of this awful disease.

Overall the atlas is beautifully presented with succinct text descriptions as well as numerous high quality photographs and some schematic drawings. The colour reproduction is very realistic, making this a very attractive book to read even when one has just a few minutes to spare. The converse is that while most topics are very well written and concise, there is only a limited reference list and the very interested will need to look further into primary citations. Nevertheless, the atlas does a very good job at being an atlas.

Each chapter is generally very readable and highlights many of the most important issues in current lung cancer management. Clearly, there are rapid advances in certain aspects of lung cancer management that mean that some of the newer innovations are not well covered, such as endobronchial and endoscopic ultrasound. On the other hand, it is very strong in areas where there has been adequate time for a new test or intervention to be evaluated. It would have been nice to have a little bit more on spiral CT (low dose) for lung cancer screening because of its highly topical nature.

In terms of the therapy chapters, important concepts and practical management issues are well-discussed. The chapter on the advances in the treatment of metastatic non-small cell lung cancer is very clear in terms of the possible agents that have proven efficacy. It would have been nice to have a bit more on the targeted biological therapies, which admittedly is discussed briefly in chapter 13. This chapter contains a hotch-potch of various topics, which though mentioned in the earlier chapters, are nonetheless important for their potential impact in the future.

Overall, this book is a very beautifully illustrated atlas, produced in combination with concise descriptions. It also comes with a mini CD-ROM and will be an important component of any substantial library of lung cancer publications.

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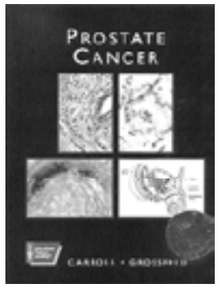
Prostate cancer



P Carroll et al (ed)

Published by B C Decker (2002)
Distributed in Australia by Elsevier
ISBN: 1-5500-9130-1. 386 pages
plus index.
RRP: A$306.05

This is one of a series of Atlases of Clinical Oncology endorsed by the American Cancer Society that cover a diverse range of oncological subjects. These books are issued with a CD-ROM inside the front cover, available as a package only. The CD provides the complete text and colour illustrations, aiming, according to the publishers "to complement traditional … learning methods".

Prostate Cancer provides an overview of the aetiology, epidemiology, genetics, anatomy, pathology and management of prostate cancer. It is extensively referenced and provides the reader with a fairly comprehensive review of relevant research, both at the molecular and clinical level. It does not, however, attempt to synthesise many of the controversies of the management of prostate cancer into clinically useful recommendations, and for this reason should be viewed more as an information resource. Readers seeking practical guidelines for the management of their patients would be disappointed.

The reviewer, as a radiation oncologist, found the radiotherapy sections disproportionately brief in relation to the importance of this modality in the treatment of the disease and in comparison with more esoteric sections dealing with newer experimental local therapies, such as high-intensity focused ultrasound (HIFU) and thermal therapy. There is clearly a surgical slant in the authorship and chapter structure although the discussion of management options is reasonably balanced on the whole. The book has strong sections on the nature and management of post-treatment morbidities, relating both to surgery and radiotherapy.

There is a detailed chapter on the palliative management of prostate cancer patients, although again, the useful role of radiopharmaceutical agents in this setting, such as Strontium-89, were in the reviewer's opinion, underplayed in contrast to less proven options. The extensive use of complementary and alternative medicines in this disease are appropriately highlighted in their own chapter. Unfortunately but inevitably perhaps, some sections, like the one on bisphosphonates, are already out-of-date.

Overall, I think this is a useful resource for clinicians, students or scientists interested in prostate cancer and the electronic format may make it more attractive for some readers – in fact providing two complete volumes for the price of one.

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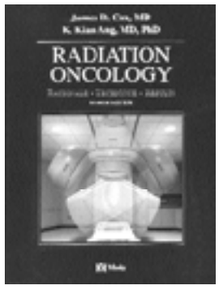
Radiation oncology



J Cox et al

Published by Mosby (2003)
ISBN: 0-7216-7494-1. 1,002 pages
plus index.
RRP: A$368.50

The only difficulty I had reviewing this new textbook by Cox and Ang, was retrieving it from registrars and fellow consultants once the word about the text circulated through the department. It is the textbook of radiation oncology. It is comprehensive and authoritative.

The initial four chapters cover the general principles of radiobiology, physics, combining radiotherapy with surgery and radiotherapy combined with chemotherapy. This is not an unusual approach in such a textbook, however, it is in these chapters we start to see what differentiates this text from other similar RT 'bibles'. The discussion of fractionation is such an example. This extends from the theoretical to a discussion of clinical trial results and then the lessons learned from fractionation trials. This pattern is followed through the textbook where clinical results are not only presented but there is an overview to place the relevance of the results before the reader. The rest of the textbook follows a standard approach of chapters dedicated to an organ or a region. This however extends to coverage of all topics relevant to a particular region. For example the chapter on the eye covers pterygia, benign tumors and graves opthalmopathy.

Every chapter has an extensive coverage of the acute and late effects of radiotherapy. The coverage of organ toxicity far exceeds any other textbook that I am aware of, both in terms of clarity and comprehension. The text also tackles controversial issues in a manner which is scientifically rigorous and easy to understand. An example of such is the discussion of controversial areas in the management of thyroid carcinoma, including the rationale of radioactive iodine and the aspects of follow up including radioactive iodine scans.

The textbook also has a colour plate section that is largely related to computer dosimetry. There are three histology plates and one clinical photo of peau d'orange. I am a little curious as to why they have added just the one such clinical photo.

There is the failure to describe dose prescriptions in terms of ICRU terminology, namely GTV, PTV and CTV. These concepts are mentioned in the preliminary chapters but are rarely mentioned in the general text.

The text is stated as being the eighth edition. It previously appeared under the lead author of Moss, however significant revisions make the book fresh. The authors should be rewarded with establishment of this textbook as the major reference source for radiation oncology registrars and fellows. I would recommend it be immediately added to any oncology library and indeed to our college training syllabus.

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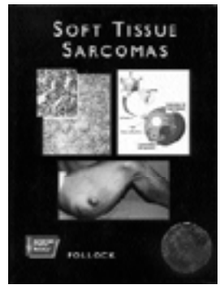
Adelaide, SA



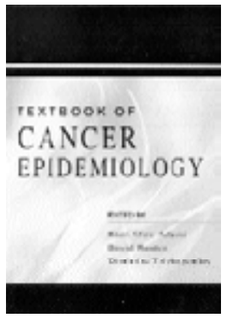
Soft tissue sarcomas

R Pollack (ed)

Published by BC Decker (2002) Distributed in Australia by Elsevier
ISBN: 1-5500-9128-x. 414 pages plus index.
RRP: A$323.34

This is one of a series of Atlases of Clinical Oncology published by the American Cancer Society. Its editor is Dr Raphael Pollock, Chairman of Surgical Oncology at MD Anderson Cancer Center in Houston.

This is a handsome text, lavishly illustrated and beautifully presented. It is comprehensive with chapters on epidemiology, pathology, imaging, biopsy and staging and prognosis followed by sections on various anatomical sites. There are then chapters covering topics such as radiotherapy, chemotherapy, metastasis, local recurrence and rehabilitation.



There is extensive coverage of the common and uncommon sites and types of sarcoma. In addition, there is good coverage of the borderline pathologies such as atypical lipomata that frequently give rise to confusion. The chapter on radical amputations is welcome – these procedures are rarely performed, but must be in the armamentarium of the surgical oncologist caring for patients with sarcoma. Recent developments in the molecular biology and pharmacology are included, but will necessarily become dated quickly.

Most of the authors are faculty members and the institutional approach of the MDACC is apparent, with many references to investigational institutional protocols. Discussion of pre- versus post-operative EBRT reveals a similar institutional influence.

As with most multi-author texts, there is repetition and variability between chapters. The advantage is that each of the sections stands alone and can be used as a reference, but the depth of coverage of the topics varies, and the message is not always consistent.

Selection of what should be included in a text and to what depth is always challenging. There are some inconsistencies in the choices, such as the 21 pages on extremity sarcomas and 26 pages on head and neck sarcomas. The important issues are well-covered, although areas such as the surgical strategy for retroperitoneal sarcoma need more emphasis.

The imaging section is disappointing. There is a very technical discussion of MRI techniques followed by presentation of many images. Unfortunately the resolution is variable, and the labeling of images is sparse. Inclusion of images of the common differential diagnoses that may be confused with sarcoma is vital in this type of work.

The important issues of screening for recurrence needs better editing. The chapter on imaging suggests that surveillance MR should be done three to six monthly. The section on staging and prognosis points out that local recurrence does not influence overall survival, and the section on extremity sarcoma reports that almost all recurrences are detected clinically, throwing doubt on the need for any routine follow-up imaging.

This is an excellent book for advanced surgical trainees with an interest in surgical oncology. Surgical oncologists will find it useful as a reference when encountering less common lesions. At $323 it is unlikely that general surgeons or orthopaedic surgeons without a specific interest could justify the cost. It makes an excellent addition to a surgical library. It comes with a CD-ROM for easy reference and for preparation of lectures.

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Textbook of cancer epidemiology

H-O Adami et al (eds)

Published by Oxford University Press (2002)
ISBN: 0-1951-0969-4. 575 pages plus index.
RRP: A$195.00

This is a new textbook, edited by Hans-Olov Adami, David Hunter and Dimitrios Trichopoulos, with contributions from 24 experts from Europe, North America and Australia. Highly

Calendar of meetings

Calendar of meetings – Australia and New Zealand

Date	Name of Meeting	Place	Secretariat
2003			
July			
24-25	Royal College of Nursing Australia National Conference	Gold Coast QLD	Royal College of Nursing PO Box 219 Deakin West ACT 2600 Tel: +61 2 6282 5633 Fax: +61 2 6282 3565 Email: canberra@rcna.org.au Web: www.rcna.org.au
25-26	6th Annual CNSA Winter Congress	Sydney NSW	Michelle McBean MP Events Suite 1, 2 Walton Street Kew VIC 3101 Tel: +61 3 9852 9941 Fax: +61 3 9852 9961 Email: michelle@mpevents.com.au
August			
15-17	5th Annual Scientific Meeting of the Australasian Gastro-Intestinal Trials Group	Canberra	Australasian Gastro-Intestinal Trials Group Locked Bag 77 Camperdown NSW 1450 Tel: +61 2 9562 5072 Fax: + 61 2 9562 5094 Email: AGITG@ctc.usyd.edu.au Web: www.gicancertrials.org.au
24-29	World Congress on Medical Physics and Biomedical Engineering Debates on Radiation Oncology and Chemotherapy	Sydney NSW	Tour Hosts GPO Box 128 Sydney NSW 2001 Tel: +61 2 9248 0800 Fax: +61 2 9248 0894 Web: wc2003@tourhosts.com.au
September			
3-6	kConFab, Australian Ovarian Cancer Study and Family Cancer Clinics of Australia and NZ "Familial cancer 2003: Research and Practice"	Couran Cove QLD	Heather Thorne Peter MacCallum Cancer Institute, Melbourne Email: heather.thorne@petermac.org Web: http://www.kconfab.org/
9-12	7th Australian Palliative Care Conference – Time to Reflect	Adelaide SA	Lesley K Woods APMEA Conventions 68 Greenhill Road Wayville SA 5034 Tel: +61 8 8274 6055 Fax: +61 8 8274 6000 Email: lwoods@sapmea.asn.au Web: www.sapmea.asn.au
November			
15-19	6th International Symposium on Paediatric Pain: "Pain in Childhood: The Big Questions"	Sydney NSW	Dianna Crebbin DC Conferences Pty Ltd PO Box 571 St Leonards NSW 2065 Tel: +61 2 9439 6744 Fax: +61 2 9439 2504 Email: mail@dcconferences.com.au
16-20	9th International Conference on Oral Cancer	Melbourne VIC	ICMS 84 Queensbridge Street Southbank VIC 3006 Tel: +61 3 9682 0244 Fax: +61 3 9682 0288
26-28	30th COSA Annual Scientific Meeting	Perth WA	Ruth Lilian Pharma Events PO Box 265 Annandale NSW 2038 Tel: +61 2 9280 0577 Fax: +61 2 9280 0533 Email: conferences@pharmaevents.com.au
28-29	Sentinel Lymph Node Biopsy and Block Dissection	Perth WA	Dr Robert Davies CTEC University of Western Australia Email: rjdavies@cyllene.uwa.edu.au Web: www.ctec.uwa.edu.au

2004

April

25-29	18th World Conference on Health Promotion and Health Education	Melbourne VIC	Conference Manager Tel: + 61 3 9667 1313 Fax: +61 3 9667 1375 Email: 2004wchphe@vichealth.vic.gov.au

August

4-8	International Society for Nurses in Cancer Care 13th International Conference on Cancer Nursing	Sydney NSW	MP Events Tel: +61 3 9852 9941 Fax: +61 3 9852 9961 mail: enquiries@mpevents.com.au

November

21-26	Australian Health and Medical Research Congress	Sydney NSW	The Australian Society for Medical Research 145 Macquarie Street Sydney NSW 2000 Tel: +61 2 9256 5450 Fax: +61 2 9252 0294 Email: asmr@world.net Web: www.asmr.org.au
24-26	31st COSA Annual Scientific Meeting	Canberra ACT	Clinical Oncological Society of Australia GPO Box 4708 Sydney NSW 2001 Ph: +61 2 9036 3100 Fax: +61 2 9036 3101 Email: cosa@cancer.org.au

CALENDAR Of MEETINGS – International

Date	Name of Meeting	Place	Secretariat
2003			

August

3-8	12th World Conference on Tobacco or Health: Global Action for a Tobacco Free Future	Helsinki Finland	Dr Lisa Elovainio, MD, Secretary Gen Cancer Society of Finland & Pres Finnish Centre for Health Promotion Helskini, Finland Fax: +358 9 135 1093 Email: lisa.elovainio@cancer.fi
10-14	10th World Conference on Lung Cancer	Copenhagen Denmark	International Conference Services Vancouver, Canada Fax: +1 604 681 1049 Email: franziska@meet-ics.com Website: www.2003worldlungcancer.org
31 Aug – 2 Sept	Brachytherapy for Prostate Cancer	Kiel Germany	ESTRO Office avenue E. Mounierlaan 83/12 1200 Brussels Tel: +32 2 775 9340 Fax: +32 2 779 54 94 Email: info@estro.be Website: www.estro.be
31 Aug – 4 Sept	Physics for Clinical Radiotherapy	Leuven Belgium	ESTRO Office avenue E. Mounierlaan 83/12 1200 Brussels Tel: +32 2 775 9340 Fax: +32 2 779 54 94 Email: info@estro.be Website: www.estro.be

September

15-18	7th ESTRO Meeting on Physics and Radiation Technology for Clinical Radiotherapy	Geneva Switzerland	ESTRO Office avenue E. Mounierlaan 83/12 1200 Brussels Tel: +32 2 775 9340 Fax: +32 2 779 54 94 Email: info@estro.be Website: www.estro.be
21-25	ECCO 12 – the European Cancer Conference	Copenhagen Denmark	FECS Conference Unit Brussels, Belgium Fax: +322 775 0200 Email: ECCO12@fecs.be Website: www.fecs.be
21-25	22nd Annual European Society for Therapeutic Radiology and Oncology (ESTRO 22)	Copenhagen Denmark	ESTRO Office Brussels, Belgium Fax: +322 779 5494 Email: info@estro.be Website: www.estro.be
23-25	2nd International Symposium on signal transduction modulators in cancer therapy	Amsterdam Netherlands	Symposium Secretariat STM-2003 PO Box 77 3480 DB Harmelen The Netherlands Tel: +31 3 4856 7667 Fax: +31 3 4844 6057 Email: congress@nddo.org Web: www.nddo.org

October

8-11	17th Asia Pacific Cancer Conference	Bali Indonesia	Indonesian Society of Oncology Dept of Anatomic Pathology Faculty of Medicine University of Indonesia PO Box 3929 Jakarta 10039, Indonesia Tel: +62 2 1392 8829 Fax: + 62 2 1392 8829 Email: apcc17@cbn.net.id
8-11	SIOP 2003: International Society of Paediatric Oncology	Cairo Egypt	SIOP, Congrex Holland Amsterdam, The Netherlands Fax: +31 (0)20 5040 225 Email: siop@congrex.nl Website: www.congrex.nl
12-16	Basic Clinical Radiobiology	Santorini Greece	ESTRO Office Brussels, Belgium Fax: +322 779 5494 Email: info@estro.be Website: www.estro.be
19-23	45th ASTRO Annual Meeting American Society for Therapeutic Radiology and Oncology)	Salt Lake City Utah USA	ASTRO Fairfax, Virginia, USA Fax: +1 703 502 7852 Email: meetings@astro.org Website: www.astro.org

November

2-7	XVI FIGO World Congress of Gynecology and Obstetrics	Santiago de Chile Chile	International Federation of Gynecological Oncologists London, United Kingdom Fax: +44(0) 207 935 0736 Email: figo@figo.org Website: www.figo.org/figo2003.asp
9-14	Evidence-Based Radiation Oncology: Methodological Basis and Clinical Application	Lisbon Portugal	ESTRO Office Brussels, Belgium Fax: +322 779 5494 Email: info@estro.be Website: www.estro.be
19-21	10th Hong Kong International Cancer Congress	Pokfulam Hong Kong	10th HKICC Congress Secretariat Department of Surgery University of Hong Kong Medical Centre Queen Mary Hospital Hong Kong Tel: +852 2818 0232 Fax: +852 2818 1186 Email: mededcon@hku.hk Website: www.hkicc.org

December

3-6	26th Annual San Antonio Breast Cancer Symposium	San Antonio Texas USA	Cancer Therapy & Research Center SACI, Rich Markow San Antonio, Texas, USA Fax: +1210 949 5009 Email: Rmarkow@saci.org Website: www.sabcs.org

2004

January

26-28	40th Annual Meeting of the Society of Thoracic Surgeons	San Antonio Texas USA	Society of Thoracic Surgeons Chicago, Illinois, USA Fax: +1312 527 6635 Email: sts@sba.com

February

15-17	2nd Multidisciplinary Colorectal Cancer Congress	Noordwijk Netherlands	Congress Care PO Box 440 5201 AK's-Hertogenbosh Netherlands Te: +31 7 3683 1238 Email: info@congresscare.com Web: www.colorectal2004.org

March

16-20	4th European Breast Cancer Conference	Hamburg Germany	EBCC 2004 Secretariat Federation of European Cancer Societies Avenue E Mounier 83 Brussels, Belgium 1200 Tel: +32 0 2775 0201 Email: ebcc4@fecs.be Web: www.fecs.be/conferences/ebcc4
18-21	57th Annual Cancer Symposium of the Society of Surgical Oncology	New York City New York USA	D K Kubis, SSO Arlington Heights, Illinois, USA Fax: +1847 427 9656 Email: diannekubis@acaai.org Website: www.surgonc.org

27-31	95th Annual Meeting of the American Association for Cancer Research (AACR)	Orlando Florida USA	American Association for Cancer Research Philadelphia, Pennsylvania, USA Fax: +1 215 351 9165 Email: meetings@aacr.org Website: www.aacr.org
31 Mar- 3 Apr	12th Congress of the European Society of Surgical Oncology	Budapest Hungary	ESSO 2004 Secretariat Federation of European Cancer Societies Avenue E Mounier 83 Brussels, Belgium 1200 Tel: +32 0 2775 0201 Email: esso4@fecs.be Web: www.fecs.be/conferences/esso4
April			
29 April – 2 May	Oncology Nursing Society (ONS) 29th Annual Congress	Anaheim California USA	ONS, Meeting Services Team Pittsburg, Pennsylvania, USA Fax: +1412 921 6565 Email: meetings@ons.org Website: ww.ons.org
June			
5-8	40th ASCO: Annual Conference for the American Society of Clinical Oncology	New Orleans LA USA	ASCO 1900 Duke Street Suite 200 Alexandria, Virginia 22314 USA Tel: +17 0 3299 0150 Email: asco@asco.org
July			
3-6	18th Meeting of the European Association for Cancer Research	Innsbruck Austria	EACR 18 Secretariat Federation of European Cancer Societies Avenue E Mounier 83 Brussels, Belgium 1200 Tel: +32 0 2775 0201 Email: eacr18@fecs.be Web: www.fecs.be/conferences/eacr18
September			
16-19	SIOP 2004: International Society of Paediatric Oncology	Oslo Norway	Congrex Holland BV PO Box 302 Amsterdam, Netherlands 1000 AH Tel: +31 2 0504 0200 Email: siop@congrex.nl Web: www.siop.nl
October			
3-7	ASTRO: 46th Annual Meeting	Atlanta USA	American Society for Therapeutic Radiology and Oncology 12500 Fair Lakes Circle Suite 375 Fairfax, Virginia 22033 USA Tel: +17 0 3227 0170 Email: meetings@astro.org
3-8	10th Biennial Meeting of the International Gynecologic Cancer Society	Edinburgh Scotland	International Gynecologic Cancer Society PO Box 6387 Louisville, Kentucky, USA Tel: +1 50 2891 4460 Web: www.igcs.org
24-28	23rd Annual European Society for Therapeutic Radiology and Oncology Meeting (ESTRO 23)	Amsterdam Netherlands	ESTRO 23 Secretariat Avenue E Mounier 83 Brussels, Belgium 1200 Tel: +32 2775 9340 Email: info@estro.be Web: www.estro.be
29 Oct- 2 Nov	29th European Society for Medical Oncology Annual Meeting	Vienna Austria	ESMO Secretariat via la Santa 7 CH-6962 Viganello-Lugano, Switzerland Tel: +41 9 1973 1919 Web: www.esmo.org/congress2004
December			
3-6	27th Annual San Antonio Breast Cancer Symposium	San Antonio Texas USA	Cancer Therapy & Research Center SACI, Rich Markow San Antonio, Texas, USA Fax: +1210 949 5009 Email: Rmarkow@saci.org Website: www.sabcs.org
15-16	4th International Meeting of Hepatocellular Carcinoma: Eastern and Western Experiences	Wanchai Hong Kong	4th HCC-EWE Congress Secretariat Department of Surgery, University of HongKong Medical Centre Queen Mary Hospital, Pokfulam Tel: + 85 2 2818 0232 Fax: + 85 2 2818 1186 Email: hccewe04@hku.hk Web: www.hcc-ewe.org

2005

April			
16-20	96th Annual Meeting of the American Association for Cancer Research	Ahaheim California USA	AACR 615 Chestnut Street 17th Floor Philadelphia, PA USA 19106-4404 Tel: + 1 21 5440 9300 Email: meetings@aacr.org
28 Apr- 1 May	Oncology Nursing Society's 30th Annual Congress	Orlando Florida USA	Oncology Nursing Society 125 Enterprise Drive Pittsburgh, Pennsylvania 15275-1214 USA Tel: +1 86 6257 4667 Email: meetings@ons.org Web: www.ons.org
June			
23-26	2nd Quadrennial Meeting of the World Federation of NeuroOncology	Edinburgh Scotland	EANO 6 Secretariat Federation of European Cancer Societies Avenue E Mounier 83 Brussels, Belgium 1200 Tel: +32 0 2775 0201 Email: eano6@fecs.be

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
Cancer Foundation of 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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Professor A Coates AM, MD, FRACP, AStat

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Assoc Professor S Smiles RN, RM, ICC, BHA, GradDipPSEM
Dr R Walters RFD BMedSc, MBBS, RACGP
Professor J Ward MBBS, MHPEd, FAFPHM, PhD
Dr K White PHD

THE CLINICAL ONCOLOGICAL SOCIETY OF AUSTRALIA INC

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

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

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President Elect
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Dr D Goldstein MBBS, MRCP (UK), FRACP
Professor J Thompson BSc(Med), MBBS, FRACS, FACS, MD

MEMBERSHIP

Further information about COSA and membership applications are available from
GPO Box 4708, Sydney, NSW 2001.

Membership fees for 2003

Ordinary Members: $140
Associate Members: $80
(includes GST)

INTEREST GROUPS

Breast Oncology
Cancer Research
Data Managers
Epidemiological
Gastrointestinal Oncology
Gynaecological Oncology
Lung Oncology
Medical Oncology
Melanoma and Skin
Oncology Nursing
(Cancer Nurses Society of Australia)
Paediatric Oncology
(ANZ Childhood Cancer Study Group)
Palliative Care
Pharmacy
Psycho-Oncology
Radiation Oncology
Regional and Rural Oncology
Social Workers
Surgical Oncology