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FORUM: Pancreatic cancer

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Awards

Reports

PANCREATIC CANCER

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Abstract

Adenocarcinoma of the pancreas* takes the lives of 2500 Australians annually and because of the devastating effects of its diagnosis, has long been the poor cousin to other cancers. People with pancreatic cancer rarely survive to be champions of this disease. It has been noted to have the highest mortality to incidence ratio of any cancer and by 2020, will likely have the highest mortality of any cancer. Accordingly it is imperative that we drive awareness, research and treatment of this disease. Australia is privileged to have some of the best researchers in the world in the field of pancreatic cancer. This issue of *Cancer Forum* aims to take you through carcinogenesis, genomics and biology, and then into the clinical realms of epidemiology, diagnostics, treatment and palliation of pancreatic cancer. In each chapter we have asked Australian researchers and clinicians to review current knowledge, and then to inform us of their own practice.

Pancreatic cancer is a lethal disease with a five year survival of less than 5%.[1] The majority of patients present with locally advanced, or metastatic disease that is not amenable to surgical resection, which currently offers the only chance of cure. Of the 10-20% of patients who undergo resection the majority (~80%) still succumb with a median survival of less than two years.[2] Long-term survivors are rare and usually associated with those who undergo resection for small non-metastatic tumours with negative margins and clear lymph nodes.[3,4] This poor survival is partly responsible for the significant delay in understanding of pancreatic cancer when compared to commoner cancers with better survival.

Fortunately, recent advances in technology have accelerated our understanding of the biology of pancreatic cancer and tumour-host interactions. Recent initiatives such as the Australian Pancreatic Cancer Genome Initiative (APGI, pancreaticcancer.net.au/apgi) and the International Cancer Genome Consortium (ICGC, icgc.org) have seen major progress in the acquisition of high quality biospecimens for molecular studies in comprehensive cancer cohorts. Whole genome sequencing has facilitated identification of potentially actionable genomic changes with greater sensitivity and specificity.[5,6] Nic Waddell, a senior biostatistician on the APGI/ICGC project, summarises those findings for us.[7] As tissue requirements and costs for genome sequencing decrease, the potential to select treatments in a 'personalised' manner based on tumour biology moves closer to the clinic.[8]

Understanding biology underpins understanding cancer development and informs treatment

Andreia Pinho and colleagues review the mounting evidence that stromal factors may be crucially important not only in determining the development and behaviour of carcinoma, but in influencing treatment response and, ultimately, prognosis.[9] Stromal and epithelial cells may interact through direct cell-cell contact, or via paracrine signalling, and various non-cellular components in the stroma may influence either or both cell types. Many of these factors may contribute to cancer progression and metastasis through altered cell adhesion, epithelial-mesenchymal transition, matrix remodelling (facilitating tumour cell migration), and neovascularisation.

Models to recapitulate pancreatic cancer and inform future human therapies

In order to maximise benefit to patients, clinical trials should be conducted in populations based on molecular characteristics.[10] This highlights the importance of biomarker driven therapeutic development. Such trials are expensive, labour intensive and pose significant logistical difficulties, which in pancreatic cancer, are further compounded by the rapidity of clinical deterioration and the small percentage of patients who are well enough to receive more than one line of treatment. Anouschaka Akerman and her colleagues from the laboratory show us that useful animal models need to be orthotopic and model both stromal and tumour components together

to maximise the translational impact of modelling novel therapeutics.[11] Additionally, advances in nanoparticle technology are showing the way in dealing with previously 'undruggable targets', a key issue for pancreatic cancer, and intravital preclinical imaging of live tumours is providing new insight into the behaviour of the disease. It is hoped that these techniques will allow accelerated preclinical testing of new agents against newly discovered targets.

Pancreatic cancer diagnosis and screening

Pancreatic cancer evolves through non-invasive precursor lesions, the majority from microscopic ductal lesions known as pancreatic intraepithelial neoplasia, with a small percentage from cystic lesions - intraductal papillary mucinous neoplasms or mucinous cystic neoplasms.[12,13] Recent studies also estimate that a period of 10 to 20 years is required from the time of an initiating mutation, to the establishment of advanced disease, suggesting a prolonged period where intervention may be possible.[14] Early detection is essential to improve cure rates when cure relies on surgical resection. Vinh-An Phan and other gastroenterologists involved in research and development in this field take us through the processes for diagnosis of pancreatic cancer and illustrate that a pancreas protocol CT should be incorporated into diagnosis as well as an endoscopic biopsy.[15]

Strategies that facilitate the early detection of pancreatic cancer or its precursors during the broad window between early lesions and invasive cancer are extremely attractive. However, they show why screening of the general population is not feasible due to the low incidence of pancreatic cancer and the lack of a robust screening test. As a consequence, how the focus has shifted to individuals considered to be at high-risk is reviewed. Established risk factors for pancreatic cancer constitute both environmental and inherited influences and include age, ABO blood group, cigarette smoking, diabetes mellitus, obesity and a family history of pancreatic cancer.[16] It is thought that up to 10% of pancreatic cancer cases have a heritable component,[17] and there are screening trials available for at risk individuals. Skye McKay, a genetics counsellor who has led the Australian Familial Pancreatic Cancer program, has come together with other Australian experts in the field to update this topic for us.[18]

Pancreatic neuroendocrine tumours

Fortunately, a small but important proportion of pancreatic tumours have a much more positive outlook - the entire gastrointestinal neuroendocrine tumour family (also known as carcinoid tumours) share many commonalities. David Chan and colleagues, who are involved in research in this rare subtype of pancreas cancer, describe the unique features of this disease and recent developments in treatment.[19] Australia is leading the world in clinical trials that include peptide radionucleotide radiotherapy for this disease.

Treatment of pancreatic cancer from surgery to systemic therapies to radiotherapy and back again – an evolving continuum

Nick Butler and his surgical colleagues tell us that although surgery is the only treatment that can offer cure, the rates of cure are disappointing, even in the most experienced hands, and outline approaches to optimise the selection of appropriate candidates.[20] Australia has been at the forefront of research into the use of neoadjuvant chemotherapy and radiotherapy to improve outcomes from surgical resection of pancreatic cancer.[21] Chelsie O'Connor and her co-authors lead a discussion about the principles and application of radiotherapy,[22] and Alycea McGrath's team expands on the specific role in locally advanced disease where emerging data may resurrect its role.[23] Like other treatment modalities, the technology to deliver radiotherapy has improved and a more directed approach with less toxicity is now possible.

Very little progress has been made in the systemic treatment of advanced pancreatic cancer until the last five years. Recent advances are reviewed by Dhanusha Sabanathan and two other leading medical oncologists in the field.[24] Gemcitabine, a nucleoside analogue, became established as the standard therapy following the demonstration of improved survival and clinical benefit (pain, performance status and weight) against 5-fluorouracil.[25] This led to a fruitless decade of subsequent focus on combining other drugs with gemcitabine to test doublets against gemcitabine monotherapy. However, recent combination therapies, initially with 5-FU based approaches and more recently a novel nanotechnology compound (Abraxane), have for the first time shown improvement in overall survival times from about six months to 9-11 months. Most important has been the small numbers of longer term survivors and the potential for application in the adjuvant setting. A more personalised approach is also now being explored to try and improve on this.

Improving outcomes by optimising treatment accessibility

One obvious first step to improve outcomes overall is to ensure that all Australians with pancreatic cancer receive optimal treatment. Rachel Neale and Elizabeth Burmeister report the findings of the largest Australian pattern of care study for pancreatic cancer. They reveal that not all patients receive optimal treatment and that access to treatment depends on geographic and socio-demographic factors.[26]

Palliative care and psychosocial aspects of care of patients

Pancreatic cancer presents particular challenges in the relief of a complex constellation of symptoms. Wendy Muircroft and David Currow emphasise that referral to a palliative care service with a team-based approach including dietetics, gastroenterology, interventional pain expertise and liaison psychiatry is likely to deliver the best outcomes.[27] Ideally, this should include meaning-centred therapies that can help with reducing demoralisation and maintaining dignity of both patients and their carers and families. Helen Gooden and her team, which includes pancreatic cancer survivors, tell us about this most important aspect of care.[28]

We hope that this issue of *Cancer Forum* will show you the depth and breadth of Australian research into pancreatic cancer and give you cause for optimism for the future of this disease.

* Approximately 90% of pancreatic cancer is pancreatic ductal adenocarcinoma. Accordingly, unless otherwise stated, the term 'pancreatic cancer' used in this Forum refers predominantly and typically to this tumour type.

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GENOMICS OF PANCREATIC TUMOURS - WHAT WE NOW KNOW

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Abstract

Each year, over 2500 patients in Australia are diagnosed with pancreatic cancer. Pancreatic cancer is one of the most lethal tumour types with a five year survival of just 5%, thus there is a need to find alternative approaches to treatment. In recent years, the application of next generation sequencing has revealed the complex genomic landscape of pancreatic cancer, uncovering the mutation processes that occur during tumour development and has begun to identify new or repurposed therapeutic opportunities for pancreatic cancer patients. The identification of targets for therapy is a crucial goal of the large next generation sequencing studies as we move into an era of targeted or personalised medicine, where drugs will be selected based on the characteristics of a patient's tumour. Due to the large degree of heterogeneity in pancreatic cancer, a personalised approach to treatment seems particularly warranted. This review will summarise some of the key findings from genome sequencing of pancreatic cancer, describing the major driver genes and perturbed pathways, and highlighting some of the new potential and promising therapeutic opportunities that have been uncovered.

Cancer is a genetic disease caused by mutations that accumulate within the DNA sequence of cells. Cells that are normally functioning have repair mechanisms that detect and repair DNA mutations. If however, mutations occur in key regions within the genome, they can disrupt the failsafe repair and checkpoint regulatory system and may enable the mutated cells to grow uncontrollably, resulting in cancer. Mutations affecting genes that confer regulatory or growth advantages are positively selected in tissues to promote tumorigenesis and are referred as 'driver' mutations.[1] The dysregulated cellular system also permits other mutations that do not contribute to tumorigenesis to escape repair. These are referred to as passenger mutations as they are carried along in the clonal expansion of cancer cells.

In recent years, next generation sequencing has made it feasible to generate genome wide catalogues of the DNA mutations present in individual cancers. Two large sequencing initiatives were established to use this technology to sequence thousands of tumour samples from many different cancer types - *The Caner Genome Atlas* (www.cancergenome.nih.gov) and the International Cancer Genome Consortium (www.icgc.org).[2] The main goals of these consortia include cataloguing of commonly mutated genes and disrupted cellular mechanisms that might be 'drivers' of cancer, and identification of actionable markers for therapy in the hope of improving therapy selection and patient outcome. Such genomic studies have revealed the molecular basis underlying pancreatic cancer, identified molecular subtypes and discovered potential therapeutic opportunity in repurposing treatments.

Need for molecular profiling of pancreatic cancer

The term 'pancreatic cancer' describes several tumour types histologically classified on the tissue structures from which they arise. Individual or up to hundreds of samples from the most common pancreatic tumour types have been subjected to exome or whole genome sequencing, however there remain rare subtypes for which no genomic data has been generated. For the tumour types with genomic data, the studies have confirmed and identified key driver genes which are frequently mutated within each tumour subgroup (table 1). The genomic findings have reinforced that pancreatic cancer is a heterogeneous disease comprised of many distinct tumour subgroups.[3] In addition, the degree of heterogeneity between tumours from the same tumour subgroup is high, as tumours of the same subgroup may harbour a different repertoire of

mutations and few genes are mutated at high frequency within sample cohorts. Instead, many recurrently mutated genes are present only at low frequency.[4] This large number of genes mutated at a low frequency impacts on the ability to robustly identify driver mutations, genes or pathway events. One solution is to increase the number of samples studied to increase the power of detection, however this may also increase the confounding passenger mutation signal. Another is that improvements are being made to next generation sequencing analysis methods which enable integrated multiple data types to pinpoint key tumour promoting pathways.

Genome studies

Pancreatic ductal adenocarcinoma (PDAC) is the most prevalent tumour type which accounts for approximately 90% of all pancreatic tumours,[13] and has been the most comprehensively studied by genome sequencing. Genome studies were initially performed by amplicon exon sequencing of small numbers of PDAC cell lines and patient derived xenograft mouse models (n=24),[5] or cell lines (n=15).[4] Subsequently, exome sequencing was performed on large cohorts of patient tumour samples (n=99),[6] and micro-dissected tumours (n=109).[8] These exome studies identified point mutations and small indels, but had limited ability to detect chromosome structural rearrangement, an alternative mechanism of gene mutation which can result in inactivation of tumour suppressors by gene breakage or activation of oncogenes by amplification of dysregulation. The genome wide view of large rearrangements can be detected by whole genome sequencing, therefore the International Cancer Genome Consortium pancreatic project recently employed whole genome sequencing to survey the complete repertoire of somatic mutations in PDAC.[7] To optimally determine the drivers of PDAC, a recent meta-analysis of available genome data was conducted (Bailey et al, in press Nature). Together, these studies have iteratively identified the genes and pathways which are recurrently mutated in PDAC.

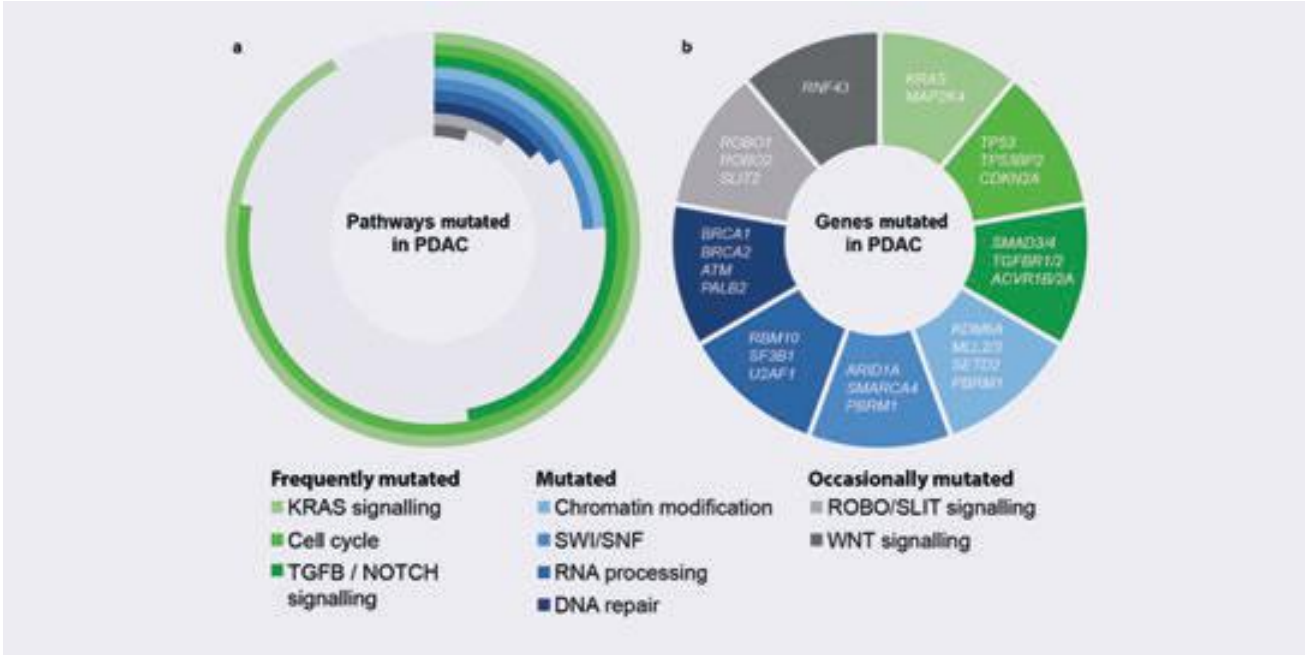
Frequent somatically mutated genes

There are four genes which are frequently mutated in PDAC (mutated in >30% of samples), and many more genes which are less frequently seen but still significantly mutated (mutated at a higher frequency than by chance alone) which affect common pathways and thus are likely to be driving the disease (figure 1). The most frequently mutated gene is the KRAS oncogene. The KRAS protein is involved in RAS signalling and cellular growth through the MAPK and PIK3CA pathways and is mutated in >90% of PDAC cases.[4-7] Mutations in the KRAS gene are clustered in hotspots and result in activation changes at codon 12 (92 % of KRAS mutated cases) and less frequently at codon 13 and 61 (~8 % of KRAS mutated cases).[5-8] The type of KRAS mutation may have clinical significance, as patients with codon 61 mutations have been shown to have a more favourable outcome to patients with other KRAS mutations.[8] The remaining three genes mutated at a high frequency are tumour suppressor genes and frequently harbour mutations combined with a loss of heterozygosity in PDAC. TP53 is an important regulator of cell response to DNA damage and is mutated in >70% of patients. CDKN2A is a cell cycle regulation gene and SMAD4 is involved in TGF-β signalling. Both are mutated in >30% of samples.[4-7]

***Table 1**: Frequently mutated genes in pancreatic cancer tumour subgroups detected by sequencing.*

Pancreatic tumour type	Driver gene	Approximate proportion of mutated samples	Reference
Ductal adenocarcinoma	KRAS	>90	5-8
	TP53	74-86	5,7
	SMAD4	36-43	5,7,8
	CDKN2A	30-41	5,7,8
Intraductal papillary-mucinous neoplasm (IPMN)	KRAS	62-74	9
	GNAS	40-61	9,10
Acinar cell carcinoma	TP53	13-31	11
Pancreatic neuroendocrine tumours	MEN1	44	12
	DAXX/ATRX	43	12
	MTOR pathway genes	15	12

***Figure 1**: Frequently mutated pathways in PDAC. A summary of the pathways and genes which are mutated in PDAC are shown: a) The proportion of PDAC samples which contain mutations in each pathway is represented by the circular histogram; b) A selection of the genes which have been reported in each pathway are shown.*



In addition to these four key driver genes, there are many genes mutated at low frequency which are also likely drivers of disease. These include the ARID1A gene, which is involved in chromatin modelling and was identified as recurrently mutated in different samples, and detected in multiple studies.[5-8] Other genes have also been detected by more than one study including TGFRB2,[4-6] MLL3 and SF3B[1,5,6] and ROBO[2,6,7] while many more genes have been identified as significantly mutated in a small percentage of samples. This so called 'long tail' of uncommon, but recurrently mutated genes, highlights the between patient tumour heterogeneity and indicates that more samples will need to be characterised to identify all drivers of pancreatic cancer.

Frequently perturbed pathways

The large numbers of genes that are recurrently mutated suggest that PDACs are highly heterogeneous with multiple pathways affected by mutation. The first study which systematically sequenced the exons of thousands of genes in pancreatic cancer described 12 core signalling pathways as driving PDAC,[5] and included pathways whose dysregulation has been described as a hallmark of many other cancer types.[14,15] The PDAC core signalling pathways have subsequently been refined as more genome data has been generated. The axon guidance pathway, particularly SLIT/ROBO signalling, was later identified as frequently mutated,[6] and subsequently shown to be frequently methylated in PDAC.[16] The chromatin modelling SWI/SNF pathway was also identified in 42% of cases and frequently involves mutations in ARID1A which occur in 15% of cases and has been associated with a poor outcome.[8] A summary of the genes and pathways perturbed in PDAC is shown in figure 1.

Mutational signatures

Cancer genomes may carry tens to thousands of somatic mutations. A handful of these mutations will have a functional consequence and act as drivers of disease, while the vast majority are passenger or bystander mutations which have little functional consequence. However, all the mutations (driver and passenger) can reveal information about the aetiology of each tumour. Genomic mutations range from single base substitutions to large chromosomal structural rearrangements and the pattern or distribution of these mutations can reveal important insights into how the tumours arose. In particular, the sequence context of single base substitutions can be used to identify the underlying mutational processes or signatures which have occurred in tumour development.[17,18] For many signatures the cause is unknown, while others are associated with mutagenic exposure e.g. tobacco smoking, ultra-violet light and defective DNA damage repair.[17,18]

In PDAC, at least six mutation signatures have been described (see http://cancer.sanger.ac.uk/cosmic/signatures). These include two signatures that are present in most PDACs and are ubiquitously expressed in many other tumour types, one of which is associated with 'ageing' or deamination of 5-methylcytosine, while the cause of the other signature is not known. Other mutation signatures detected include two signatures thought to be caused by the AID/APOBEC family, however

the precise mechanism resulting in the AID/APOBEC signature in PDAC is not known. The remaining two signatures are linked with defects in DNA damage repair. The first is termed the 'BRCA signature', and is associated with a defective homologous recombination DNA repair pathway.[7,19,20] Tumours which contain a high proportion of mutations classified within the profile of the 'BRCA signature' are present in approximately 14% of PDAC samples. These tumours are also associated with unstable tumour genomes which contain a high number of rearrangements.[7] In PDAC, many of the tumours with a high proportion of 'BRCA signature' mutations contain pathogenic germline variants or somatic mutations in key genes involved in homologous recombination, including BRCA1, BRCA2, ATM and PALB2.[7] However, for some 'BRCA signature' high tumours, the genes or processes driving this signature have yet to be identified. The second DNA damage repair signature correlates with a mismatch repair (MMR) deficiency and has been identified in microsatellite unstable tumours which are associated with a hypermutation phenotype.[17] Microsatellite instability and the underlying MMR defects have been shown to occur occasionally in PDAC (<10% cases),[21] and PDAC tumours with a high mutation rate have been associated with loss of the mismatch repair gene MLH1.[4] However, to better understand the prevalence of MMR in PDAC and determine what is driving the MMR signature, a systematic screen of a large cohort of PDAC is required.

Patterns of rearrangements reveal genomic subtypes

The patterns of large chromosomal rearrangements have been used to classify PDAC into four molecular subtypes,[7] which are termed as 'stable', 'scattered', 'locally rearranged' and 'unstable'. Similar groups have also been described in other tumour types, including oesophageal and ovarian cancer.[20,22] The stable subtype contains few genomic rearrangements and comprises 20% of PDAC samples. The scattered subtype contains a modest number of chromosome rearrangements distributed throughout the genome and comprises 36% of samples. In contrast, the locally rearranged PDACs contain focal clusters of breakpoints on one or few chromosomes resulting in amplification of several oncogenes (30% of samples). The genomic location of the focal amplifications affects a variety of candidate PDAC oncogenes, each amplified in a small subset of patients, suggesting that the locally rearranged PDACs are promiscuous in their selection of oncogenes. The candidate oncogenes include the ERBB2 gene which encodes the HER2 oncoprotein, FGFR1, MET, CDK6, PIK3R3 and PIK3CA. The unstable subtype contains many structural rearrangements (>200) distributed throughout the genome.[7] The unstable genomes are associated with a high number of mutations contributing to the BRCA signature and frequently contain mutations or pathogenic germline variants in genes involved in homologous recombination.

Opportunity for targeted treatment

PDAC is an aggressive disease with a five year survival of 5%. The majority of PDAC patients with advanced disease will receive gemcitabine based chemotherapies which is the standard of care, but this only provides a marginal survival advantage. Thus there remains a pressing need to improve therapy regimes. Personalised or targeted treatment, whereby drugs will be selected based on the characteristics of the tumour will become more prevalent. The large degree of heterogeneity in PDAC means it is an ideal disease for a personalised approach. In support of this there have been several reviews discussing some of the therapeutic opportunities in PDAC and a phase II trial (IMPaCT) was established to implement and test the value of precision medicine for recurrent or metastatic pancreas cancer.[23-26]

Targeting the DNA repair pathway

The large amount of PDAC mutation data has revealed an abundance of therapeutic opportunity. Of particular note is the potential to target defects in DNA damage repair pathways. Individual case reports of patients with advanced gemcitabine resistant disease that harbour defects in the homologous recombination pathway are showing positive responses to DNA damaging agents.[7,27] Genome studies revealed that tumours with defective homologous recombination can be associated with a BRCA signature mutational profile and unstable rearrangement patterns, and comprise 14% of PDAC samples.[7] Prospective patient clinical data and preclinical mouse models have demonstrated the potential utility of targeting these tumours with platinum based therapy. A challenge now is to identify those tumours with defective homologous recombination, so there is need for a test, other than whole genome sequencing, which has clinical utility to accurately and rapidly identify tumours that have a defective homologous recombination pathway.

Defects in an alternative DNA repair pathway, MMR, occur in small number of PDAC tumours. Similar to other cancer types such as colorectal,[28] these tumours are associated with hypermutation. Due to the evidence suggesting that a high mutation burden may predict the likely chance of success of cancer immunotherapies,[29] further work is warranted to determine whether this group of MMR defective PDAC tumours will respond to immunotherapies.

Other candidate targets for therapy

Oncogenic driver mutations are major treatment targets for molecular cancer therapies. There are several genes which are amplified at low frequency in PDAC (<5%) for which there are inhibitors developed for different tumours, including HER2, CDK4/6, FGFR and PI3-kinases, which have the potential to be utilised in PDAC treatment. HER2 amplification is one of the best characterised and occurs in 20% of breast cancers. Targeting this event with the anti-HER2 monoclonal antibody trastuzumab has revolutionised the outcome of patients with HER2 positive aggressive breast cancer.[30,31] HER2 amplification has been detected in other tumours types including oesophageal, lung, bladder and gastric cancer, raising the possibility that anti-HER2 therapy can be repurposed to other tumour types. Encouragingly, in gastric cancer it has

been shown that HER2-overexpressing tumours treated with trastuzumab gain a survival advantage.[32] In PDAC, amplifications of HER2 occur in 2% of cases, which makes it an attractive target for therapy.[33]

Pathways which are perturbed in PDAC can also be targeted therapeutically, although identification of these pathways in each tumour can be problematic. The genome sequencing studies have been immensely useful and have identified the genes which are significantly mutated in these pathways, which may represent markers of therapy response. For example, a small proportion of PDAC samples contain mutations in RNF43, which is involved in Wnt signalling. The presence of RNF43 mutation has been shown to act as a predictive biomarker for Wnt inhibitors in PDAC cell lines.[34] In addition, other candidate therapeutic targets which are mutated in small sets of PDAC include mutations in the splicing factor SF3B1, as SF3B1 mutant breast cancer cells are sensitive to a SF3b complex inhibitor spliceostatin A.[35] These and other candidate targets now need to be verified experimentally for efficacy to determine if they can be used in treatment of PDAC.

Conclusion

There has been enormous progress in our understanding of the genes and pathways mutated in pancreatic cancer. These findings have informed about the mutational processes during tumour development and revealed new therapeutic opportunities. Pancreatic cancer is a heterogeneous disease and so it makes sense that this disease will benefit from a personalised approach to patient treatment. Although not specific to pancreatic cancer, a number of challenges remain for targeted therapy. These include development of suitable biomarkers of therapy selection, the within tumour heterogeneity which means some cells will contain the targeted mutation but other cells may not, and the potential of drug resistance development. However, in the near future it is anticipated that large collaborative clinical trials using many of the markers identified by genome sequencing, will commence in the treatment of PDAC.

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ROLE OF THE MICROENVIRONMENT IN CHRONIC PANCREATITIS AND PANCREATIC CANCER

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Abstract

Chronic pancreatitis, an inflammatory disease of the exocrine pancreas, has been reported to be a major risk factor for the development of pancreatic ductal adenocarcinoma. Evidence from pre-clinical mouse models has shown that both diseases share a common origin in the digestive enzyme-producing acinar cells, through acinar to ductal metaplasia. Moreover, both diseases are characterised by the presence of an abundant stroma, the components of which include activated pancreatic stellate cells and immune cell infiltrates, which signal to epithelial cells through the production of cytokines and chemokines. In this review we explore the links between chronic pancreatitis and pancreatic ductal adenocarcinoma, with particular reference to the role of the microenvironment in both diseases. A better understanding of the nature of the epithelial and stromal changes, as well as their interactions, has led to trialling novel therapeutic strategies for the prevention and/or treatment of pancreatic cancer.

Pancreatitis and pancreatic cancer - diseases of the exocrine pancreas

The pancreas is a glandular organ composed of two distinct compartments, exocrine and endocrine. The exocrine compartment constitutes the majority of pancreatic tissue, in which the endocrine islets of langerhans are embedded. While the endocrine islets regulate glucose homeostasis, the exocrine acinar cells secrete enzymes essential for digestion of food. The exocrine duct cells secrete mucins and a bicarbonate-rich fluid, that is transported to the duodenum via a branched network of intra and inter-lobular ducts that drain into the main pancreatic duct[1].

Chronic pancreatitis incidence in industrialised countries ranges from 3.5 to 10 per 100,000 population.[2] It is a progressive inflammatory disorder that arises from repeated overt or silent episodes of acute pancreatitis, where deregulated secretion and premature activation of acinar enzymes results in increasing residual damage to the pancreas (the necrosis-fibrosis sequence). The resulting damage eventually results in chronic pain, maldigestion and diabetes. The histopathologic features of this disease include acinar atrophy, fibrosis, fatty replacement, chronic inflammation and abnormal, distorted ducts.[2,3] In the majority of patients, the disease results from a combination of genetic and environmental factors, with alcohol consumption being the best-defined risk factor.[3] Smoking is a risk factor for disease progression.[4,5]

Pancreatic ductal adenocarcinoma (PDAC) is the most common neoplasm of the pancreas, accounting for more than 85% of pancreatic cancer cases.[6] Despite the relatively low incidence of about 6-12 per 100,000 per year in western countries,[7] PDAC is the fifth cause of cancer related death in Australia and the fourth in the United States, but is predicted to become the second leading cause of cancer-related death by 2030[8,9]. The astonishing mortality (median survival of <6 months and a 5-year survival rate of <5%)[6] is attributed to late diagnosis and to the tumour being often refractory to existing therapies such as gemcitabine. Novel therapies (Abraxane, 5-Fluorouracil/Irinotecan/Oxaliplatin) have sparked some hope, but often only add a few weeks to the median survival of six months. The heterogeneity of PDAC may be the cause of failure of most drugs in clinical trials that have comprised biologically unselected cases.[10] To apply drugs in a more targeted fashion, pancreatic tumour biology needs to be unravelled.

In recent years, progress has been made in our understanding of the origin of PDAC. The most widely accepted model of PDAC progression is that the tumour originates in histologically well-defined precursor lesions through the accumulation of multi-step genetic alterations. These non-invasive preneoplastic lesions are named pancreatic intraepithelial neoplasias (PanINs) and have been found to harbour many of the genetic alterations that are found in PDAC.[11] Mutations in the KRAS oncogene are thought to be the initiating event

during PDAC progression, being found in 93% of cancer cases,[12] and in approximately 36-44% of early PanIN lesions and 87% of advanced PanIN lesions.[11] During the PanIN-PDAC progression, KRAS mutations are followed by loss of tumour suppressor genes such as INK4A/CDKN2A, TP53 and SMAD4.[11]

Chronic pancreatitis predisposes to pancreatic cancer

Evidence from epidemiologic studies

Pancreatitis is a risk factor for pancreatic cancer.[13,14] A meta-analysis of 22 studies found a 5.1 fold increased relative risk of developing pancreatic cancer in patients with unspecified pancreatitis, a 13.3 fold increase in relative risk in patients with chronic pancreatitis and a 69 fold increase for hereditary pancreatitis.[15] Despite the increased risk, only around 5% of patients diagnosed with chronic pancreatitis will develop carcinoma over a period of 20 years.[15] Hereditary pancreatitis has been associated with mutations in several genes including PRSS1, PRSS2, SPINK1 and CTRC. These individuals have a cumulative risk of developing pancreatic cancer of 40-55%.[16]

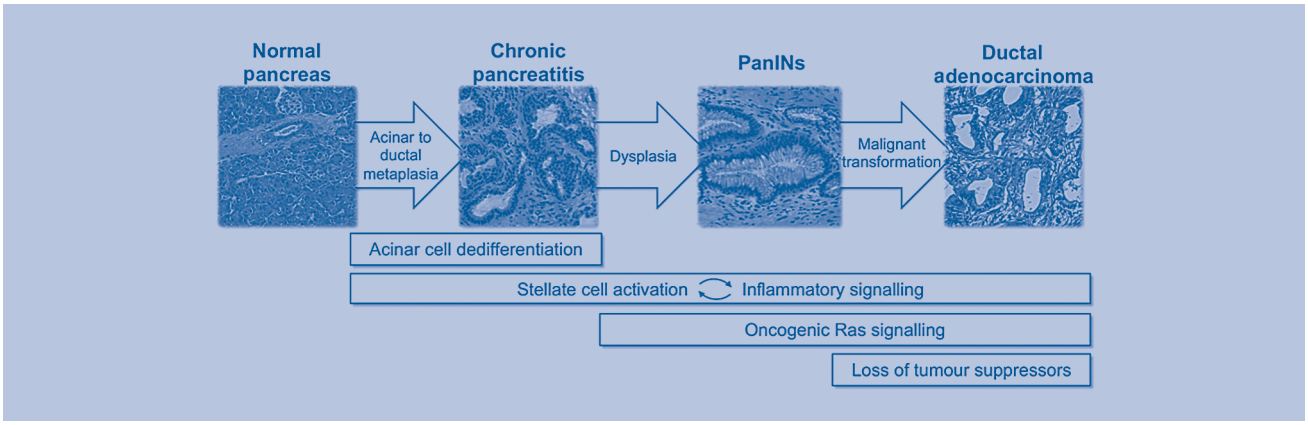
Evidence from experimental mouse models

Chronic pancreatitis and PDAC were historically regarded as unrelated diseases that arose from different cells in the pancreas, i.e. acinar and ductal cells, respectively. Evidence has now accumulated for a common origin of both diseases in acinar cells.[17,18] Pancreatic acinar cells can lose their differentiated state and re-acquire characteristics very similar to embryonic and adult duct cells, a process called 'acinar to ductal metaplasia'. This metaplasia has been observed in clinical samples and has been well documented in experimental rodent models of pancreatitis. The most widely used model involves treatment with the cholecystokinin agonist caerulein, which induces local oxidative stress, inflammation, oedema and loss of the acinar parenchyma that is transiently replaced by a duct-like epithelium, reminiscent of human pancreatitis.[17,18] Genetic lineage tracing experiments in mice have shown that the intermediate ductal metaplastic epithelium present in this model can arise from acinar cells.[19-21] We have further documented how during pancreatitis, acinar cells can dedifferentiate and acquire features of pancreatic progenitor duct-like cells.[22]

Mouse models, where oncogenic Kras was activated specifically in acinar cells early in embryonic development, developed neoplastic lesions and invasive ductal carcinoma, supporting the idea that acinar cells can be the cell of origin of PDAC.[23-25] Adult acinar cells are more refractory to Kras-driven neoplastic transformation.[23,24,26] Even if the cells dedifferentiate in pancreatitis, they undergo growth arrest through activation of a p53-dependent senescence program,[22,27] which constitutes a barrier to malignant transformation. Nevertheless, in the presence of mutant Kras, chronic pancreatitis renders acinar cells susceptible to transformation by the oncogene, leading to the development of the full spectrum of PanINs and PDAC.[23,25,28] More recently, the ductal transcription factor Sox9 has been shown to be required for the occurrence of acinar to ductal metaplasia and consequent initiation of PDAC, acting through the activation of the EGFR/ERBB signalling pathway.[29,30]

In summary, PDAC is most commonly preceded by PanIN lesions that can originate from acinar cells through acinar to ductal metaplasia. This results from the combination of genetic alterations in epithelial cells (KRAS oncogenic mutation and loss of tumour suppressors) and tumour-promoting signalling derived from the surrounding stromal cells, including activated stellate cells and inflammatory components (figure 1), as detailed below.

***Figure 1**: Acinar to ductal metaplasia, as it occurs in chronic pancreatitis, is a recognised precursor of pancreatic ductal adenocarcinoma. Signalling from activated stellate cells and immune cell infiltrates contribute to the development of pancreatitis and cooperate with oncogenic Ras signalling and loss of tumour suppressor barriers in the subsequent progression to pancreatic intraepithelial neoplasias (PanINs) and, ultimately, to invasive ductal adenocarcinoma. Adapted from Pinho et al. Cancer Letters 2015.*



Microenvironment in chronic pancreatitis and pancreatic cancer

Chronic pancreatitis and pancreatic cancer are both characterised by the presence of a dense stroma, composed of extracellular matrix (ECM) proteins, including collagen, and other cell types such as pancreatic stellate cells, endothelial cells, neurons and immune cell infiltrates.[31]

Pancreatic stellate cells

Pancreatic stellate cells (PSCs) are resident cells of the normal pancreas, constituting 4-7% of all parenchymal cells.[32] In response to pancreatic injury or inflammation, quiescent PSCs undergo activation to become myofibroblast-like cells, which expressα-SMA (alpha smooth muscle actin). Upon activation, PSCs lose their vitamin A-containing lipid droplets, proliferate, migrate, produce ECM components and secrete cytokines and chemokines.[33] Cytokines and growth factors produced by acinar cells, inflammatory cells, platelets, ductal cells, endothelial cells and by PSCs themselves can activate PSCs, and induce cellular responses through paracrine and autocrine mechanisms. Chemokines produced by PSCs contribute to the recruitment of inflammatory cells to the inflamed pancreas. PSCs also produce matrix metalloproteinases and their inhibitors, being involved in the maintenance of normal tissue architecture by regulating ECM turnover. Additionally, PSCs play a 'macrophage-like' role in the pancreas, contributing to organ restitution and homeostasis by phagocytising necrotic acinar cells.[33,34]

Activated PSCs can have two fates. If the inflammation and injury are limited, as in an acute episode of pancreatitis, PSCs might undergo apoptosis or revert to quiescence. If the inflammation and injury are sustained or repeated, PSC activation is perpetuated, leading to development of pancreatic fibrosis, as observed in chronic pancreatitis.[2,33,34]

Activated PSCs are also responsible for the production of the ECM proteins that constitute the abundant stroma around pancreatic tumours.[35] For many years, data acquired from both in vitro and in vivo models reinforced the notion that PSCs contribute to cancer progression.[36] In this regard, it has been shown that pancreatic cancer cells recruit PSCs to their vicinity and promote their activation with consequent increases in proliferation and ECM synthesis. In turn, PSCs stimulate tumour cell proliferation, inhibit cancer cell apoptosis, promote cancer cell migration and epithelial-mesenchymal transition.[36,37] Moreover, several studies have shown that PSCs not only stimulate fibrosis, local tumour growth and metastasis, but also lead to chemoresistance.[38]

Two recent studies have generated controversy by proposing that pancreatic cancer stroma may protect against cancer progression.[39, 40] In these studies, depletion of PSCs in mouse models of the disease was achieved either by genetic targeting or drug based inhibition,[38,40] resulting in the development of more aggressive and undifferentiated tumours. These apparent contradictory findings highlight the possibility that the role of PSCs may be context-dependent and emphasise the need for further studies on the mechanisms mediating stromal-tumour interactions in PDAC.

A central role for inflammation

Immune cells and endothelial cells in the pancreas also produce inflammatory cytokines and chemokines that, together with reactive oxygen species, cause epithelial cell damage and increased proliferation. Inflammatory mediators, such as cyclooxygenase-2 (Cox2), NF-κB and STAT3, play key roles with respect to inflammation. In turn, inflammation can generate sustained and exacerbated secondary oxidative injury and, as such, mediate the promotion of inflammatory infiltration and acinar cell injury.[41,42]

Various studies using genetically engineered mouse models have shown that genes involved in inflammatory pathways have a role in pancreatic cancer development.

Cox2 is activated by inflammatory cytokines and its expression is upregulated in pancreatitis and pancreatic cancer.[42] Interestingly, transgenic overexpression of Cox2 induces chronic pancreatitis and the formation of PanINs.[43, 44]

In a KRAS mutant background, inflammation overcomes barriers that prevent tumour development. A well-defined tumour suppressive barrier inhibited by pancreatitis is senescence.[22, 28, 45] In animals bearing a KRAS oncogenic mutation, a mild inflammatory stimulus in the pancreas triggers an NF-kB mediated positive feedback mechanism, which amplifies Ras activity to pathological levels, causing the development of chronic inflammation and preneoplastic lesions.[46] Another study showed that, also in a KRAS mutant context, TNF-α–induced activation of the NF-kB pathway in pre-malignant epithelial cells creates a feed forward loop that retains the transformed cells in an inflammatory state.[47]

STAT3 activation has also been shown to be essential for initiation and progression of pancreatic cancer. STAT3 contributes to cancer initiation by promoting the de-differentiation of the acinar cells during pancreatitis, which consequently become more vulnerable to Kras-mediated transformation. The STAT3 pathway can be activated in pancreatic epithelial cells by both paracrine and autocrine mechanisms.[48,49]

Inflammatory signalling coming from the epithelium can also exert paracrine effects on stromal components. GM-CSF is one of the inflammatory cues from the tumour cells that modulate the microenvironment.[50] Chemokine production by the tumour epithelium also promotes connective tissue growth factor secretion from the stromal cells.[51] Interestingly, loss of mutant KRAS in the tumour epithelium results in involution of the stroma and its inflammatory components.[52]

In summary, the pancreatic microenvironment, including stellate and immune cells, have an important role both in pancreatitis and in pancreatic tumour development.

The epithelial cells themselves also produce inflammatory molecules, both at precursor stages and in established tumours, leading to the remodelling of the microenvironment. A better understanding of this tumour-stroma crosstalk could provide the platform for the development of novel therapeutic strategies for prevention and treatment of pancreatic cancer.

Improved detection, chemoprevention and treatment of pancreatic cancer

Novel discoveries that improve our understanding of the mechanisms mediating initiation of pancreatic tumours will be critical for the development of better detection strategies, together with major advances in sophisticated imaging techniques that can detect early neoplastic lesions. In addition, new ways are being devised to target the pro-tumourigenic effects of the stromal stellate and immune cells.

Approaches targeting stellate cells

The hedgehog signalling pathway has been shown to mediate interactions between PSCs and PDAC cancer cells. Inhibition of this pathway using IPI-926 in combination with gemcitabine in a pre-clinical model of PDAC had an inhibitory effect on tumour growth, attributed to the consequent increased concentration of intra-tumoural gemcitabine.[53] However, a phase 2 clinical trial with IPI-926 had to be prematurely stopped due to significantly reduced survival of patients. Concordantly, a more recent study reported that genetic inactivation of the hedgehog pathway in a mouse model decreased tumour stroma, but increased tumour vascularity, resulting in increased aggressiveness.[40] These results underscore a need for better understanding of the mechanistic complexities of targeted pathways, as well the importance of confirming therapeutic effects in a range of pre-clinical models before using them in the clinic.

Enzymatic degradation of the ECM component hyalunoran using PEGPH20 has been shown to deplete the stroma in an animal model of PDAC, increasing the delivery of gemcitabine and improving survival.[54] A randomised clinical trial is now ongoing to evaluate PEGPH20 as a first-line therapy for patients with metastatic pancreatic cancer,[55] but the results have been variable. Blockade of the angiotensin II receptor using olmasartan or losartan have also shown promising effects in reducing stroma and reducing tumour growth in pre-clinical models of PDAC.[56,57] A phase 2 trial is currently ongoing to evaluate the efficacy of the use of losartan in combination with FOLFIRINOX and proton beam radiation.[55]

A very recent study has also shown promising results for the vitamin D receptor ligand calcipotriol. In an orthotopic model of pancreatic cancer, calcipotriol was shown to induce quiescence of PSCs leading to stromal remodelling, suppression of pancreatitis, reduced tumour volume and increased survival.[58] Further studies are now needed to evaluate the safety and efficacy of calcipotriol in the clinical setting.

Anti-inflammatory agents

The established link between inflammatory pathways and cancer development suggests a potential prophylactic and/or therapeutic use of anti-inflammatory agents for pancreatitis and pancreatic cancer.

Numerous nonsteroidal anti-inflammatory drugs (NSAIDs) have shown an effect in prevention and/or treatment of pancreatic cancer in experimental studies. These include Cox2 specific inhibitors such as celecoxib, apricoxib or NS-398, as well as non-specific NSAIDs such as aspirin, nimesulide or sulindac.

A recent epidemiological study found that aspirin significantly reduced deaths due to pancreatic cancer after five years of follow up.[59] Accordingly, recent case-control studies suggest a reduction in risk of pancreatic cancer for long-term users of NSAIDs.[60,61]

Regarding treatment for pancreatic cancer with anti-inflammatory agents, several early phase trials support the feasibility of Cox2 inhibitors for therapeutic use.[55] Although the study of Cox2 inhibitor apricoxib in combination with gemcitabine and erlotinib did not reach its endpoint, it showed a trend towards benefit with the anti-inflammatory compound, but at the cost of increased incidence of gastrointestinal haemorrhage.[62]

Several clinical trials are now testing the addition of anti-inflammatories to chemotherapy for pancreatic cancer, most in a palliative setting, but also as an adjunct to surgery and adjuvant chemotherapy.[18,55] Results from these clinical studies will be essential to inform the potential of these agents as valuable chemopreventive and/or therapeutic approaches for pancreatic cancer.

Conclusion

Evidence from the study of mouse models in combination with epidemiological and patient-derived data have challenged prevailing dogmas and established a connection between chronic pancreatitis and pancreatic cancer. These diseases not only have mechanistic pathways in common, but also share the presence of an abundant stroma, including stellate and immune cells, which through the production of cytokines, chemokines and ECM components, establish a microenvironment that influences pancreatic epithelial cell differentiation and growth. The study of the interaction between pancreatic epithelial cells and the microenvironment has generated more questions for further research, but has also provided clues for the development of novel preventive and therapeutic approaches to tackle pancreatic cancer.

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NOVEL THERAPEUTICS AND PRECLINICAL IMAGING FOR PANCREATIC CANCER – VIEW FROM THE LAB

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Abstract

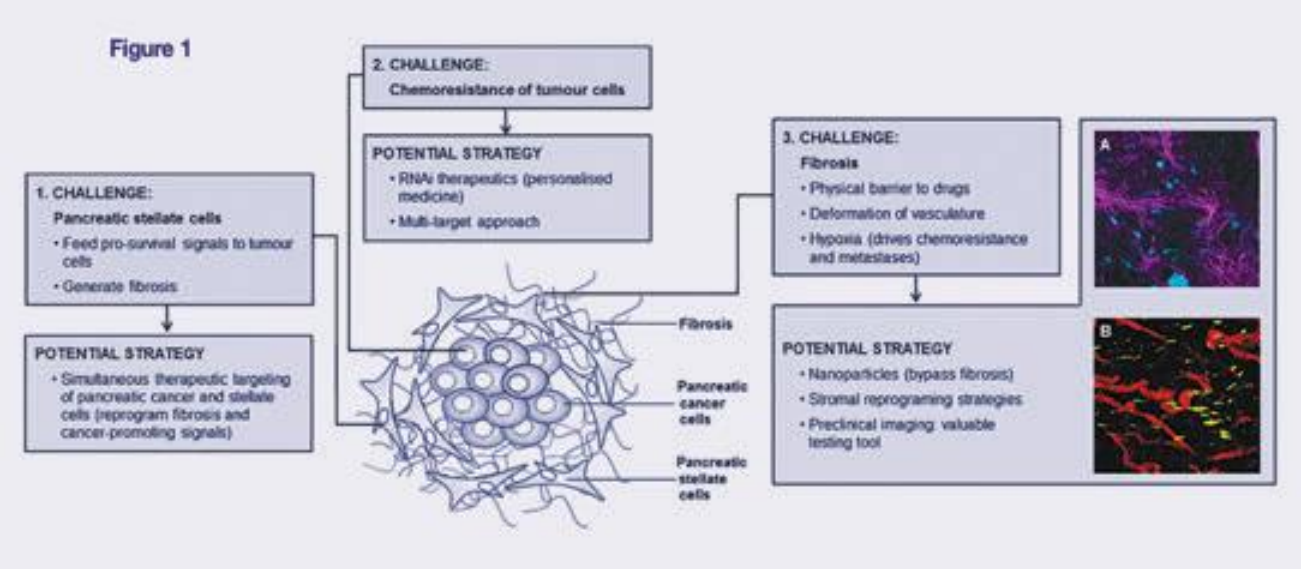
Pancreatic cancer is a devastating disease with a five-year survival rate of 6%. A key driver of disease progression is the tumour microenvironment, which is characterised by fibrosis. A dynamic interplay between tumour cells, pro-fibrogenic pancreatic stellate cells and a dense extracellular matrix impedes effective drug delivery and promotes chemoresistance and metastases. In addition, mutations in pancreatic cancer are highly heterogeneous, making it difficult to effectively treat all patients with one approach. Thus, any effective pancreatic cancer treatment should consider targeting both pancreatic cancer cells and the stromal compartment. While basic research has provided promising new leads on therapeutic targets for this disease, many of them remain 'undruggable' by conventional approaches. Advances in nanoparticle technology and intravital preclinical imaging of live tumours is providing new insight into the behaviour of the disease in vivo and guiding how best to target this disease with higher specificity and lower off-target toxicity. Here, we describe in brief, key advancements in both rapidly emerging fields and highlight their current and future application in the treatment of pancreatic cancer.

Tumour microenvironment

By 2030, pancreatic cancer is predicted to become the second leading cause of cancer-related deaths in western nations.[1] The poor prognosis is due to late clinical presentation, metastasis and chemoresistance. A major driver of the aggressive nature of pancreatic cancer is the microenvironment.[2] Pancreatic cancer is characterised by extensive stromal reaction or fibrosis surrounding tumour elements.[3] Fibrosis distorts the tumour vasculature, creating hypoxia and nutrient deprivation.[4-6] The fibrosis also acts as a physical barrier to drug delivery.[2,6] This environment drives chemoresistance and metastases of cancer cells. The stroma is complex and involves multiple cell types including immune, endothelial, fibroblasts and stellate cells.[3] This review will focus on pro-fibrogenic stromal pancreatic stellate cells (PSCs). PSCs are activated by tumour cells, which causes them to proliferate and deposit excessive fibrotic proteins.[6] While activated, PSCs promote tumour cell proliferation, invasion, metastasis and chemoresistance.[6] This complex interaction between tumour cells, PSCs and the surrounding microenvironment is a major reason many therapeutic approaches have failed in pancreatic cancer and needs to be considered when designing new therapeutic approaches (figure 1).

***Figure 1**: Strategies to visualise and overcome barriers to therapeutics in pancreatic cancer.*
There are currently several barriers to effective drug delivery in pancreatic tumours. 1. Pancreatic stellate cells are responsible for orchestrating fibrosis and feed pro-survival signals to tumour cells. Simultaneous targeting of both tumour and stromal pancreatic stellate cells is a potential strategy in pancreatic cancer treatment. 2. Chemoresistance and genetic heterogeneity of pancreatic cancer cells make it extremely difficult to treat all patients with a single approach. Multi-target approaches using RNA interference (RNAi) therapeutics can help overcome this problem. RNAi therapeutics can inhibit any target at the gene level. These can be delivered using nanoparticles, which can also be tailored to specifically target tumour cells/stromal cells. RNAi therapeutics can be combined with nanoparticle vehicles and advanced genomics to deliver personalised medicine based on the genetics of a patient's tumour, with high efficacy and minimal off-target toxicity. 3. Fibrosis can act as a physical barrier to drug penetration. It distorts tumour vasculature, resulting in a hypoxic microenvironment, driving chemoresistance and metastases. To overcome this barrier, nanoparticles can be used to bypass fibrosis and reach tumour cells. Stromal remodelling strategies can also enhance

drug access to tumour cells. Preclinical imaging approaches of the pancreatic tumour microenvironment offer insight into the molecular basis of pancreatic cancer and can improve the development of new therapies in this disease. It allows for real-time analysis of the interaction between all cells in the tumour microenvironment, vessels and extracellular matrix. (A) Live Second Harmonics Generation imaging of collagen I fibres surrounding metastatic pancreatic cancer cells in an intrasplenic model of liver metastasis. Purple: Collagen; Blue: Pancreatic cancer cells. (B) Intravital imaging of blood vasculature in a subcutaneous xenograft model of pancreatic cancer using quantum dot imaging 37. Red: Vasculature (Quantum dots); Yellow: Pancreatic cancer cells.



Current pancreatic cancer chemotherapies

Gemcitabine has long been the first line treatment for patients with unresectable pancreatic cancer. In recent years, gemcitabine and abraxane® (albumin-bound paclitaxel) combination therapy has become a standard of care for unresectable pancreatic cancer.[7] More aggressive polychemotherapeutic regimens such as FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, oxaliplatin) are also used in the clinic.[8] The survival benefit of these new approaches is only in the vicinity of a few extra months (gemcitabine + Abraxane® extends median survival by eight weeks over gemcitabine; FOLFIRINOX extends median survival by 17 weeks over gemcitabine).[7,8] Clearly, new therapeutic approaches are urgently needed.

New therapeutic targets

There are two main hurdles that make pancreatic cancer difficult to treat - the chemoresistant nature of the cancer cells and the extensive fibrosis. Any effective pancreatic cancer treatment should consider targeting both the pancreatic cancer cells and the stromal reaction (figure 1). Recent discoveries at the bench have identified novel therapeutic targets that hold promise for reprogramming the stroma, modulating fibrosis dynamics and enhancing our ability to kill pancreatic tumour cells.

Several studies have demonstrated the potential benefit of targeting aspects of the stromal reaction in tissue culture and mouse models of pancreatic cancer. For example, the anti-fibrotic drug pirfenidone, which is used to treat idiopathic pulmonary fibrosis, reduced fibrosis, tumour growth and metastatic spread, and improved the efficacy of gemcitabine in an orthotopic xenograft.[9] Novel work showed that the vitamin D receptor on PSCs is a master regulator of their cancer-promoting phenotype.[10] Administration of a vitamin D analog into a clinically relevant spontaneous pancreatic cancer mouse model reduced fibrosis, improved drug access and when combined with gemcitabine, improved survival.[10] Enzymatic depletion of hyaluronic acid, which is an abundant component of pancreatic fibrosis, in a similar mouse model, improved drug access and efficacy.[11,12] More recently, the texture of fibrosis can predict pancreatic cancer patient outcome.[13] The group showed that by inhibiting lysyl oxidase, an enzyme that increases the stiffness of fibrosis, they could suppress tumourigenesis and metastatic spread and enhance gemcitabine efficacy.[13] These studies highlight the need to reprogram the stroma in order to overcome a major barrier to pancreatic cancer treatment. However, caution must be taken when targeting the stroma, as studies have demonstrated some components can help contain pancreatic cancer,[14,15] but this is dependent on the therapeutic target and the cells affected. Thus, it is important to examine the effects of targeting one stromal component on other cells in the stroma.

The growing understanding of pancreatic cancer cell biology has allowed scientists to focus on new and more effective molecular targets for pancreatic cancer. Major goals for researchers studying pancreatic cancer include to identify new molecular targets that can impair tumour growth and metastasis, reduce off-target toxicity compared to traditional therapies, and improve the efficacy of existing therapeutics. McCarroll et al recently showed that inhibition of III-tubulin, a cytoskeletal protein,

was able to halve tumour growth and metastatic spread in an orthotopic pancreatic cancer mouse model.[16] Ideal therapeutic targets for pancreatic cancer are not just proteins. For example, microRNA-21, a small RNA sequence that downregulates tumour suppressors, is upregulated in pancreatic cancer.[17,18] Inhibition of this target in a mouse model of pancreatic cancer was also able to reduce tumour growth and increase tumour sensitivity to gemcitabine.[19] While targets like these hold great promise for pancreatic cancer treatment, their translation to the clinic is hindered by their 'undruggable' status, that is, there are currently no pharmacological inhibitors against them. Exciting new progress in the field of nanotechnology is set to challenge this perception.[20]

Nanoparticle therapeutics: targeting the 'undruggable'

Nanoparticles are delivery vehicles ideally between 10-100 nanometres in diameter.[21,22] They are capable of carrying a drug or RNA interference (RNAi) therapeutics. RNAi makes it possible to inhibit any target gene, with high specificity. Nanoparticle technology is already in use in the clinic, including for example albumin-bound paclitaxel (table 1) and in clinical trials for a variety of cancers (table 2). More recently, Boyer et al published a first-generation nanoparticle for delivery to pancreatic tumours and demonstrated that it was capable of delivering and releasing RNAi therapeutics into pancreatic cancer cells in vitro.[23]

***Table 1**: Nanoparticle-based therapies in clinical use for cancer.*

Composition	Trade name	Disease	Administration	Reference
Liposomal doxorubicin	Myocet	Combination therapy with cyclophosphamide in metastatic breast cancer	Intravenous	58
Liposomal-PEG doxorubicin#	Doxil/Caelyx	HIV-related Kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer	Intramuscular	59-61
Albumin-bound paclitaxel	Abraxane®*	Metastatic breast cancer, metastatic pancreatic cancer	Intravenous	62, 63
Methoxy-PEG-poly(D,L-lactide) taxol	Genexol-PM	Metastatic breast cancer	Intravenous	64
PEG-L-asparaginase	Oncaspar	Acute lymphoblastic leukaemia	Intravenous, intramuscular	65

*The field of nanotherapies has exploded in the last five years, resulting in the use of nanoparticle-based therapies in the treatment of several malignancies. Albumin-bound paclitaxel is currently employed as a therapy for pancreatic cancer. There is ongoing work by several groups towards establishing the ideal nanoparticle for use in the treatment of pancreatic cancer. #PEG, Polyethylene glycol.

***Table 2**: Current clinical trials testing nanoparticle therapies in cancer.*

Composition	Trade Name	Disease	Administration	Status	Reference	Clinical Trial Number
Liposomal doxorubicin	Doxil	Soft tissue sarcoma	Intravenous	Phase 1/2	66	NCT00949325
Polyglutamate paclitaxel	Xyotax	Metastatic breast cancer	Intravenous	Phase 2	67	NCT00265733
PEG-camptothecin#	MAG-CPT (PNU 166148)	Advanced solid cancers	Intravenous	Phase 1	68	NCT00004076
Liposomal irinotecan	MM-398	Metastatic pancreatic cancer	Intravenous	Phase 3	69	NCT01494506

#PEG, Polyethylene glycol.

Nanoparticles must be stable in the bloodstream and able to deliver their cargo to tumour cells if they are to be used in a therapeutic setting.[24] They are often charged to enable them to bind their cargo. However, this charge can trigger immune responses and bind proteins in the blood that hinder their function. One way to improve the stability of nanoparticles is by addition of neutral charged polymers to the surface of nanoparticles. For example, the addition of polyethylene glycol has been used to shield nanoparticles in the bloodstream.[25] An appealing feature of nanoparticles is the ability to target them to specific cell types by attaching targeting moieties. This reduces off-target toxicity commonly associated with conventional chemotherapy.[24] For example, studies have employed vitamin A-conjugated nanoparticles to deliver RNAi therapy to hepatic stellate cells and PSCs in mouse models of hepatic and pancreatic fibrosis.[26,27] The group demonstrated that they could effectively deliver RNAi therapy to inhibit a protein involved in production of fibrosis, specifically in stellate cells.[26] Notably, these nanoparticles/RNAi therapies were able to resolve pancreatic and hepatic fibrosis.[26,27]

Nanoparticles therefore have the potential to transform treatment for pancreatic cancer, especially in the context of recent advances in pancreatic cancer genomics. We now know that there are only a few common mutations in pancreatic cancer, making personalised medicine essential.[28] Using nanoparticles/RNAi therapies and advanced genomics, clinicians could eventually be able to administer a specific cocktail of RNAi therapeutics based on the genetics of a patient's tumour, with minimal off-target toxicity and high efficacy. In addition, nanoparticles can be applied in combination therapies, to package and deliver enzymes or drugs such as Abraxane® (table 1) to specific cell types, thus avoiding off-target toxicity and enhancing tumour penetrance.

Preclinical imaging in pancreatic cancer

High resolution preclinical laboratory imaging technologies are being employed to unravel the biological events in pancreatic cancer. These approaches have shed light on the spatio-temporal regulation of events driving pancreatic cancer at the single cell and subcellular levels. Here, we describe how complementary preclinical imaging approaches offer insight into the molecular basis of pancreatic cancer and facilitate the development of new therapies.[29,30]

Imaging the tumour microenvironment

Pancreatic cancer progression occurs in a complex three-dimensional microenvironment with reciprocal feedback from the surrounding host tissue. *In vitro* models combined with immunohistochemical analysis of patient tissues have been used to characterise the pancreatic tumour microenvironment.[3,31,32] While these approaches give insights into the interactions between cancer cells and their surrounding stroma, they are rather static and therefore do not fully recapitulate the intricacy of pancreatic cancer biology. However, direct imaging of stromal components has provided insight into the complexity of tissue structures and functions during disease development.

Second harmonic generation (SHG) imaging, a label-free technique, is used to characterise the extracellular matrix texture and organisation in pancreatic cancer fibrosis. SHG imaging assessed collagen remodelling following dual treatment with gemcitabine and signal transducer and activator of transcription 3 (STAT3) inhibitors in a mouse model of pancreatic cancer,[33] while gemcitabine delivery upon stromal intervention/reduction was monitored using dual SHG and fluorescence doxorubicin imaging.[12,34] Recent SHG imaging of a human pancreatic tissue microarray (>80 patients) revealed a positive correlation between collagen abundance, tumour stage and resistance to chemotherapy.[13]

The metabolic activity of cancer can be observed using fluorescence lifetime imaging of cellular Nicotinamide adenine dinucleotide (NADH) and FADH fluorescence (ratio of free to bound NADH),[35] an approach used for identification of cancerous or precancerous lesions *in vivo*.[36] While quantum dot imaging in a live xenograft model of pancreatic cancer provided information regarding drug targeting of cancer cells in relation to the proximity to blood vessels,[37] and supported the hypothesis that enhancing tumour vasculature patency may improve drug penetrance in pancreatic cancer tissue.[11,12] Engineering stromal and cancer cells to express fluorescent reporters has been employed to visualise the cross-talk between cancer cells and stroma, and implicated PSCs in the onset of angiogenesis and in colonisation of distant organs.[38] Yang et al implanted RFP-pancreatic cancer cells in a green fluorescent protein-expressing host to directly visualise tumour-stroma interactions and drug response of both cancer and stromal cells.[39] Imaging the tumour microenvironment allows us to understand the complexity of pancreatic tumours and fine-tune how to best modulate the pancreatic tumour-associated stroma.

Live imaging of biosensors to monitor tumour cell signalling

The development of fluorescent biosensors has enabled us to dissect the dynamics of molecular events and has

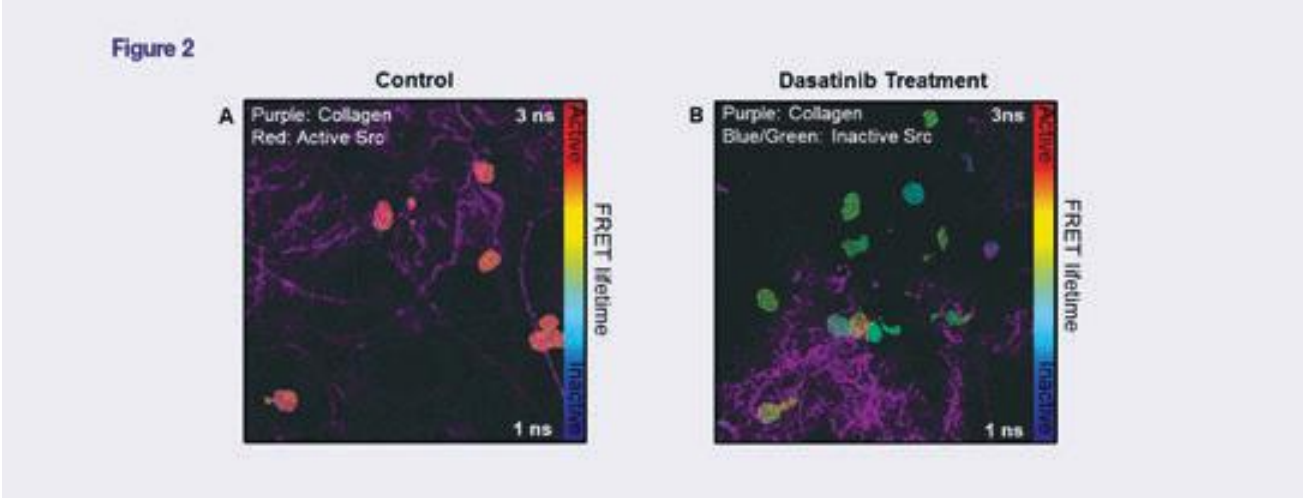
provided insights into their spatio-temporal regulation. As such, imaging of biosensors has shed light on mechanisms occurring in pancreatic cancer *in vivo*, such as changes in cell proliferation, survival, invasion, metastasis and response to chemotherapy. For example, live imaging of the prototypical RhoGTPases, RhoA and Rac-1, which are known to drive cancer cell migration, has been achieved using Förster Resonance Energy Transfer (FRET) biosensors and revealed a subcellular regulation of the small GTPases at the leading edge of invading cells *in vitro* and *in vivo*.[40,41] Similarly, live monitoring of cell-cell adhesion dynamics upon anti-migratory drug treatment was recently assessed using a fluorescence recovery after photobleaching biosensor to monitor E-cadherin stability in pancreatic cancer.[42]

Live imaging of fluorescent biosensors is an emerging preclinical tool for cancer research. For instance, various probes such as Fucci sensors, CDK1-FRET biosensor and photo-marking H2B-Dendra reporter are used to elucidate the dynamics of cell proliferation and give insights on the efficacy of anti-proliferative drugs.[43-45] Similarly, the use of Akt, Erk and PAK-FRET biosensors have helped us untangle the molecular mechanisms governing cell survival and signal transduction in vivo.[46,47] More recent developments may provide further insights into signalling pathways in pancreatic cancer. For example, polarisation resolved imaging of homo-FRET between identical fluorophores can visualise clustering of molecules commonly deregulated in cancer.[48,49] Simultaneous imaging of several FRET biosensors in a single cell using spectral unmixing or homo-FRET based biosensors can help us probe the spatio-temporal dynamics of intertwined signalling events which often involve complex molecular feedback loops.[50] This information can allow us to circumvent regulation loops that may lead to chemoresistance. For a list of biosensors and fluorescent techniques used to image cancer figure 2 see eg. of FRET imaging to monitor Src activity in live tumours).51 We suggest that using these tools for future pancreatic cancer research will rapidly expand our understanding of the molecular events occurring during pancreatic cancer progression and therapeutic intervention.

Multi-modal imaging

Simultaneous imaging of different aspects of pancreatic cancer provides a detailed picture of cancer response to preclinical strategies and may facilitate therapeutic discovery.[30,44] A fluorophore-labelled lectin antibody was administered in mice bearing pancreatic tumours and used in combination with immunohistochemistry to image the effect of combination therapy on tumour vasculature.[11] Likewise, Wang et al designed a gemcitabine-loaded magnetic albumin nanosphere to conduct simultaneous targeted chemotherapy and magnetic resonance imaging of drug delivery.[52] These approaches allow us to assess the level of drug penetration into cancer tissue. Integrating multi-modal imaging technologies has also been employed to monitor drug targeting in a dynamic, context-dependent and subcellular level. For example, intravital imaging has been used to monitor the intracellular pharmacokinetics of PARP-1 and microtubule inhibitors.[53,54] Longitudinal imaging using surgically implanted imaging windows allows us to integrate the spatio-temporal and contextual complexity of cancer progression. In particular, this technique was used to characterise the formation of a metastatic niche during

***Figure 2**: Live intravital imaging of pancreatic cancer signalling: monitoring Src kinase activity using FRET imaging. FRET imaging of a Src biosensor in a xenograft model of pancreatic cancer with or without dasatinib treatment. Representative lifetime maps of 'ON' cells (top panel, control treatment) and 'OFF' cells (bottom panel, dasatinib treatment)[37]. FRET lifetime scale is shown on the right of each panel, from 1 nanosecond (1ns) to 3 nanoseconds (3ns).*



liver colonisation by cancer cells, as well as monitor live events within the abdominal body cavity including in situ pancreatic biology in real-time.[55] Importantly, this new approach will enable us to monitor drug kinetics in real-time within the same mouse (pre- and post-dosing) and is set to provide a reliable new tool for future therapeutic intervention studies in pancreatic cancer (figure 1).

Application of imaging technologies in the clinic

The use of sensitive imaging technologies may also improve the management of pancreatic cancer in the clinic. One example developed by VisEn Medical Inc is theinjection of a proteolytically activated fluorophore coupled with fibre-optic confocal microscopy, which allows highly sensitive characterisation of tumour stage, lymph node status and fluorescence-guided surgery.[56] Lastly, a surface-enhanced resonance Raman scattering nanoparticle has been used to detect macroscopic pancreatic lesions to identify tumour margins, and represents a tool for pancreatic resection.[57]

Conclusion

The tumour microenvironment is highly complex and future therapies will likely require multi-cellular and multi-gene targeting approaches. Nanotechnology has potential to enhance both the delivery and specific targeting of pancreatic cancer, while state-of-the-art imaging technologies increase our understanding of the biology of the disease and facilitate the discovery of new treatments. In conclusion, marriage of nanoparticle delivery with advanced molecular imaging is set to rapidly improve the management and future treatment of pancreatic cancer.

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PANCREATIC CANCER DIAGNOSIS AND SCREENING

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Abstract

Pancreatic cancer is uncommon, but is projected to become the second leading cause of cancer-related death by 2030. The dismal five year survival of 5% reflects the advanced stage of the disease at presentation, at which time surgery is not possible. The establishment of clinical and pathological diagnosis currently relies on dedicated 'pancreatic protocol' CT, MRI/cholangiopancreatography, endoscopic ultrasound and guided fine needle aspiration. Given surgical resection of early stage cancer is curative at least in some cases, the concept of screening high-risk individuals to detect the cancer at its earliest stage has been evaluated over the last 10 years. Although the advances in imaging modalities, particularly those without radiation exposure, such as endoscopic ultrasound and MRI have made screening programs safe and feasible, studies demonstrating the impact of these programs on survival outcomes are lacking. Thus, screening of high-risk individuals is not ready for widespread clinical practice and should be conducted by clinicians who have expertise in endoscopic ultrasound for screening of high-risk individuals in a research setting with prospective data collection.

Despite the reduction in incidence of all other cancers in recent years, there has been an increase in pancreatic cancer incidence over the last three decades and it is projected to be the second most common cause of cancer death by 2030.[1] Improvement of survival relies heavily on early detection, with surgical resection perceived as the only curative option.[2] Unfortunately, only 20% of patients are suitable for surgery at diagnosis.[3] Diagnosis predominantly requires imaging techniques (CT, MRI/cholangiopancreatography [MRCP], endoscopic ultrasound [EUS]) and tissue acquisition. One strategy for improving outcomes in patients with pancreatic cancer is to develop effective screening protocols to identify more patients at an earlier stage, by identifying highly specific biomarkers or 'high-risk' individuals for pancreatic cancer. Unfortunately, thus far, there are no reliable tumour markers or biomarkers for the early detection of pancreatic cancer.[4] This review focuses on diagnosis and screening of pancreatic cancer.

Diagnosis

Clinical manifestations

The majority of patients with pancreatic cancer present late as they are often asymptomatic in the early stage of their disease. The most common symptoms at diagnosis are either painless jaundice or vague epigastric pain radiating to the back. This is because over two thirds of pancreatic cancers are located in the head of the pancreas and cause obstruction of the biliary tract.[5] Other non-specific complaints include anorexia, weight loss, lethargy and change in bowel habit. In advanced disease, symptoms of gastric outlet obstruction (post-prandial nausea and vomiting) can occur secondary to duodenal stricture caused by direct tumour invasion, suggesting that clinical manifestations can be an indicator of disease staging. Abdominal pain and weight loss are more frequently found in patients with later stages of disease.[6]

Investigations

Although a number of conventional imaging modalities can be used for the work-up of pancreatic cancer (table 1),[7] contrast 'pancreatic protocol' multi-detector row computed tomography (MDCT) is the best initial imaging modality for both the diagnosis and staging of patients with suspected pancreatic cancer.[8] MRI with MRCP has similar sensitivity and specificity in detection of pancreatic cancer and can be used as an alternative to MDCT depending on the local expertise and availability. MRI is most useful in cases where CT fails to show a mass lesion within the pancreas, or tumours are suspected to be smaller than 1cm, either in the pancreas or liver.[9] For pancreatic lesions less than 2cm, EUS has a sensitivity of 93%, which is significantly greater than that from MDCT (53%) and MRI (67%) (table 2),[10-17] and has a major role in patients who have had cross sectional imaging but were still unable to definitively rule out pancreatic lesions. The sensitivity

of trans-abdominal ultrasound is poor and it is therefore not used.[18,19] The role of positron emission tomography with CT (PET/CT) in the work-up of pancreatic cancer remains unclear. In a recent prospective study of 56 patients, PET/CT altered management in 16% of patients due to detection of metastases that was not identified by other imaging modalities.[20] Given its relatively small impact in the overall management, PET/CT is not routinely recommended in the work-up of pancreatic cancer.

Serum carbohydrate antigen sialyl Lewis, also known as Ca19-9, greater than 1000U/ml in conjunction with a pancreatic mass is highly diagnostic of pancreatic cancer. However, Ca19-9 is not specific to pancreatic cancer and can be markedly increased in biliary obstruction. The overall sensitivity and specificity of Ca19-9 for predicting the presence of pancreatic cancer in a patient with a pancreatic mass, are both 80%.[21] A normal Ca19-9 result does not exclude pancreatic cancer.[22] Monitoring serum Ca19-9 level is also useful in assessing the therapeutic response to various types of treatment in patients with pancreatic cancer. In patients undergoing surgical resection, postoperative decrease to less than 200 U/mL has been shown to be a strong predictor of survival.[23] In patients with locally advanced pancreatic cancer undergoing neoadjuvant chemoradiotherapy, a level less than 90 U/mL is associated with increased overall survival with the possibility of surgical resection.[24]

EUS-FNA has become the preferred technique for establishing tissue diagnosis, with sensitivity of 85% and specificity 98%.[25] It is a safe procedure with complication rates of approximately 1%,[26] and the risk of tumour seeding is significantly lower than that of the percutaneous approach.[27] Contrast enhancement and elastography are adjunctive techniques during EUS evaluation, as both can increase the sensitivity and accuracy of pancreatic cancer detection and help target the best area for FNA.[28,29]

***Table 1**: Summary of imaging modalities for detection of pancreatic cancer.*

Imaging modality	Sensitivity	Specificity	Advantages	Disadvantages
Trans-abdominal ultrasound	50-90%	98%	Minimally invasive, inexpensive	Unreliable for exclusion
MD CT	75-100%	70-100	Good assessment of vascular invasion and distant metastases	Less sensitive for lesions ≤2cm
MRI/MRCP	84-100%	88%	Better ductal assessment; vascular invasion	
EUS	Approaching 100%	95%	EUS FNA; high accuracy even with lesions < 2cm; local staging	Invasive, limited imaging range

***Table 2**: Diagnostic accuracy of EUS, CT and MRI for identifying pancreatic mass.*

Publications	Sample size	MRI	CT	EUS	P-value
Palazzo 1993	64		69%	96%	<0.05
Yasuda 1993	29		72%	100%	<0.05
Muller 1994	49	83%	69%	94%	<0.05 (EUS vs CT) NS (EUS vs MRI)
Nakaizumi 1995	232		65%	94%	<0.05
Gress 1999	81		74%	100%	<0.05
Mertz 2000	35		53%	93%	<0.05
DeWitt 2004	80		86%	98%	<0.05
Borbath 2005	59	88%		98%	NS

NS – non significant

Staging of pancreatic cancer

Accurate disease staging is crucial to the management of pancreatic cancer, as surgical resection carries significant morbidities and mortality. MDCT is the imaging modality of choice for the assessment of vascular involvement and distant metastasis.[30-32] If MDCT is not available, MRI/MRCP can be considered an appropriate alternative.[33] When available, EUS should also be used for tumour (T) and nodal (N) staging, especially as an adjunct examination during EUS guided biopsy. A recent meta-analysis showed that for resectability, EUS has a similar sensitivity (87 vs 90%) and higher specificity (89 vs 69%) compared to MDCT,[34] but is superior to CT for detection of tumour invasion at the portal vein confluence (table 3).[14,16,35-37] Furthermore, EUS has a higher sensitivity over MDCT for detecting (and sampling) coeliac lymph nodes and small ascites.[38,39] EUS however, has limited ultrasound penetration range and cannot detect distant metastatic disease.[40] Therefore, EUS and MDCT have complementary roles in the staging of pancreatic cancer.

***Table 3**: Accuracy of EUS/CT/MRI in staging pancreatic cancer.*

Publications	Sample size	MRI	CT	EUS	P-value
Gress 1999	81		60%	93%	<0.001
Ahmad 2000	63	77%		69%	NA
Ramsay 2004	27	83%	76%	63%	NS
Soriano 2004	62	75%	83%	67%	NS
DeWitt 2004	53		77%	77%	NS

NS – non-significant

Screening for pancreatic cancer

Most patients with pancreatic cancer remain asymptomatic until the tumour has grown to an unresectable stage.[3] Given the five-year survival of patients with resected tumours less than 1cm in size is as high as 78%,[41,42] the most logical way to improve survival is via the identification of early disease or precursor lesions by screening asymptomatic individuals. There are three known histologically well-defined precursor lesions involved in pancreatic carcinogenesis called pancreatic intraepithelial neoplasms (PanINs), intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms.[43] A recent study indicated that there was a 10 year interval between the initial mutation and the birth of the first pancreatic cancer founder cell, and another six years for the development of the clone with metastatic potential.[44]

Currently, a population based screening program is not feasible due to the low incidence of pancreatic cancer (approx. 11:100,000 in Australia) and the lack of simple, safe, accurate, inexpensive and non-invasive diagnostic tests for early lesions.[45] As proposed by the International Cancer of the Pancreas Consortium (CAPS) however, screening individuals with a greater than 5% lifetime risk or five-fold increased relative risk of developing pancreatic cancer (i.e. high-risk individuals) may be cost-effective and is under evaluation.[46]

A number of inherited and acquired conditions significantly increase the risk of pancreatic cancer (table 4 and 5). Up to 10% of pancreatic cancer results from a genetic susceptibility and/or familial aggregation.[47] Although they are rare, Peutz-Jeghers syndrome (PJs), hereditary chronic pancreatitis and familial pancreatic cancer syndrome (FPC) are the three conditions that subject patients and their first-degree relatives to the highest risk of developing pancreatic cancer (table 4) (8-60% lifetime risk). FPC is characterised by two or more first-degree relatives with pancreatic cancer in the absence of a known cancer syndrome, and thus, those with two or more relatives with pancreatic cancer (with at least one being a first degree relative) should be considered for screening.[46] Although there is a higher prevalence of patients with Lynch syndrome and hereditary breast-ovarian cancer syndrome, the lifetime risk of developing pancreatic cancer with these syndromes is only approximately 5%.[48]

***Table 4**: Hereditary conditions with sufficiently high life-time risk of pancreatic cancer warrant screening and surveillance.*

Condition	Gene	Pattern	Prevalence	Relative risk	Lifetime risk
Peutz Jeghers syndrome	STK11, LKB1	Autosomal dominant	1:100000	132	30-60%
Hereditary chronic pancreatitis	PRSS1	Autosomal dominant	0.3:100000	50-70	40%
Familial atypical multiple mole melanoma syndrome	CDKN2A, p16-Leiden	Autosomal dominant	unknown	20-34	17%
Familial pancreatic cancer syndrome - 3 or more FDR - 2 FDR	PALLD, BRCA2, CDKN2a, PALB-2, FANC-G, FANC-C	Mostly autosomal dominant	unknown	32-48 8-28	16-23% 3-8%
Hereditary breast and ovarian cancer syndrome	BRCA2	Autosomal dominant	1:400-800*	5-10	5%
Lynch syndrome	MLH1, MSH2, MSH6, PMS2, EPCAM	Autosomal dominant	1:440	5-10	3.7%
Cystic fibrosis	CFTR	Autosomal recessive	3:10000	5	<5%
Ataxia telangectasia	ATM	Autosomal recessive	1:40000-100000	3-8	<5%

*Prevalence of BRCA1/2

***Table 5**: Non-genetic risk factors for developing pancreatic cancer.*

Condition	Relative risk	Lifetime risk
Chronic pancreatitis	14	~5%
Type 1 or new onset type 2 diabetes	2-8	<5%
Obesity	2	<5%
Smoking	2	<5%

Of the acquired pancreatic conditions that carry an increased risk of pancreatic cancer, mucinous cystic neoplasm and main- or branch-duct type IPMNs have significant increased lifetime risk of developing pancreatic cancer that warrant interval surveillance (MRI or EUS). Currently, there are a number of guidelines on the management of these high-risk cystic neoplasms and this will not be further discussed in this review. Longstanding chronic pancreatitis is another risk factor for developing pancreatic cancer where screening may be justified. Although smoking, obesity and diabetes (type 1 and new onset type 2) are risk factors for pancreatic cancer, the proportion of attributable disease is small and they are not current indications for screening.[49]

EUS and MRI/MRCP are the imaging modalities of choice for screening as they have sufficient sensitivities and specificities to detect small lesions (or early cancer) and do not carry the risks of radiation exposure.[46] The high resolution of EUS enables the detection of lesions 5mm (or smaller), which can also be biopsied for tissue diagnosis during the procedure.[46,50] MRCP is the best modality for visualising cyst communication with the main pancreatic duct.[51] ERCP is not recommended due to risk of pancreatitis and low yield.[46] Ca19-9 has no role in detection of precursor lesions or early pancreatic cancer. Currently many biomarkers are under research (serum carcinoembryonic antigen-related cell adhesion molecules [CEACAM], Span -1, MIC-1, pancreatic juice analysis for Kras mutation), but not currently in routine clinical use.

The age with which to commence screening varies depending on the condition and also remains an evidence-free zone. The CAPS consortium recommends patients with hereditary chronic pancreatitis commence screening at 40 years of age, since there is a younger age of onset of pancreatic cancer. Other subjects with high-risk conditions should commence screening at age 50 years or 10 years younger than the youngest pancreatic cancer in the family. Smoking is a strong risk factor in familial pancreatic cancer kindreds, particularly in men and people less than 50 years old, as it increases the risk of pancreatic cancer by 2-3.7 times over the inherited predisposition and lowers the age of onset by 10 years.[52] Currently, there is no consensus as to when screening should cease and should be judged on an individual basis.

Patient preference and fitness for surgery are important factors, which should be incorporated into the decision-making.

The optimal interval for surveillance also remains unclear. Available data from the CAPS Consortium suggest a 12-month surveillance interval for high risk individuals with no pancreatic lesions found at baseline assessment.[46] For those with abnormalities found on baseline imaging, the interval varies dependent on the nature of the lesion. Non-suspicious cysts should have surveillance after 6-12 months, while newly detected indeterminate solid lesions or indeterminate main pancreatic duct strictures should have repeat imaging at three months. Subjects with IPMN should continue surveillance according to the international consensus guidelines.[53]

Current data supporting screening is limited to prospective observational studies in high-risk individuals (table 6).[22,50,51,54-60] Poley et al were the first to evaluate the role of EUS, MRI and/or CT scans in screening of 44 high risk individuals, consisting those with a history of FCP, PJS, familial atypical multiple mole melanoma syndrome (FAMM) and BRCA2.[55] Seven patients had branch duct IPMNs and three had pancreatic adenocarcinoma, proven on surgical resection. The largest study to date (n=192) is a multicentre, prospective cohort study (CAPS 3) of high-risk individuals, using CT, MRI and EUS imaging.[51] Positive findings were detected in 42% (92/216) of patients. Pancreatic mass (84 cystic and three solid) and dilated pancreatic duct (n=5) were identified by one of the imaging modalities and prevalence of these lesions appeared to increase with age. Of all imaging modalities, EUS appeared to have the highest diagnostic yield (CT, MRI and EUS detected pancreatic abnormality in 11%, 33.3% and 42.6% of patients respectively). Among the pancreatic lesions, 82 were IPMNs and three pancreatic neuroendocrine tumours. Five patients underwent surgery and three of them had high grade dysplasia in <3cm IPMNs and multiple intraepithelial neoplasms, suggesting that screening of asymptomatic high risk individuals can detect curable non-invasive high grade lesions. In contrast, the National German Familial Pancreatic Cancer Registry reported a lower rate of pancreatic abnormalities in their high risk individuals (5%), with the majority of the abnormalities being non-malignant.[22,56] This study was the first to raise concern about the potential harm of a screening program and highlights the extreme importance of discussing all positive findings in a pancreatico-biliary multi-disciplinary meeting to determine the optimal surveillance interval, need for biopsy, further investigation or surgery.

Overall, the current data indicate that diagnostic yield of neoplastic pancreatic lesions varies significantly (5% to 50%), whereas the detection rate for pancreatic cancer is only 1% to 2% (table 6). These data are consistent with the findings from a recent systematic review of 542 high-risk individuals screened.[61] The vast range seen in those studies is likely due to differences in the definition of high-risk subjects, measured outcomes and use of varying screening modalities. In particular, the definition of 'positive yield' varies from precursor lesion (cysts, branch duct IPMN) to early cancer. As such, most recent studies that defined positive yield as early stage 1 cancer or high-grade dysplastic precursor lesions often have a lower detection rate (1-2%), whereas those that included cystic lesions, IPMNs or PanINs of any grade of dysplasia tend to report a much higher yield (up to 50%).[50,54,58,60]

The ability to detect 'PanIN' lesions by EUS is controversial and the sonographic features of PanIN are non-specific and not well validated. PanIN may have sonographic features similar to that of chronic pancreatitis, as PanINs are multifocal and are often associated with lobular centric atrophy and fibrosis,[62] which are also seen in chronic pancreatitis or age related parenchymal fibrosis.[46] Furthermore, the ability to recognise 'lobularity' on EUS is very operator-dependent, and cannot be distinguished from other disease processes.

***Table 6**: Summary of studies on screening and surveillance of pancreatic cancer in high-risk individuals.*

Study (reference)	Screening modality	Sample size	At-risk population	All lesions identified (%)	pancreatic cancer identified (%)
Canto et al. 2004	EUS	38	5	5 (13%)	1
Canto et al. 2006	EUS	78	6	6 (8%)	1
Poley et al. 2009	EUS	44	FPC, PJS, BRCA, p16, p53, HP	7 (16%)	3
Langer et al. 2009	EUS, MRCP	76	FPC, BRCA	4 (5%)	0
Verna et al. 2010	EUS, MRCP	51	FPC, BRCA, p16	4 (8%)	2
Ludwig et al. 2011	MRCP	109	FPC, BRCA	7 (6%)	1
Al-Sukhni et al. 2012	MRCP	262	FPC, PJS, BRCA, p16, HP	19 (7%)	2
Schneider et al. 2011	EUS, MRCP	72	FPC, BRCA, PALB2	11 (15%)	1
Vasen et al. 2011	MRCP	79	P16	14 (18%)	7
Canto et al. 2012	MRCP, EUS, CT	216	FPC, BRCA, PJS	93 (43%)	1

Several studies have addressed the psychological impact of screening programs. Axilbund et al found genetic counselling to be helpful to more than 90% of high-risk individuals despite the inability to identify a causative gene.[63] More importantly, patients who participated in a screening program did not experience increased anxiety or perception of cancer risk,[64] and 80% of the participants felt the advantages of screening outweighed the risks.[65] Overall, available data suggest that screening is not associated with any adverse impact on the patient's psychology.

Conclusion

Pancreatic cancer carries a dismal prognosis, largely due to the late stage of disease at presentation. Early detection is of utmost importance given that surgical resection is the only treatment option that is curative at least in some cases. There are multiple suitable imaging modalities (EUS, MRI/MRCP and MDCT) used for detection and staging of pancreatic cancer, each with its own strengths and weaknesses. EUS FNA is the preferred method for tissue diagnosis of pancreatic masses and may be used in conjunction with pancreas protocol CT for staging. Screening for pancreatic cancer in high-risk individuals is currently driven by consensus guidelines recommended by the International CAPS consortium. Long-term outcome data to determine the clinical impact and utility of a screening program, especially on survival, are awaiting. It is therefore important that all screening programs are conducted in a research setting within centres with the appropriate training and expertise in performing EUS in high-risk individuals.

Conflicts of interest

Dr Phan has no conflicts of interest.

Dr Saxena has received consulting fees from Olympus Australia, Pentax Medical and Cook Medical. She is a consultant for Boston Scientific. She has received research support from Cook Medical and Boston Scientific. She is on the scientific advisory board member for Oncosil Medical Ltd.

Dr Alina Stoita has no conflicts of interest.

A/Prof Nguyen has no conflicts of interest.

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INHERITED PANCREATIC CANCER

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Abstract

Up to 10% of pancreatic cancer cases have a heritable component. Some of these are clearly defined tumour predisposition syndromes known as hereditary pancreatic cancers, but most are familial cases, defined by family history and where the underlying genetic causes remain unknown. Genetic counselling is important in suspected inherited pancreatic cancer cases, to enable risk assessment and relevant genetic testing. Screening trials are available for at-risk individuals (i.e. >5% lifetime risk), although more long-term data is required to determine the risks, benefits and optimal approaches to pancreatic cancer surveillance.

Pancreatic cancer is a lethal disease with an overall five-year survival rate of 6%. It is the fifth most common cause of cancer death in Australia.[1] Surgical resection offers the only potential for cure, but is limited because the majority of patients present with locally advanced or metastatic disease. Although early detection of pancreatic cancer is recognised as the best strategy to improve patient outcomes, population screening is not recommended because of low incidence and the lack of a robust screening test. Screening tests need to demonstrate validity, reliability yield, acceptable cost and the availability of accepted treatment to align with the World Health Organisation principles of early disease detection.[2]

Pancreatic cancer is aetiologically complex, arising from a combination of environmental and genetic factors. Established environmental risk factors include age, cigarette smoking, diabetes mellitus and obesity.[3-5] Up to 10% of pancreatic cancer has a heritable component, presenting in three different clinical settings: 1. Hereditary tumour predisposition syndromes which account for 15-20% of the burden of inherited disease; 2. Hereditary pancreatitis; 3. Familial pancreatic cancer, defined as a family with at least two first-degree relatives with pancreatic cancer who do not fulfill the diagnostic criteria for a hereditary tumour syndrome.

Hereditary tumour predisposition syndromes

Germline mutations in the BRCA1 and BRCA2 genes cause approximately 45% of hereditary breast-ovarian cancer. In addition to an increased risk of breast and ovarian cancer, pathogenic germline BRCA2 mutations place carriers at modestly increased risk of pancreatic cancer.[6] In familial pancreatic cancer, the prevalence of pathogenic BRCA2 mutations increases with the number of affected relatives - 6-12% in families with two or more with pancreatic cancer and 16% in families with three or more with pancreatic cancer,[7,8] and within ethnicities known to carry founder mutations. BRCA2 prevalence in unselected, likely sporadic pancreatic cancer cohorts range from 0.7 - 3.6%.[9,10] The relative risk of pancreatic cancer in BRCA2 mutation carriers is 3.5-6 fold (table 1).[11] The lack of reported pancreatic cancer or breast-ovarian family history in BRCA2 pancreatic cancer patients is likely due to reduced penetrance for pancreatic cancer rather than a pancreatic cancer specific genotype-phenotype correlation for BRCA2 mutations.

In contrast, the role of BRCA1 mutations and predisposition to pancreatic cancer is less well defined. Initial studies in BRCA1 mutation positive families with young-onset breast or ovarian cancer suggested a 2.26 fold (95% CI = 1.26–4.06) increased risk of pancreatic cancer, however BRCA1 mutations are uncommon in families reporting a history of pancreatic cancer alone.[12]

Familial melanoma is an autosomal dominant syndrome characterised by predisposition to melanoma and pancreatic cancer. Germline mutations in the CDKN2A gene have been reported in 25% of all melanoma prone families.[13] CDKN2A carriers have a 13 to 22-fold risk of developing pancreatic cancer (table 1), which may be a genotype- phenotype effect. The CDKN2A-pancreatic cancer relationship has not been demonstrated in Australia, likely due to a broad spectrum of mutations.[13] Reports of CDKN2A prevalence in familial pancreatic cancer vary (3.3% - 21.4%) and are not always associated with personal/family history of melanoma.[14,15]

Peutz-Jegher syndrome is an autosomal dominant disorder caused by germline STK11 mutations. Clinical presentation includes gastrointestinal tract polyposis and mucocutaneous pigmentation, often around the lips.[16] The pancreatic cancer risk in Peutz-Jegher syndrome individuals is 132 fold (95% CI = 44–261) (table 1).[17] Mutations in STK11 account for less than 1% of inherited pancreatic cancer.

Lynch Syndrome is caused by germline mutations in the DNA mismatch repair (MMR) genes MSH2, MLH1, MSH6

and PMS2. Patients have an increased risk of early-onset colorectal and endometrial cancer, as well as lower risk of other tumour types including pancreatic cancer. A prospective cohort study of 446 MMR mutation carriers identified two pancreatic cancer cases, corresponding to a SIR of 10.68 (95% CI 2.7 – 47.7) and a 10-year pancreatic cancer risk of 0.95% (table 1).[18] The prevalence of germline MMR gene mutations in pancreatic cancer patients with a personal or family history of colorectal cancer is as high as 10% but may represent selection bias.[9,19]

Familial adenomatous polyposis is primarily caused by mutations in the adenomatous polyposis coli (APC) gene. Patients are at risk for thyroid tumours, gastric, duodenal and ampullary adenocarcinoma. The relative risk for pancreatic cancer has been reported as 4.46 (95% CI 1.2 – 11.4),[20] but this may be due to coding errors as recent data suggests the prevalence of pancreatic cancer is low.[21]

Li-Fraumeni syndrome is a rare highly penetrant autosomal dominant cancer predisposition syndrome, frequently caused by mutations in the TP53 gene. It is characterised by early onset tumours including sarcoma, adrenocortical carcinoma, breast cancer, leukaemia and brain tumours. The risk of pancreatic cancer is increased but unquantified.[22]

Hereditary pancreatitis

Hereditary pancreatitis is a rare autosomal dominant form of pancreatitis. Mutations in the cationic trypsinogen gene (PRSS1) are found in up to 80% of cases. Patients with hereditary pancreatitis have a significantly increased risk of developing pancreatic cancer, estimated to be 58-fold (95% CI 23 – 105) (table 1).[23] Cigarette smoking is a major co-risk factor for pancreatic cancer development, increasing the risk by two-fold and lowering age at diagnosis by 20 years.[24]

Familial pancreatic cancer

Familial pancreatic cancer is defined as a kindred, with at least two first-degree relatives with pancreatic cancer not otherwise fulfilling the diagnostic criteria for a hereditary tumour syndrome.[25] The relative risk of developing pancreatic cancer increases with each additional affected first-degree relative: one first degree relative 4.6 (CI 0.5 – 6.4); two first degree relative 6.4 (CI 1.8 – 16.4); three first degree relative 32.0 (CI 10.2 – 74.7) (table 1).[26] The risk is two to three times higher in smokers, particularly males under the age of 50.[27] The presence of pancreatic cancer cases <50 years confers an additional risk.[28] Furthermore, familial pancreatic cancer kindreds have other cancers including breast, ovarian, endometrial and melanoma.[29,30]

Many familial pancreatic cancer kindreds demonstrate probable autosomal dominant inheritance, yet less than 25% have a mutation identified. PALB2 and ATM are moderate risk familial pancreatic cancer susceptibility genes accounting for 4.2% and 3.6% respectively.[31,32] Whole genome sequencing technology holds the potential to identify additional lower-penetrance genes that contribute to the remaining familial pancreatic cancer cases.

***Table 1**: Genetic risk factors for pancreatic cancer.*

Genetic risk group	Syndrome	Relative risk (95% CI)	Estimated lifetime pancreatic cancer risk (70 – 80 years)
STK11	Peutz Jeghers syndrome	132 (44-261)	11 – 32%
PRSS1	Hereditary pancreatitis	58 (23-105)	20 – 40% (higher range in smokers)
CDKN2A	Familial melanoma	38 (10-97)	17%
BRCA2	HBOC/familial pancreatic cancer	3.51 (1.87-6.58)	3 – 8 %
MSH2, MLH1, MSH6, PMS2	Lynch syndrome	8.6 (4.7-15.7)	3.6% [33]
BRCA1	HBOC	2.26 (1.26-4.06)	2.1%
APC	Familial adenomatous polyposis	4.46 (1.2 – 11.4)	Elevated but not defined
TP53	Li-Fraumeni Syndrome	Elevated but not defined	Elevated but not defined
PALB2	Familial pancreatic cancer	Elevated but not defined	Elevated but not defined
ATM	Familial pancreatic cancer (monallelic)	Elevated but not defined	Elevated but not defined
Clinical risk group	**Syndrome**	**Relative risk (95% CI)**	**Estimated lifetime pancreatic cancer risk (70 – 80 years)**
General Population	NA	1	0.96%
1 FDR pancreatic cancer	Familial pancreatic cancer	4.6 (0.5 - 6.4)	4%
2 FDR pancreatic cancer	Familial pancreatic cancer	6.4 (1.8 - 16.4)	8-12% [26]
≥3 FDR pancreatic cancer	Familial pancreatic cancer	32 (10.2 - 74.7)	16-30% [26]

Genetic counselling and testing for inherited pancreatic cancer

Obtaining a complete three-generation pedigree of malignancy, including pathological confirmation where possible, is important as it can suggest an underlying genetic predisposition or common environmental factor. It also facilitates risk assessment and discussions of genetic testing and risk-reducing strategies in family members.[29] PancPro is a Bayesian model developed from National Familial Pancreatic Tumour Registry pedigree data. It calculates the risk that a person carries a high-penetrance pancreatic cancer gene and the age-related risk of developing cancer.[34] PancPro demonstrates an observed to predicted pancreatic cancer ratio of 0.83 (95% CI, 0.52 to 1.20).[35]

Testing for known pancreatic cancer susceptibility genes is carried out by local familial cancer clinics according to genetic testing and clinical management guidelines (e.g. eviQ,[36] National Comprehensive Cancer Network).[37] When clinically indicated (table 2), genetic testing is best offered to individuals with a confirmed diagnosis of pancreatic cancer. Because of the high mortality rate, storing DNA from pancreatic cancer cases with any family history is important. Genetic testing in unaffected individuals is informative only when the mutation in an affected relative is known.

Affected and unaffected family members may be eligible to participate in familial pancreatic cancer research projects. Familial pancreatic cancer registries have been established to further understand the aetiology of familial pancreatic cancer, identify candidate pancreatic cancer susceptibility genes and provide high-risk populations for early detection studies.[38]

Early detection in inherited pancreatic cancer

Screening the general population for pancreatic cancer is not feasible because of its low incidence, absence of a suitable biomarker or imaging modality and lack of proven early interventions. However, it has been proposed that a high-risk population could benefit from early detection strategies. Global screening studies are underway to determine appropriate screening modalities and parameters.

The primary imaging modalities utilised in these studies are endoscopic ultrasound, magnetic resonance imaging with/without magnetic resonance cholangiopancreatography and computerised tomography. Findings from the pancreatic cancer screening studies to date are difficult to consolidate because of differing populations, imaging modalities and endpoints used. Many studies have successfully demonstrated that precursor lesions or invasive cancers can be detected in a significant proportion of at-risk individuals, but none to date have successfully demonstrated better outcomes for patients.

There is also no consensus as to the timing, inclusion criteria and initiation/cessation ages for pancreatic cancer surveillance programs. Guidelines suggest those with a minimum 5-10 fold-increased risk should be considered. An international consortium agreed that the following groups: familial pancreatic cancer with at least two first degree relatives affected; patients with Peutz-Jeghers syndrome; patients carrying BRCA1/2, CDKN2A, or MMR gene mutations with at least one FDR affected should be screened if eligible for surgical treatment.[41]

Conclusion

Inherited cases of pancreatic cancer are rare, which hinders understanding of the genetic etiology and then introduction of clinical management guidelines for this complex disease. Family cancer clinics are important for assessing family history and identification of possible hereditary tumour predisposition syndromes. Familial pancreatic cancer research cohorts are vital for identification

***Table 2**: Clinical indications for cancer predisposition assessment.[39,40]*

Clinical criteria	Syndrome to consider	Gene(s) to consider
PC diagnosed any age, if any of the following criteria are met: • ≥ 2 cases pancreatic cancer in close relatives • ≥ 2 cases breast, ovarian or prostate cancer in close relatives • Ashkenazi Jewish ancestry	Familial pancreatic cancer, hereditary breast and ovarian cancer	BRCA1, BRCA2, PALB2, ATM BRCA1, BRCA2, PALB2 BRCA1, BRCA2
Pancreatic cancer and ≥1 PJ polyp	Peutz-Jegher syndrome	STK11
Pancreatic cancer and ≥ 2 additional cases of any Lynch syndrome associated cancer in the same person or close relative	Lynch syndrome	MSH2, MLH1, PMS2, MSH6
≥ 3 cases of pancreatic cancer and/or melanoma in close relatives or pancreatic cancer and melanoma in the same person	Familial melanoma	CDKN2A
Personal history of ≥2 attacks of acute pancreatitis of unknown aetiology, a family history of pancreatitis, or early age of onset of chronic pancreatitis	Hereditary pancreatitis	PRSS1

of additional pancreatic cancer susceptibility genes and defining effective screening protocols translatable into clinical practice.

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Useful links

https://www.eviq.org.au/

http://www.genetics.edu.au/

http://www.pancreaticcancer.net.au/afpacc

https://www.pancare.org.au/patient-support-services/clinical-trials/

http://bcb.dfci.harvard.edu/bayesmendel/pancpro.php

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PANCREATIC NEUROENDOCRINE TUMOURS – A RARE PANCREATIC TUMOUR

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Abstract

Pancreatic neuroendocrine tumours are rare tumours that can either present with syndromes from excess hormonal production or from mass effect – from the primary or metastases. They vary widely in clinical course, with the main determinants of outcome being TNM staging and pathological grade. The available treatment options depend largely on the grade of the tumour – somatostatin analogues, targeted agents, chemotherapy and PRRT for IG1 and G2 PNETs, and chemotherapy as the mainstay of treatment for high grade NET/NECs. The paucity of randomised evidence in the treatment of this disease argues for ongoing research to understand the molecular genetics underlying PNETs, to develop possible future treatment options, as well as optimising use of existing ones.

Neuroendocrine tumours (NETs), formerly known as carcinoid tumours, arise from cells in the neuroendocrine system, a diverse population of hormone-producing cells distributed throughout the gastrointestinal tract as well as the bronchial system. Although NETs have been increasing in incidence, they still remain a rare tumour (being defined by the RARECARE group as incidence less than 6/100,000 per year).[1]

Pancreatic neuroendocrine tumours are generally abbreviated as PNETs. PNETs were previously named 'islet cell tumour' or 'pancreatic carcinoid', but the use of these terms is discouraged. PNETs comprise 5-10% of neuroendocrine tumours, and 1-2% of all pancreatic tumours.[2] In contrast to other pancreatic tumours, PNETs are distinguished by marked heterogeneity – in histology, clinical course and prognosis. Neuroendocrine malignancies are named as neuroendocrine tumours (NET) if well or moderately well differentiated histologically, or neuroendocrine cancers (NEC) if poorly-differentiated.

The incidence of PNETs in Australia has been gradually increasing. Statistics from the South Australian Cancer Registry showed an incidence rate of 0.15/100,000 a year in 1980-2006, comprising 6.5% of all NETs diagnosed in that period.[3] However, this incidence has been rising steadily over the last 20 years. The increasing survival rate from PNETs over that time likely reflects earlier diagnosis of disease and initiation of appropriate management.[4]

Histology can vary in PNETs according to the grade of tumour. Well-differentiated tumours express somatostatin receptors (SSTRs), have low mitotic counts (<2) and a Ki67 proliferative index of <2%. As tumours become less well differentiated, expression of SSTRs is lost and the mitotic count and Ki67 increase. Ultimately, a high-grade undifferentiated NEC can look identical to other undifferentiated carcinomas.

The initial World Health Organisation (WHO) classification in 1980 divided NETs by histological appearance into carcinoid tumours, mucocarcinoid tumours, mixed carcinoid adenocarcinoma and pseudotumour lesions. Since then, there has been a shift towards quantitative measures such as mitotic count and Ki67, culminating in the most recent European Neuroendocrine Tumour Society/World Health Organisation (ENETS/WHO) scheme of 2010 (table 1), which is the current standard for pathological reporting. However, routinely performing these counts can be time-consuming for pathologists, and samples can contain areas of both high-grade and low-grade disease. This poses challenges both in terms of accurate diagnosis and optimal management.

***Table 1**: 2010 World Health Organisation (WHO) classification of neuroendocrine tumours.*

Grade	Mitotic count (mitoses per 10 high power fields)	Ki-67 index	Traditional nomenclature	WHO/ENETS nomenclature
Grade 1	<2mit/10HPF	<3%	Carcinoid, islet cell tumour	Neuroendocrine tumour, Grade 1
Grade 2	2-20mit /10HPF	3-20%	(Atypical) carcinoid, islet cell tumour	Neuroendocrine tumour, Grade 2
Grade 3	>20mit/10HPF	>20%	Small cell carcinoma, large cell neuroendocrine carcinoma	Neuroendocrine carcinoma (large cell or small cell type)
Mixed adenoneuroendocrine carcinoma				
Hyperplastic and pre-neoplastic lesions				

Mit: Mitoses, HPF: High power fields, ENETS: European Neuroendocrine Tumour Society

Clinical presentation and workup

PNETs are classified as functional and non-functional, and these present in very different ways. The production of functional hormones can produce classical presentations, such as hypoglycaemia (insulinoma), gastric ulcers (gastrinomas), diarrhoea (vasoactive intestinal peptide), hyperglycaemia (glucagon) and even gallstones (somatostatinoma). In contrast, non-functioning tumours can grow slowly over months or even years and present with signs related to local mass effect – abdominal pain, anorexia, weight loss and nausea. Tumours in the head of the pancreas may present earlier with biliary obstruction. Unlike adenocarcinoma, differential outcomes have not been demonstrated for PNETs according to site within the pancreas.

Historically, diagnosis followed presentation with reported symptoms in most cases. However, the development of improved imaging modalities with increasing adoption has led to earlier diagnosis. Currently, PNETs present with functional syndromes in approximately 30% of cases. Approximately 10-15% of PNETs occur in the context of a genetic syndrome – either known from family history or as a new presentation. Germline mutations in a number of genes are associated with PNET including multiple endocrine neoplasia syndrome, type I (MEN1) and Von-Hippel Lindau syndrome (VHL). Clinicians should take a family history from all patients with PNETs and refer for evaluation by a cancer genetics service where needed.

Clinical workup for patients with PNETs consists of serum hormone levels, tissue biopsy, radiology and nuclear imaging. Serum Chromogranin A is the test of choice for PNETs, with good sensitivity, although false low-level elevations can occur in chronic kidney disease, congestive heart failure and medications such as proton pump inhibitors.[5] Other markers such as serum serotonin, urinary 5-HIAA (requiring a 24 hour collection) and specific hormone tests in keeping with presenting symptoms should also be considered.

Imaging modalities such as CT and MRI of the abdomen can often be helpful in defining the presence of a lesion and evaluating for liver metastases, and CT-guided biopsies (for example, of mesenteric masses) /endoscopic ultrasound (pancreatic masses) can often establish a tissue diagnosis. However, nuclear imaging has been increasingly used for staging and monitoring of response.

Nuclear imaging has been increasingly employed in establishing the extent and predicting behaviour of PNETs. DOTATATE/DOTATOC PET scans have replaced ^{111}In-based octreoscan in Australia for G1 and G2 NET, giving much greater sensitivity and spatial resolution particularly with concurrent CT.[6] FDG-PET, which relies on high cellular uptake of glucose, is useful in NEC. G2 NETs may be positive in both DOTATATE-PET and FDG-PET, reflecting varying degrees of cellular differentiation. While both FDG and DOTATATE PETs may be helpful in baseline staging of NETs (particularly G2 NETs), the FDG PET can be omitted in selected patients with low-grade NETs (e.g Ki67 <5%).

***Table 2**: Summary of imaging modalities for PNET*

Imaging modality	Potential use	Limitations	Sensitivity
CT- using specific protocol of portal venous imaging for NET	Initial evaluation of primary; detection of metastases	Poor detection of small lesions	80-84% (7)
MRI	Defining pancreatic primary	Less accessible than CT	85% (8)
EUS	High-resolution imaging, particularly for small PNET; allows biopsy	Skilled endoscopist required	97% (9)
Octreoscan	Now obsolete technique to document presence of somatostatin receptors	Poor sensitivity - Ga68 DOTATATE should be preferred if available	15-30% (10)
Ga68 DOTATE/TOC PET	Imaging of somatostatin receptor expressing tumours	Less widely available but superior to octreoscan	82-90% (6)
FDG-PET	Detection of high-grade/dedifferentiated disease or mixed disease	Unlikely to detect G1 NET; useful for G2 and NEC	66-78%

Treatment

Patients diagnosed with NETs can vary greatly both in terms of their general status and aggressiveness of their disease. Therefore, benefit from a multidisciplinary approach may lead to optimal outcomes.[11] Interested surgeons, nuclear medicine specialists, endocrinologists, histopathologists and medical oncologists are essential to formulate an accurate treatment plan in a complex disease.

Given the heterogeneity of NETs, the relatively low incidence and the multiple treatment modalities available, it has been hard to accrue patients to and complete clinical trials in NETs. However, global efforts and formation of international consortiums have allowed progress to be made based on randomised phase 3 trials. COMMNETS (detailed below) was formed in response to the need for an international NET consortium in the Asia-Pacific region.

Surgical resection with curative intent is the standard of care for localised disease. Control of hormone secretion around the time of surgery with SSAs is important. There is scant evidence for adjuvant therapy after NET resection, but adjuvant chemotherapy is sometimes offered for NEC.

Most patients present with disseminated disease (80% with liver metastases) at diagnosis. Therapeutic options vary significantly depending on the grade of the tumours, which are usually divided into options for G1-2 PNETs and G3 NECs.

Grade 1-2 PNET

Somatostatin analogues (SSAs) - octreotide, lanreotide, pasireotide - act on the somatostatin receptors and inhibit release of various pro-growth hormones such as GH, glucagon and insulin. They were initially used for symptomatic relief in NETs, but have recently been also shown to control tumour growth.[12,13]

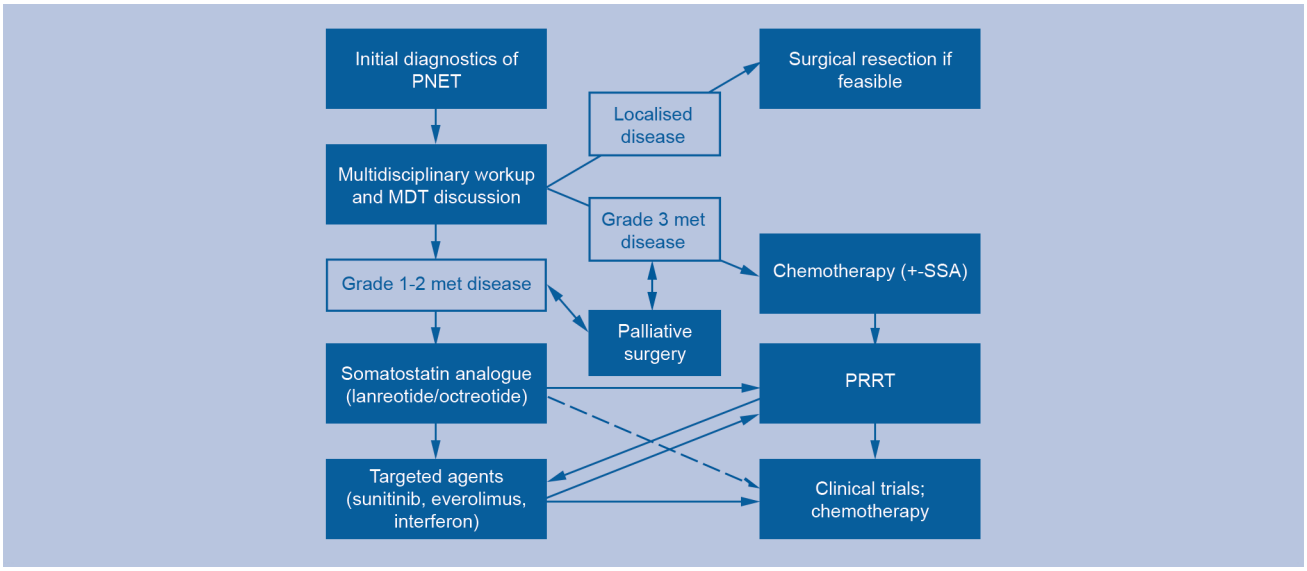
Two long-acting SSAs, octreotide LAR and lanreotide, are available in Australia for routine clinical use. SSAs can be administered by the GP, in oncology centres or under currently available pharmaceutical company-sponsored drug administration programs. It is often preferable to give the initial dose in a clinic environment, but subsequent linkage to home injection services offers convenience and quality of life, particularly important in a disease which may have a long clinical course.

Dose escalation of SSAs for patients who progress on the standard dose is a therapeutic strategy under ongoing investigation.

Various biological or 'targeted' agents show activity in PNETs (table 3), with the most commonly used being sunitinib (a multitargeted tyrosine kinase inhibitor) and everolimus (a mTOR inhibitor). Treatment modalities recently investigated include the combination of everolimus and bevacizumab, octreotide and interferon, as well as octreotide and bevacizumab. The optimal use, sequencing and combination of biological agents is still an open question in the management of G1-2 PNETs.

Unfortunately, the use of PBS-funded sunitinib and everolimus are restricted in Australia. According to regulations, patients who have progressed on sunitinib are not eligible for funded everolimus and vice versa. While relatively less data exists to assess the efficacy of using these agents sequentially, this funding paradigm deprives clinicians of access to both drugs in an individual patient.

***Figure 1**: NET management pathway*



PRRT: Peptide receptor radionuclide therapy
Met: Metastatic

***Table 3**: Summary of major RCTs in targeted agents.*

Trial	Intervention	Comparator	# Patients	Mean age	Site of primary	OS HR (95% CI)	PFS HR (95% CI)
Yao 2014	Everolimus	Placebo	79	54	Pancreas	0.91(0.31-2.67)	0.28(0.13-0.59)
Yao 2011	Everolimus	Placebo	410	58	Pancreas	1.05(0.71-1.55)	0.34(0.26-0.44)
Raymond 2011	Sunitinib	Placebo	171	57	Pancreas	0.41(0.19-0.89)	0.41(0.26-0.66)
Pavel 2011	Everolimus + Octreotide LAR	Placebo + Octreotide LAR	429	60	Mixed	1.06(0.79-1.43)	0.77(0.59-1.00)

Interferon-A has been used for many years, particularly in northern Europe. There is good control in some cases of refractory diarrhoea and the drug can produce long-lasting tumour responses, but the chronic toxicity of marked fatigue and mood depression, as well as the lack of high level comparative evidence, have limited its widespread adoption in clinical practice.

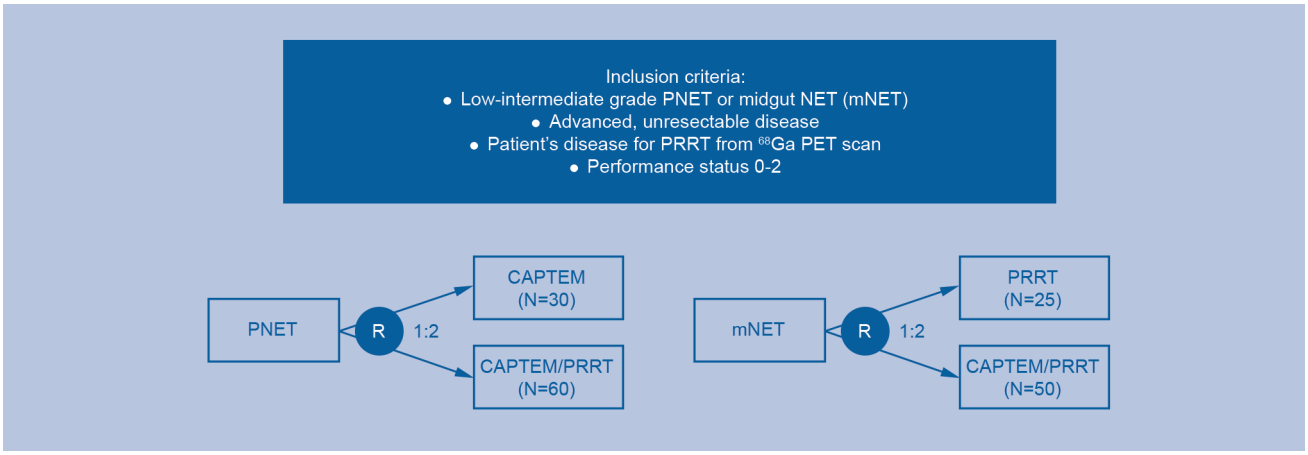
The role of peptide receptor radionuclide therapy (PRRT) has been increasingly explored in the management of metastatic G1 and G2 PNETs over the last 20 years. Similar in concept to targeted radiation (^{131}I) for thyroid cancer, PRRT utilises a peptide which attaches to the somatostatin receptor expressed on PNETs, linked to a radionuclide (most commonly ^{177}Lutetium and ^{90}Yttrium) which emits a beta particle. The recently reported NETTER-1 trial showed that PRRT was superior to increased doses of octreotide in controlling midgut NETs. Potential short-term adverse events from PRRT include nausea, vomiting and flare of symptoms; long-term adverse events include renal impairment and bone marrow toxicity, although these are only significant in <1% of treated patients.

Currently, PRRT in Australia is available in a limited number of centres in each state in Australia. Each centre has slightly differing protocols, but the current protocol employed by Royal North Shore Hospital involves day treatment on one day every eight weeks, with four cycles in total.

Radiosensitising capecitabine is used by some centres before and after PRRT for each cycle. A multicentre phase 2 randomised control trial (CONTROL NETS) investigating the combination of CAPTEM (capecitabine/temozolomide chemotherapy) and PRRT for metastatic PNETs/midgut NETs (figure 2) is has opened in Australia under the auspices of the Australian Gastrointestinal Trials Group (http://agitg.org.au/clinical-trials/trials-open-to-recruitment/control-nets/).

The selection of PRRT compared to use of a targeted agent such as sunitinib or everolimus remains a difficult clinical dilemma in treatment of G1-2 PNETs, and the grade of tumour, potential side effects (e.g. hyperglycaemia for everolimus, fatigue for sunitinib) and biological aggressiveness all play a part in the individualised decision.

***Figure 2**: CONTROL NETS schema*



CAPTEM: Capecitabine/temozolomide combination chemotherapy

Liver-directed treatments are often employed in the management of PNETs given their propensity to metastasise to the liver. Trans-arterial bland embolisation or chemoembolisation can be used for this purpose, taking advantage of the dual blood supply to hepatic tissue. Selective internal radionuclide therapy uses the same rationale to deliver ^{90}Y-bound microspheres as targeted radiotherapy to hepatic sites of disease. However, there are no randomised trials and limited non-randomised information to allow comparison to the other treatment modalities.

Well-to-moderately differentiated tumours tend to be relatively chemoresistant. Different chemotherapeutic agents have been trialled in this setting including temozolomide, fluoropyrimidines and platinum agents, but all with disappointing results, with response rates for single agents in the 5-10% range and 20-30% with combination therapy.[14]

Surgical debulking, either for the primary or hepatic lesions, is occasionally considered in the treatment of metastatic PNET. This can be for symptomatic relief, prophylactically to prevent symptoms from a large tumour, or as part of an aggressive treatment strategy involving resection of oligometastatic disease. These options should be discussed in a multidisciplinary context with the input of experienced hepato-pancreatico-biliary surgeons.

Grade 3 NEC

Poorly differentiated NETs/NECs are treated using a different treatment paradigm to G1-2 NETs, reflecting that they behave in a much more aggressive way, akin to small cell lung cancer (another high grade tumour of neuroendocrine origin). They are usually FDG avid (conventional PET) and do not take up DOTATATE as they are too poorly differentiated to express the somatostatin receptor. Chemotherapy upfront is standard of care, with platinum/etoposide doublets the mainstay of treatment. There is some evidence that CAPTEM is a reasonable regimen for tumours with Ki67<55%.[15] PRRT for NEC can result in suboptimal treatment due to areas of de-differentiated disease which do not express somatostatin receptors and hence do not take up administered PRRT.

Prognosis and support

PNETs are curable if resected early. However, the majority of cases present with liver metastases at diagnosis. This is reflected in the correlation between TNM staging and prognosis with five-year survival decreasing from 92% (stage I disease) 57% (stage IV disease).[16] Other poor prognostic factors include G3 disease as well as features on FDG PET scan; in one retrospective series patients with FDG positive disease had a median survival of 15 months compared to 119.5 months for FDG negative patients.[17]

As with all cancers, patients diagnosed with rare tumours need much more than medical expertise. In Australia, NET patients have access to the Unicorn Foundation for support and educational resources. The Unicorn Foundation (unicornfoundation.org.au) was founded in 2009 with its main aim to promote awareness within the medical profession (both specialists and particularly GPs), and general public, and to provide patients facing a diagnosis of a NET with access to support groups throughout the country. They aim to reach the often disadvantaged rural patient population by funding a specialist NET nurse who is accessible via the telephone or email for advice on all aspects of living with a diagnosis of a NET. The Unicorn Foundation has many affiliations with international support networks and is active in raising funds and supporting research into NETs.

Given that patients with PNETs benefit from multidisciplinary care in a centre with expertise in NETs management,[18] several organisations have attempted to formalise this process both to optimise patient care and collaborate in research. The Clinical Oncology Society of Australia has published guidelines (wiki.cancer.org.au/australia/COSA:NETs_guidelines) regarding NET management. Internationally, the European Neuroendocrine Tumour Society and the North American Neuroendocrine Tumour Society (ENETS and NANETS) have also published their guidelines. ENETS has an accreditation process for 'Centres of excellence'.

In Australia, COMMNETS is a new initiative that aims to foster collaboration between the commonwealth countries in NETs. The inaugural COMMNETS conference was held in Hawaii in November 2015 involving delegates from Australia, New Zealand, Canada and Singapore (http://agitg.org.au/commnets-2015/). Barriers to care were identified and research priorities agreed upon using a modified Delphi process to generate a position document 'Gaps in NET research'.

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PANCREATIC CANCER: IS THE SURGEON STILL RELEVANT?

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Abstract

Despite advances in multimodal therapy, surgery remains central to the management of patients with resectable pancreatic adenocarcinoma. Complete surgical clearance of disease offers the only real, albeit slim, chance of cure. For the greater proportion of patients with resectable macroscopic but occult microscopic disease, who ultimately recur early, short-term outcomes are still better compared to other currently available treatment modalities. Morbidity rates following pancreatic resection are worse than cancer surgery data for other intra-abdominal sites however, and involved margins are an unsurprising predictor of poor oncological outcome. Patient selection is therefore key. Refinements in surgical technique and treatment algorithms, such as the evolving use of neoadjuvant therapy, have improved appropriate selection for surgery, resectability rates and early postoperative outcomes. Review of contemporary Australian observational follow-up data highlights favourable local morbidity and mortality results, but persistently disappointing long-term survival outcomes reflective of the international picture. The surgeon's current role remains to achieve complete local resection with minimal morbidity. Such an achievement maximises the successful utilisation of multimodal therapies targeting microscopic disease, and preserves the remaining quality of life for those patients with ultimately incurable disease suffering from aggressive tumour biology.

Adenocarcinoma of the pancreas is arguably the most sinister of all solid organ neoplasms. The disease is predicted to become the tenth most common malignancy by the end of 2015, yet it rates as the fifth most common cause of cancer-related death. Despite advances in diagnosis and therapeutics, age-standardised mortality has not changed in over 50 years. Late detection remains a major contributor to this statistic, with over 50% of patients suffering systemic disease at diagnosis. Accordingly, reported five-year cancer specific survival was only 6% between 2007-2011, a modest improvement from 4% between 1982-1986 attributed largely to the

introduction of gemcitabine.[1] Historical US observational data from the early 1990s reported moderately improved outcomes in the 14.2% of patients undergoing surgery for resectable disease (48% one-year survival) compared to the 85.8% of patients treated non-operatively for unresectable disease (23% one-year survival).[2] However, the same series reported a three-year survival rate of only 17% in the patients managed with resection,[2] providing a dismal medium-term outlook despite radical and frequently morbid surgery. Nevertheless, operative resection has since continued to provide the main therapeutic modality in the setting of localised disease. Given that survival statistics have not changed in 20 years, and that non-invasive multimodal therapies have arguably since improved, it is important to re-evaluate the current role of curative surgery in this devastating disease.

Established surgical principles

Radical resection of the primary tumour with regional lymphadenectomy to achieve complete microscopic resection is the established goal for all surgery with curative intent. The nature of the operation is dictated entirely by tumour location within the pancreas. While extended regional lymphadenectomy improves staging, there is no evidence that it improves long-term survival.[3]

For resectable tumours in the head and uncinate process that is right-sided, relative to the superior mesenteric vein and artery, a Whipple procedure is performed. This involves en-bloc resection of the head and uncinate process with attached gastric antrum, duodenum, bile duct, gall bladder and regional lymph nodes. Reconstruction requires three anastomoses, of which the pancreaticojejenostomy (or -gastrostomy) most commonly provides morbidity in the form of leakage. Technical variations exist but are beyond the scope of this review.

Only 10% of patients with left-sided pancreatic cancer, that is involving body and tail, have resectable disease at presentation. In this situation, a distal or left-sided pancreatectomy with splenectomy is performed without the need for anastomosis. There is no role for splenic preservation in the setting of adenocarcinoma.

Resectability relates to the extent of local and systemic disease, with identification of the latter providing an absolute contraindication to curative resection. Local tumour extension is most commonly relevant to the relationship of right-sided tumours to local vascular structures. Direct involvement of the superior mesenteric vein is considered resectable where an appropriate segment of the vein below and portal vein above allows reconstruction, which can be by direct closure, segmental resection with end-to-end anastomosis, or interposition graft. A recent meta-analysis involving 19 studies, from 1994-2010, of pancreatectomies for pancreatic cancer, including 661 patients with and 2247 patients without portomesenteric venous resections found no difference in overall survival between the cohorts with and without vascular resections.[4,5] However, major venous resections may lead to greater overall rates of intra-operative and post-operative morbidity rates. On the basis of the currently available evidence, there are data to support operative exploration and resection in the presence of reconstructable mesentericoportal axis involvement. In contrast, arterial resection for locally advanced disease, as defined by encasement of the superior mesenteric artery by more than 180 degrees, offers no benefit over palliative non-resectional treatment. Pre- and intra-operative assessment of resectability is critical because of the adverse impact of involved margins on survival. A retrospective observational follow-up of 121 patients undergoing attempted curative resection in Queensland from 2007-2009 highlights the point.[6] Patients with clear margins in this series exhibited a one-year survival of 85% in contrast to a one-year survival of only 50% for those with positive margins. The issue of margin status is compounded by the significant potential morbidity, and subsequent poor quality of life associated with attempted radical surgery. The reduced life expectancy and high morbidity risk associated with attempted but failed oncological clearance clearly serves no palliative benefit to the patient.

Operability, defined as the ability of a patient to successfully undergo major pancreatic surgery, also provides a major consideration in treatment planning. Although each patient presents a unique risk profile, basic prerequisites include good functional status (ECOG 0-1), adequate renal and liver function and satisfactory haematological parameters. Recent observational follow-up data of 1863 patients with pancreatic cancer from Queensland and New South Wales reported that 97 (51%) of the168 inoperable patients with potentially resectable disease were deemed unfit because of their comorbid state.[7] The median age of patients in this series was 71, with advanced age cited as the defining cause of inoperability in a further 31 (18%) of the patients. Diabetes and malnutrition are commonly present, have an adverse impact on post-operative recovery, and should be optimised prior to resection. Right-sided tumours usually present earlier than left-sided tumours in the form of obstructive jaundice, thus explaining the comparatively higher resectability rates reported.[6-8] However, high-grade biliary obstruction adversely affects multi-organ function thus compromising operability. Equipoise persists regarding the role of pre-operative biliary decompression, and summaries of the reported data include outdated practices.[9,10] Current thinking is to offer short metal stents to patients presenting with severe symptoms or organ dysfunction in order to achieve operability, and to those where neo-adjuvant therapy is being considered.

Australian outcome and morbidity data: where are we now?

Three contemporary Australian follow-up series provide useful insights into the current surgical management of pancreatic cancer and its subsequent outcomes. The earliest of these, by Speer and colleagues,[8] describes the results from a six-year retrospective observational

follow-up study of 763 patients diagnosed with pancreatic adenocarcinoma identified through the Victorian State Cancer Registry from 2002-2003. The most recent of the articles, published this year by Burmeister and colleagues,[7] provides the largest Australian follow-up cohort to date with 1863 patients. In this study, all diagnoses of pancreatic cancer between 2007-2009 were identified again through state cancer registries, this time using those of Queensland and New South Wales to represent over 50% of the Australian population. The third article, by Wylie et al and published in 2012, provides retrospective observational follow-up data on 121 cancer patients undergoing attempted curative resection from 2007-2009.[6]

The two studies analysing all pancreatic cancer patients reported similar median ages of 71 and 72 at diagnosis.[7,8] In contrast, the median age of patients in the paper focusing on patients undergoing potentially curative surgery was some 10 years younger at 63.[6] The distribution of cancers was almost identical across the all-comer studies, with right-sided cancers contributing 72% of the disease burden.[7,8] The Victorian study reported right and left-sided resection rates of 13.7% and 8.2% respectively,[8] the combined rate of which is less than the 14.2% reported in the previously cited US data from the 1990s.[2] In comparison Burmeister and colleagues reported curative resection attempts in 20% of all patients,[7] with 15% of all patients ultimately undergoing complete resection. The same series also provides an insight into patterns of operability, with attempted resection performed in 69% of patients deemed to have potentially resectable disease.[7] Where resection was not attempted, comorbid state was the major factor in 51%, with advanced age cited as the main reason in 18%. Interestingly, 20% of patients deemed otherwise eligible for curative resection declined surgery, providing a useful indication of how marginal the risk-benefit balance of pancreatic cancer surgery is presently perceived.

A comprehensive understanding of the current risk-benefit balance in curative pancreatic surgery requires separate assessment of adverse outcome and survival data. Operative risks in pancreatic surgery are recognised to be above average in comparison to surgery on other intra-abdominal organs. Morbidity rates following pancreatic resection remain at 40-50%. A systematic review by Harnoss and colleagues of 59 of retrospective articles, which correctly applied the definitions for complications following pancreatic resection, reported median complication rates of 21.9% for post-operative pancreatic leak or fistula (n = 11,244 patients), 5.9% for post-pancreatectomy haemorrhage (n = 3311 patients), and 22.8% for delayed gastric emptying (n = 4553 patients).[11] Intra-abdominal abscess and biliary anastomotic leaks are less common complications managed in the majority of circumstances by percutaneous drainage. Despite significant complication rates, Wylie and colleagues reported a post-operative mortality following pancreatic resection of less than 2%.[6]

Unfortunately, the most striking outcome data from contemporary Australian follow-up studies are the persistently abysmal survival rates. Burmeister and colleagues reported a one-year overall survival of 22%,[7] which is even worse than the 25% one-year survival described by Niederhuber in the 1990s.[2] Furthermore, the same series saw a 50% 12-month recurrence rate in the 279 patients undergoing completed curative resection.[7] During the six-year follow-up period by Speer and colleagues,[8] 747 of 763 (97.3%) patients died. Closer analysis of the 20 patients surviving to five years darkens the picture even further, as half of these individuals did not even have cancer. Of the 10 that did, three suffered recurrence during the sixth year of follow-up, leaving only seven disease-free survivors after six years.

Is 'curative' surgery still relevant?

Given the relative mismatch between high operative risk and limited cure rates, the role of surgery with curative intent has been challenged. In 2004, adequate equipoise existed for the completion of a randomised trial comparing surgery to radical chemo-radiotherapy in 42 Japanese patients with resectable pancreatic cancer.[12] Twenty patients were assigned to resection alone, and 22 received a 5-flouracil based chemo-radiotherapy protocol. Surgical resection was found to provide better one-year survival (62% vs 32%, p=0.05), mean survival time (>17 vs 11 months, p<0.03) and an improved hazard ratio (0.46, p=0.04) thus demonstrating a clear advantage in the surgery arm. While chemo-radiotherapeutic regimens have improved since the study, the absence of further RCT on the subject provides a surrogate marker of the ongoing favourability towards surgery for localised, resectable disease.

Impact of multimodal therapy on outcome and patient selection

Post-operative chemotherapy with Gemcitabine or 5-fluorouracil has been shown to improve outcome. However, more than 30% of patients are not fit for post-operative therapy after pancreatic surgery. Furthermore, a significant proportion of patients suffer particularly dismal outcomes despite the resection of apparently localised disease. The identification of such patients would help avoid unnecessary surgery, and its associated morbidity.

Hence, there is a clear mandate for neoadjuvant therapy whereby a period of pre-operative observation provides insight into individual tumour biology. Furthermore, a pre-operative approach can increase the deliverability of cytotoxic medication and improve resectability in both resectable and borderline resectable tumours.[13,14] In Australia, we have recently demonstrated that pre-operative chemotherapy with gemcitabine and nab-paclitaxel can be delivered to patients with pancreatic adenocarcinoma.[15] Ferrone and colleagues also demonstrated that FOLFIRINOX can be safely administered in the pre-operative setting.[16] Combination neoadjuvant chemo-radiotherapy holds further promise still. Regimens

using gemcitabine, 5-fluorouracil or platinum backbones have been investigated in the phase II setting, with favourable results.[17] Further studies will be undertaken to determine the optimal timing and type of chemotherapy or chemo-radiotherapy in order to improve outcomes in pancreatic adenocarcinoma.

Refinement of the surgical approach

Subsequent to advances in multimodal therapy, the ongoing focus in surgery is to achieve complete oncological resection with enhanced early recovery and the minimisation of morbidity. Complete resection of macroscopic disease optimises the theoretical efficacy of chemotherapy to eradicate microscopic disease, and an accelerated, uncomplicated recovery enables its timely institution.

A recent systematic review identified 869 patients in 11 studies of minimally invasive Whipple procedures (pancreaticoduodenectomy. MIPD), which may be performed laparoscopically or robot-assisted.[18] There were some advantages in intraoperative blood loss, wound complications, and length of stay, compared with the open approach. However, considering the selection bias, the complexity of MIPD and lack of long-term oncologic outcomes, the current application of MIPD should be in high-volume pancreatic surgery centres on patients with small cancers distant from major vessels.

Laparoscopic distal pancreatectomy is increasingly performed as an alternative approach for open distal pancreatectomy in selected patients. Comparing laparoscopic distal pancreatectomy with open distal pancreatectomy, laparoscopic distal pancreatectomy has lower blood loss, reduced length of hospital stay, lower risk of post-operative complications and wound infection, without a substantial increase in the operative time.[19] The improved complication profile of laparoscopic distal pancreatectomy, taken together with the lack of compromise of margin status, suggests that this technique is a reasonable approach in selected cancer patients.

Conclusion

Despite advances in multimodal therapies, surgery remains central to the management of patients presenting with resectable disease. Resection offers the only real, albeit slim chance of cure. For the greater proportion of patients with resectable macroscopic but occult microscopic disease, who ultimately recur early, short-term outcomes are still improved compared to other currently available treatment modalities. The surgeon's goal is to achieve complete local resection with minimal morbidity. Such an achievement maximises the successful utilisation of adjuvant therapies targeting microscopic disease, and preserves the remaining quality of life for patients suffering from aggressive tumour biology.

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RADIOTHERAPY FOR PANCREATIC CANCER

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Abstract

The role of radiotherapy in pancreatic cancer is controversial. Its utility in treatment has been investigated in a number of clinical settings, including before and after surgery for operable cancers and in the treatment of locally advanced, inoperable disease. Adjuvant treatment has had mixed results in trials and there is now interest in better selecting patients who may benefit from neoadjuvant treatment. The benefit of radiotherapy continues to be poorly defined, due in part to the large number of differing treatment regimens that have been investigated. This article reviews the current evidence for radiotherapy in pancreatic cancer, with a focus on identifying those patients who are most likely to benefit from radiotherapy treatment. It will also discuss some of the planning considerations.

Adjuvant treatment

Successful surgical resection provides the best potential for a cure of pancreatic cancer, but distant metastatic disease remains the main source of treatment failure. Despite this, local failure occurs commonly following surgical resection and approximately 30% in autopsy series die of predominantly local progression.[1] In the adjuvant setting, the role of radiotherapy is controversial. Early randomised trials have had mixed results.

A possible benefit for radiotherapy in the adjuvant setting was demonstrated initially by a Gastrointestinal Tumour Study Group trial conducted in the 1970s.[2] Patients were randomised to receive adjuvant chemoradiotherapy (n=22) or be observed (n=21) following curative resection. The chemoradiotherapy consisted of two courses of 20Gy in 10 fractions concurrent with bolus 5-FU, with a two week break. There was an increased survival benefit in those undergoing adjuvant treatment of 20 vs 11 months. However, this trial has been criticised for old techniques incorporating low radiotherapy dose and poor patient accrual with small patient numbers.

The ESPAC-1 trial of 289 randomised post operative patients to receive either chemoradiotherapy, chemotherapy alone, a sequential combination of both or neither treatment.[3] The chemoradiotherapy employed was that utilised in the Gastrointestinal Tumour Study Group trial.[2] The chemotherapy alone treatment consisted of bolus 5-FU. Results showed a non-significant reduction in survival in those patients undergoing chemoradiotherapy, with a median survival of 15.5 months compared to 16.1 months in the no chemoradiotherapy arm, p=0.24. Despite this, local recurrence remained a major problem in this cohort, with 62% of patients developing a local recurrence. The local recurrence rate was not reduced in the patients treated with chemoradiotherapy, possibly due to the low dose of radiation and lack of radiotherapy quality control.

An EORTC trial randomised 218 patients to receive adjuvant chemoradiotherapy or to undergo observation alone.[4] The radiotherapy was similar to the previous randomised trials. However, the concurrent chemotherapy consisted of infusional 5-FU opposed to bolus administration. The study showed a non-significant improvement in median survival of 24.5 months in the treatment group compared to 19.0 months in the observation arm, p=0.208. Whether the radiation component contributed to the trend towards improved survival is open to conjecture.

The results of these trials are difficult to translate to modern radiotherapy treatments for pancreatic cancer. The above trials have been criticised for utilising older radiotherapy techniques such as two dimensional planning, smaller doses of radiotherapy, treatment breaks and bolus 5-FU as concurrent chemotherapy. Surgical techniques have also improved potentially reducing the risk of local recurrence. A large retrospective series from Johns Hopkins Hospital reviewed patients treated with median doses of 50Gy, three dimensional planning and majority with no treatment breaks.[5] There was a statistically significant median (21.2 months vs 14.4 months), two year (43.9% vs 31.9%) and five year (20.1% vs 15.4%) survival of chemoradiotherapy compared to surgery alone. It can be argued that chemotherapy alone is responsible for this benefit. However in the chemotherapy alone trials local recurrence is still a major issue.

The CONKO-001 trial randomised 368 patients with R0 (negative margins) (>80%) or R1 resection to Gemcitabine

x 6 vs observation alone.[6] The median disease-free survival was 13.4 months vs 6.9 months favouring the treatment arm, p<0.001. This trial reported local recurrence rates of 34% in the Gemcitabine arm and 41% in the observation arms, suggesting that 30-40% of patients would benefit from further local treatment such as radiotherapy and hence justifying it's use in many centres, especially in the United States.

The RTOG 9704 trial conducted in North America, where adjuvant radiotherapy is used more often than in other countries had some of the best loco-regional control rates.[7] The study delivered radiotherapy with contemporary doses (50.4Gy) and had good quality control. 5-FU based chemoradiotherapy was sandwiched between either gemcitabine chemotherapy or 5-FU chemotherapy. Locoregional control rates were 25% and 30% respectively. Despite this, over 70% of patients developed distant metastases.

Identifying patients with higher risk of local recurrence

The cohort that would most benefit from adjuvant radiotherapy has not been established. A meta-analysis demonstrated a survival benefit from chemoradiotherapy in patients with positive margins, highlighting the importance of local control, despite pancreatic cancer having a high propensity for metastatic spread.[8] The role of the addition of adjuvant radiotherapy continues to be studied, with a current trial (RTOG 0848) randomising patients to 5-FU based CRT or further CTx alone in patients who have not progressed during induction with Gemcitabine chemotherapy, evaluating end-points of overall and disease-free survival.

There is a growing interest in identification of biomarkers that may differentiate those patients who are more likely to progress locally rather than distantly and therefore benefit from aggressive local treatment. An autopsy study found that positive staining for the intracellular protein DPC4 (or SMAD4) suggested a patient was more likely to recur locally.[1] Only 22% of patients with no metastatic disease at biopsy showed loss of expression of DPC4. Conversely, 73% of patients with extensive metastatic disease demonstrated loss of staining.

Neoadjuvant treatment for maximal local control prior to definitive surgery

Over the last 20 years there has been interest in neoadjuvant chemotherapy and chemoradiotherapy in both resectable and unresectable pancreatic cancer at risk of R1 resection and/or local recurrence. The rationale for neoadjuvant treatment includes early treatment of micrometastatic disease and allowing time for micrometastases to declare themselves prior to undergoing extensive surgery. Neoadjuvant treatment allows for an assessment of tumour responsiveness and can overcome the issue of delayed post-operative treatment due to surgical complications or the need for recovery of adequate performance status.

A phase 2 neoadjuvant trial treated patients with seven weekly gemcitabine infusions (400mg/m2) plus radiotherapy 30Gy/10# over two weeks, with surgery 4-6 weeks after completion of neoadjuvant treatment.[9] Eighty-six patients were enrolled in the study and 74% underwent successful surgery. The other patients were deemed inoperable due to disease progression, decline in performance status or extra pancreatic disease at time of surgery. In the patients who underwent surgery, median survival was 34 months with a 27% five year survival. Importantly, there was only an 11% local recurrence rate.

The French SFRO 97-04 phase II trial of 41 patients combined 5-FU-cisplatin chemotherapy with 50Gy of radiation followed by surgical resection.[10] Sixty-three per cent of patients underwent surgical resection with an 80.7% R0 resection rate. There was a low median follow-up period of only 11 months, however the local recurrence rate was only 4% with 48% one year survival.

Locally advanced disease

A number of studies assessing the benefit of chemoradiotherapy have been conducted in the locally advanced/unresectable population. There is extensive heterogeneity between the studies and results have been mixed. Radiotherapy regimens in this cohort are discussed in detail in this issue of *Cancer Forum*.[11]

Radiotherapy technique

In this current era, with a paucity of good evidence for radiotherapy in pancreatic cancer, it is imperative that patients are treated with good quality radiotherapy.

Compliance with standardised radiotherapy technique has been shown to improve patient outcomes in the post-operative setting. A secondary analysis of the adjuvant RTOG 9704 trial was undertaken to determine whether deviation from radiotherapy protocols including simulation, image verification, target volume delineation and normal tissue dose constraints influenced survival outcomes.[10] Fifty-one per cent of patients were treated as per protocol and had a median survival of 1.74 years, compared with a median survival of 1.46 years if treated less than per protocol, p=0.0077. Patients were also significantly less likely to recur if they were treated as per protocol, p=0.016.

Concensus panel guidelines for delineation of the clinical target volume in the post-operative pancreatic head cancer were developed for the RTOG 0848 adjuvant trial and have been published with an atlas available from the RTOG website.[12,13] American-French consensus recommendations for radiotherapy technique in locally advanced pancreatic cancer have also been published.[14]

Volumes can be safely reduced by omitting prophylactic nodal irradiation in the locally advanced setting. A study of 74 patients with locally advanced disease gave 36Gy/15# concurrent with full-dose gemcitabine 1000mg/m2 and treated the gross tumour volume (GTV) + 1cm only.[15] Only 5% failed in the peri-pancreatic nodes justifying the reduction in treatment volumes. The risk of gastrointestinal

toxicity has been found to correlate with planning tumour volume (PTV) with statistically significant lower risk with PTV volumes <260cc.

New techniques

Intensity modulated radiotherapy (IMRT) has reduced toxicity rates in radiation treatment of pancreatic cancer. A systematic review comparing with 3D conformal radiotherapy found lower rates of ≥ grade 3 nausea and vomiting 13.4% vs 7.8%, p<0.001 and ≥ grade 3 diarrhoea 11.6% vs 2.0%, p<0.001.[16] There was also a lower incidence of late toxicity in the IMRT arm, predominantly gastrointestinal bleeding or duodenal ulcer, 10.6% vs 5.0%, p=0.017. There were no differences in overall or progression-free survival.

Increased dose conformality is being assessed to allow for radiotherapy dose escalation. A phase 1/2 trial of IMRT with breath-hold or 4D-CT to accurately account for organ motion and generate an internal target volume allowed for a dose escalation of 55Gy in 25 fractions with full-dose gemcitabine (1000mg/m2).[17] Dose-limiting toxicity was seen in 24% and deemed to be safe. The treatment was not without its complications however, with cases of duodenal bleed and perforation, and two patients dying of possible treatment related causes.

A retrospective series of patients undergoing five fractionated treatments of 7-10Gy showed similar local control rates (81% at 12 months) with less toxicity.[19] Late grade three toxicity was seen in only four patients (5.3%) and consisted of gastrointestinal bleeding and anorexia requiring nasogastric feeding. This trial demonstrates that more fractionated treatments reduce toxicity, however stereotactic radiotherapy for pancreas cancer remains investigation.

Conclusion

It appears there may be a benefit of radiotherapy for a subset of patients with pancreatic cancer, however that group is not well defined from the evidence at this stage and perhaps further evaluation of biomarkers will identify that group. It is evident that poorly delivered radiotherapy in high doses and toxic chemotherapy is harmful to patients, negating any possible benefit of further local treatment.

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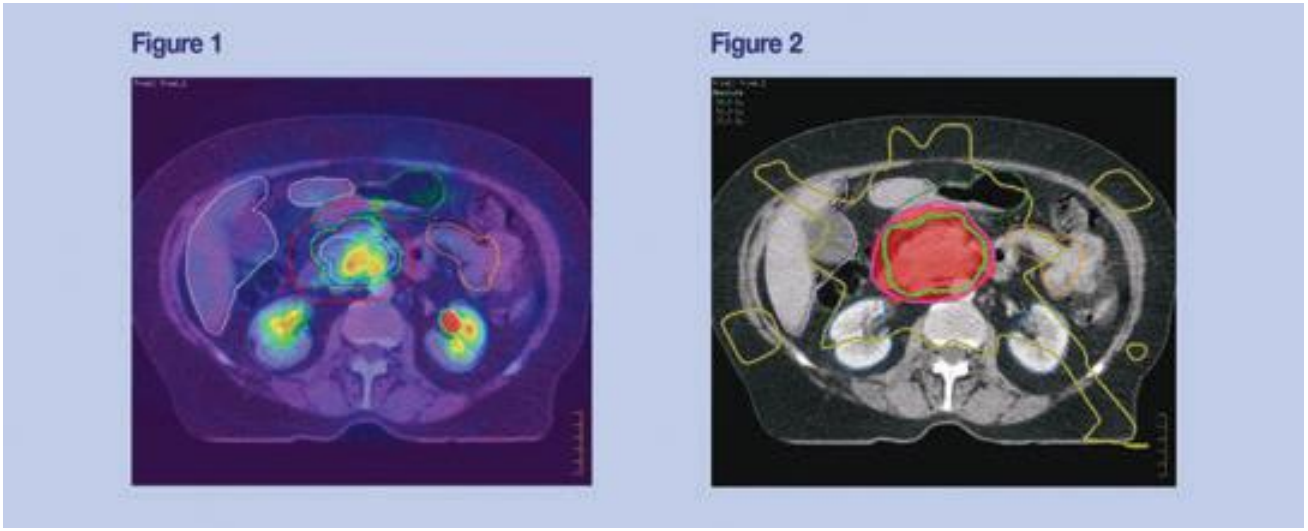
***Figure 1**: CT/PET fusion demonstrating IMRT volumes. GTV – light blue, CTV – light green, PTV - red. Organs at risk: liver – purple; stomach – green; kidneys – dark blue; small bowel - orange.*

***Figure 2:** Isodose lines for same plan - 95% isodose line in magenta, 100% isodose line in green. Note sculpting of dose around the stomach.*



Stereotactic radiotherapy

There is growing interest in the use of stereotactic radiotherapy in order to reduce treatment margins and reduce treatment time with higher doses per fraction. A series of 77 patients treated with a single fraction of 25Gy demonstrated a 12-month freedom from local progression rate of 84%.[18] However, there was a 25% rate of grade 2 or greater late toxicity at 12 months consisting of gastric ulceration, duodenal or biliary stricture and one episode of bowel perforation.

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RADIOTHERAPY IN LOCALLY ADVANCED PANCREATIC CANCER

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Abstract

While radiotherapy was considered an important treatment modality in locally advanced pancreatic cancer for several decades, the presentation of the LAP 07 trial results have impressed a concept that radiotherapy provides no benefit in this patient group. Further analysis however, revealed that the use of radiotherapy in the LAP 07 trial was associated with better local control and a greater chemotherapy-free interval, both meaningful palliation benefits. Further, the initiation of radiation was delayed by a four month period of induction treatment that employed a drug with only an 8% response rate, and progression free survival control of 3.1 months. A detailed review of the literature to date demonstrates that modern radiotherapy in locally advanced pancreatic cancer has a significant local effect, is well tolerated and associated with improved quality of life through providing durable local control, and in a subset population, resulting in long-term survival. Perhaps the most important conclusion of the LAP 07 study, which was very well conducted, is that delaying a local therapy for four months is not an effective sequencing strategy when the induction treatment is of borderline efficacy in a cancer with a rapid progression characteristic. While newer agents are improving survival, the outlook remains dismal. Optimising the integration of radiation needs to be a priority to define how this modality can assist the modest gains that have come about from a very large number of chemotherapy sequencing studies.

Pancreatic cancer is the tenth most common cancer diagnosed in Australian men and women, but is the fourth most common cause of cancer mortality.[1] At diagnosis, approximately one third of patients present with locally advanced disease and approximately half with metastatic disease, leaving only 10 to 20% suitable for resection.[2] As a group, locally advanced pancreatic cancers (LAPCs) tend to be characterised by their proximity to critical vascular structures, rendering them unsuitable for resection, even in the absence of gross metastatic disease. LAPC is associated with poor survival, approximately 5 to 11 months.[3]

LAP 07

LAP 07 trial design and endpoints

The results of the LAP 07 trial were presented at the 2013 American Society of Clinical Oncology Annual Meeting. In this large trial, patients of good performance status with LAPC (n = 442) were first randomised to four months of gemcitabine (1000mg/m2/week x3) with or without erlotinib (100mg/day). Patients who did not have disease progression were further randomised to radiotherapy treatment of 54 Gy, with concurrent capecitabine (1600mg/m2/day), or two additional months of the same chemotherapy.[4] Patients who received erlotinib at first randomisation continued with this drug from the completion of protocol until further disease progression. The primary objective was to assess whether chemoradiotherapy increased overall survival.

LAP 07 shortcomings

A widely reported outcome from the study, median overall survival for the chemotherapy only arm was 16.5 months, appeared very good. This is misleading however, as it relates to the outcome for the selected 61% of patients who remained eligible to progress to the four month second randomisation point. Two thirds of the patients who did not proceed to second randomisation (26% of all patients) had disease progression, and one tenth had treatment toxicity.

At the time of the LAP 07 trial development, single agent gemcitabine was the standard of care for metastatic pancreatic cancer. This stems from an initial landmark study that showed improved median survival with gemcitabine compared to 5-fluorouracil (5-FU) by approximately five weeks (5.6 months versus 4.4 months), and improved clinical benefit (based on a non-validated health-related quality of life tool) in patients with advanced pancreatic cancer.[5] Multiple other studies have replicated the additional but modest benefit of this drug in locally advanced and metastatic pancreatic cancer, including progression-free survival of 3.1 months and a response rate of 8.2%.[6]

The LAP 07's investigation of the role of erlotinib concluded that its use was not beneficial in LAPC. The added toxicity was quite substantial, with 37.3%, 32.9%, 24.5% and 6.6% experiencing grade 3 or 4 neutropaenia, coughing, dyspnoea and diarrhoea respectively. This is in contrast to just 5.9% of patients treated with radiotherapy experiencing grade 3 or 4 nausea.

Common induction program practices prior to the study employed neoadjuvant periods of 1-2 months, as it was recognised that occult metastatic disease could present quite quickly in this condition. It was hypothesised that extending the neoadjuvant period might improve the selection of patients who would benefit from the addition of radiotherapy. However, no benefit to survival was observed by extending the period to four months, which exceeded the median progression-free survival of 3.1 months.

Evidence that modern radiotherapy is effective

Radiotherapy has a useful response rate and increases R0 rates

Multiple phase 1 and 2 trials (summarised in table 1) demonstrate improved response rates and increased R0 resection rates with neoadjuvant chemoradiotherapy. In one retrospective study of patients with borderline and LAPC (n = 41), investigators attempted to compare the relative contributions of neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy to outcomes.[7] Patients receiving radiotherapy (58.5%) were treated to a dose of 45 Gy to 50.4 Gy, with concurrent gemcitabine, cisplatin or capecitabine at radiosensitising doses. Patients treated with chemotherapy only received gemcitabine alone, or gemcitabine in combination with capecitabine or oxaliplatin. A complete pathological response was only attained in patients receiving radiotherapy – 12% of patients vs 0% for chemotherapy alone. The addition of radiotherapy significantly increased the likelihood of a partial response – 46% vs 17% (P = 0.03). The use of radiotherapy more than doubled the R0 surgical resection rate – 96% vs 35% (P < 0.0001).

***Table 1**: Studies on neoadjuvant chemoradiotherapy in pancreatic cancer.*

Reference	Study design	Treatment	No. of participants	Resectability	Resection rate (%)	R0 resection rate (%)	Median OS (mo)
Joensuu et al (2004)[29]	Prospective	RT 50.4 Gy + GEM	28	BR	75	-	25.0
Calvo et al (2004)[30]	Retrospective	RT 45 - 50.4 Gy +Tegafur + IORT 10 -15 Gy	15	BR	60	78	10.0 (Res 22.0, Unres 7.0)
Pipas et al (2005)[31]	Prospective	DOC + GEM → RT 50.4 Gy + GEM	24	Res (17%) BR (29%)	71	76	14.0
Talamonti et al (2006)[32]	Prospective	GEM → RT 36 Gy + GEM	20	Res (70%) BR (30%)	85	94	18.0 (Res 26.0)

Brown et al (2008)[33]	Retrospective	RT 50.4 Gy + GEM / 5-FU / CAP	13	BR	100	85	-
Varadhachary et al (2008)[34]	Prospective	GEM + CIS → RT 30 Gy + GEM	30	Res	66	94	18.7 (Res 31.0, Unres 10.5, P < 0.001)
Small et al (2008)[35]	Prospective	GEM RT 36 Gy + GEM → GEM	41	Res (41%) BR (23%) Unres (36%)	44	-	-
Evans et al (2008)[36]	Prospective	RT 30 Gy + GEM	86	Res	74	86	22.7 (Res 34.0, Unres 7.0, P < 0.001)
Lind et al (2008)[37]	Prospective	OX + CAP → RT 50.4 Gy + OX + CAP	17	BR	47	100	19.0
Katz et al (2008)[38]	Prospective	GEM (alone or in combination) → RT 50.4 Gy or 30 Gy + GEM / CAP / 5-FU / paclitaxel	84	BR	38	97	21.0 (Res 40.0, Unres 15.0)
Maximous et al (2009)[39]	Prospective	RT 54 Gy + GEM	25	Unres	32	25	12.0
Satoi et al (2009)[40]	Retrospective	RT 40 Gy + CIS + 5-FU or RT 40 Gy + GEM	16	BR	69	27 (R0 + R1)	-
Turrini et al (2009)[41]	Retrospective	RT 45 Gy + 5-FU + CIS	101	Res	61	92	17.0 (Res 23.0, Unres 11.0, P = 0.002)
Landry et al (2010)[42]	Prospective	RT 50.4 Gy + GEM → GEM or GEM + CIS + 5-FU RT 50.4 Gy + 5-FU → GEM	21	BR	30 18	33 50	19.4 (Res 26.3) 13.4 (Res 26.3)
Piperdi et al (2010)[43]	Prospective	RT 50.4 Gy + GEM / 5-FU / CAP	8	BR	75	100	16.1
Turrini et al (2010)[44]	Prospective	RT 45 Gy + DOC	34	Res	50	100	15.5 (Res 32.0)
Chun et al (2010)[45]	Retrospective	RT (dose not specified) + GEM / 5-FU	74	BR	100	59	23.0
Stokes et al (2011)[46]	Prospective	50.4 Gy + CAP	34	BR	46	75	Res 23.0, Ures 12.0
Patel et al (2011)[47]	Retrospective	GEM + DOC + CAP → RT 50 Gy + 5-FU	17	BR	53	89	15.6
Chuong et al (2011)[48]	Retrospective	GEM + DOC + CAP → RT 50 Gy + 5-FU	14	BR	100	86	-
Leone et al (2012)[49]	Prospective	GEM + OX → RT 50.4 Gy + GEM	39	BR (38.5%) Unres (61.5%)	36	64	BR 27.8, Unres 12.3

Pipas et al (2012)[50]	Prospective	RT 54 Gy + GEM + cetuximab	33	Res (12%) BR (70%)	76	92	17.3 (Res 24.3, Unres 10.0)
Habermehl et al (2012)[51]	Prospective	RT 52.2 Gy + GEM → GEM	198	Ures	26	39	12.3 (R0 Res 22.1, Unres 11.9)
Papelezova et al (2012)[52]	Retrospective	RT 45 Gy + GEM	144	Res	53	78	27.0 (Surgery alone 17.0)
Estrella et al (2012)[53]	Retrospective	RT (dose not specified) + GEM or 5-FU + CAP +/- induction chemotherapy	240	Res	100	89	33.5
Barugola et al (2012)[7]	Retrospective	RT 45 Gy – 50.4 Gy + GEM / CIS / CAP or chemotherapy alone (GEM alone or GEM + CAP / OX)	41	BR (66%) Unres (34%)	100	70.7	35.0 (Surgery alone 27.0)
Arvold et al (2012)[54]	Retrospective	RT 50.4 Gy + 5-FU / CAP +/- induction GEM	70	BR (34%) Unres (66%)	20	79.0	18.7 (induction chemotherapy), 12.4 (no induction chemotherapy), P = 0.02
Kang et al (2012)[55]	Retrospective	RT 45 Gy – 50.4 Gy + GEM +/- CIS	32	BR	100	88	26.3
Katz et al (2012)[56]	Retrospective	RT 30 Gy – 50.4 Gy + GEM / 5-FU / CAP +/- induction GEM	129	BR	66	95	22.0 (Res 33.0, Unres 12,0)
Satoi et al (2012)[57]	Prospective	RT 50.4 Gy + S1	32	Res BR Unres	88	93	-
Sho et al (2013)[58]	Retrospective	RT 50 Gy – 54 Gy + GEM	61	BR	100	92	28.0
Dholakia et al (2013)[59]	Retrospective	RT 50 Gy + GEM alone or +/- OX / CAP +/- induction GEM / FOLFIRINOX / FOLFOX	50	BR	58	93	17.2 (Res 22.9, Unres 13.0, P < 0.001)
Kim et al (2013)[60]	Prospective	RT 30 Gy + GEM + OX	39	BR	62	84	18.4 (Res 25.4)
Takahashi et al (2013)[61]	Prospective	RT 50 Gy + GEM	80	BR	54	98	Res 25.0, Unres 14.0
Van Buren et al (2013)[62]	Prospective	GEM + Bevacizumab → RT 30 Gy + Bevacizumab	59	Res (50%) BR (50%)	73	88	16.8 (Res 19.7)
Eguichi et al (2014)[63]	Prospective	RT 50.4 Gy + GEM + S-1	21	Res	91	-	-

RT: radiotherapy, IORT: intraoperative radiotherapy

GEM: gemcitabine, DOC: docetaxel, CAP: capecitabine, 5-FU: 5-fluorouracil, OX: oxaliplatin, CIS: cisplatin, FOLFIRINOX: 5-FU + leucovorin + irinotecan + oxaliplatin, FOLFOX: 5-FU + leucovorin + oxaliplatin

Res: resectable, BR: borderline resectable, Unres: unresectable

Radiotherapy reduces local failure

Huguet et al in a recent review of the role of chemoradiotherapy in LAPC, identified three-dimensional (3D) -conformal radiotherapy as an 'active, well-tolerated regimen', and given that LAPC was rarely downstaged with contemporary treatment programs, the goal of treatment should be palliative with aims of prolonging survival, disease control and symptom palliation.[8] The palliative benefits of chemoradiotherapy compared to no chemoradiotherapy in LAPC were demonstrated in one prospective trial (n = 31), with improved Karnofsky's performance status (77.1 vs 65.5, P < 0.0001), reduced days in hospital (12.3 days vs 19.0 days, P < 0.05) and pain relief (response rate 80%, median duration 5.2 months).[9] This was in addition to a survival benefit (median survival 6.4 months vs 13.2 months, P = 0.0009). Closer analysis of the LAP 07 data reveals reduced local progression with radiotherapy.[10] With improved local control there would be potential to avoid biliary or gastric outlet obstruction, and hence avoid stenting or surgical procedures.

Radiotherapy improves chemotherapy free interval

Patients in the LAP 07 trial who received chemoradiotherapy achieved a greater chemotherapy-free interval than those who did not receive radiotherapy.[10] The median time to re-introduction of chemotherapy was 5.2 months versus 3.2 months.

Radiotherapy is associated with long-term survivors

The notion that we should include the presence of a tail of longer term survival as an endpoint in pancreatic cancer was emphasised at the recent American Society of Clinical Oncology plenary update of a randomised phase 3 study of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone, in patients with metastatic adenocarcinoma of the pancreas (MPACT).[11] Longer-term follow-up of this study, which has established the combination of nab-Paclitaxel and gemcitabine as a new standard of therapy for locally advanced and metastatic cancer, emphasised three year survival of 4%. The authors' experience (manuscript in preparation) of 124 patients with histologically confirmed locally advanced inoperable pancreatic cancer, employing only one cycle neoadjuvant gemcitabine prior to 3D-conformal radiotherapy (54 Gy with concurrent 5-FU), found three year survival of 13% and five year survival of 6%. Prospective randomised control trials of chemoradiotherapy in LAPC to date have generally not reported on survival rates beyond 1-2 years. The identification of a small but not insignificant 'tail' of long-term survivors is only apparent if we look.

All radiation isn't the same radiation

Radiation technique is vital

The importance of consistent technical expertise is recognised in the surgical literature. The same applies to any radiotherapy technique. A good example of this is seen in the European Study Group for Pancreatic Cancer (ESPAC) 1 study, a randomised trial of adjuvant chemoradiotherapy and chemotherapy after resection of pancreatic cancer, where the median survival of patients assigned to chemoradiotherapy was worse than those assigned to observation - 13.9 months vs 16.9 months.[12] At that time, radiation was rarely, if ever, employed at most centres and there was very little engagement with expertise. There was no funding to undertake radiation technique quality assurance, and the protocol description was confined to a brief paragraph that referred to a crude Gastrointestinal Tumour Study Group radiation technique developed in the 1970s.[13] This was in contrast to the robust contemporary standards of surgical practice that were well developed, as well as the widespread familiarity of chemotherapy protocols. Their minimalist approach to radiation quality assurance appears to have resulted in poor survival, worse than no treatment at all.[14] Bydder and Spry further suggested that the observed detriment to survival might be accounted for by inadvertent coverage of the kidneys in close proximity, leading to their later and premature failure.[14] With such confounding factors, this study does not exclude the role of radiotherapy in this setting. Rather, it suggests the ESPAC-1 radiotherapy technique should not be employed and further highlights the great need to develop safe future radiotherapy techniques and robust quality assurance processes.

Improved results with advances in modern techniques

Contemporary anatomically targeted radiation programs have now been set up to be safe and avoid adverse late renal or hepatic damage.[15,16,17]

We have previously identified the importance of 'dummy run' testing of new centres, which exposed unexpected misunderstandings of protocol writing, allowing them to be addressed.[17] Additionally, development of quality assurance assessment tools address the very complex data sets that represent modern computer planning.[18]

Intensity-modulated radiotherapy (IMRT) is a technique which uses multiple non-coplanar beams of non-uniform intensity, leading to better conformality of dose to the target volume, and less dose to adjacent critical structures, thereby reducing potential toxicities and allowing for dose escalation. This was used in a recent LAPC trial to a dose of 55 Gy to 60 Gy, in 25 fractions;[19] even with concurrent full dose gemcitabine, this combined treatment was well tolerated and achieved a median survival of 14.8 months and two year overall survival of 30%. Superior dosimetry is achievable with volumetric-modulated arc radiotherapy, a type of IMRT in the treatment of pancreatic cancer, which may translate to better toxicity profiles and the potential for dose escalation.[20]

Diaphragmatic movement is transmitted to the pancreas,

hence this target moves during the treatment; the limits of this motion increase the size of the target needed to be treated and thereby increase treatment toxicity. Four-dimensional computed tomography (CT) can reliably reduce the margin necessary for treating pancreatic cancer, reducing dose to adjacent organs.[21] Until recently, the radiation target was determined by a CT-defined target based on CT abnormality and standard anatomical risk patterns. Positron emission tomography (PET) in other cancer situations e.g. lung, has already changed the approach to target delineation. While current PET tracers are only uncommonly useful, we are likely to see more confident target delineations with future development, which will improve treatment efficacy, possibly allowing radiotherapy dose escalation and simultaneous normal tissue toxicity reduction.[22,23]

Changing landscape

Impact of stage migration from improved imaging

In the last two decades, increased utilisation of CT, improvements in multidetector CT technology, and increased utilisation and expertise in reporting of magnetic resonance imaging (MRI) and PET in pancreatic cancer have led to improved detection of smaller primary disease, hence earlier detection. Furthermore, improvement in the assessment of the vascular involvement selects out truly inoperable patients along with the better assessments of previously occult metastatic diseases.[24] The impact of better staging not only helps our patient selection, it improves outcome even when there has been no true treatment effect by this better selection. This is the process of stage migration (the Will Rogers phenomenon*);[25] patients that would not have been identified as having gross distant metastases are now identified and treated as metastatic cancer patients, thereby improving the outcomes in non-metastatic and metastatic populations. In the 1990s, phase 3 trial data found gemcitabine achieved a median overall survival for non-operable patients of 5.6 months,5 contrasting with more recent improved outcomes, employing the same regimen of 6.6 months.[11] It is likely that the Will Rogers effect is a major contributor to this survival improvement.

So how do we best integrate treatment?

Importance of durable local control with improving systemic treatments

Multiagent nab-paclitaxel and FOLFIRINOX has resulted in improved survival compared to gemcitabine alone in metastatic pancreatic cancer, 8.7 months vs 6.6 months, and 11.1 months vs 6.8 months respectively.[11,26] As in other tumour sites, the role of local control in improving overall survival may become evident as systemic treatment improves.

The vast experience from breast cancer research has demonstrated improved systemic treatments leading to improved survival for localised disease.[27] With the arrival of effective systemic treatments in breast cancer, achieving local control was thought to have limited impact on survival because of the view that a local recurrence could be treated, and that local recurrence was not thought to lead to metastatic disease. The evidence however, shows that improved local control in non-metastatic breast cancer actually improves overall survival.[27] In the Early Breast Cancer Trialists' Collaborative Group meta-analysis of local therapy, for every four local recurrences prevented by loco-regional radiotherapy, one death from breast cancer was avoided.[28] In the setting of LAPC and improving effectiveness of systemic treatment, improving local control will become an important factor in improving survival.

Paucity of radiotherapy data

There have been huge resources employed to study the effect of minor variations to drug sequencing and combinations using the clinical trial method. These collaborations have encouraged the rapid development of widespread familiarity with and expertise in the safe and effective use of systemic agents in this condition. In contrast, there have been very few resources employed to develop the optimal utilisation of radiotherapy, hence expertise is rare and largely confined to few centres who publish their own data.

A search of the PUBMED database from 1950 until October 2015, combining the MESH terms 'pancreatic neoplasms' with 'chemotherapy', 'biological agents' or 'immunotherapy', and limiting search to human phase 2 or 3 trials, excluding irrelevant trials (focused only on resectable, borderline resectable or metastatic disease), yields 338 trials,[42] of which were phase III. A similar search combining MESH terms 'pancreatic neoplasms' with 'radiotherapy', but excluding trials on stereotactic body radiotherapy and intraoperative radiotherapy, yields 53 trials, making up less than 15% of the available data for management of LAPC. While few of the systemic treatment studies have changed systemic treatment directly, the knowledge base has helped optimise schedules and sequencing, and helped foster expertise and familiarity. This contrasts with the paucity of data to define how to sequence and integrate radiotherapy in LAPC.

A summary of what LAP 07 showed us

The LAP 07 experience showed us that a program that delays the commencement of radiation by four months in patients with locally advanced disease does not improve overall survival. The induction period had been extended in this study from a common one month period to four months, based on a belief that this would identify occult liver metastases and hence improve selection. The progression-free survival for the drug was 3.1 months, however, less than the induction period, matched by a response rate of 8%. Nonetheless, the study did establish the safety and protocol compliance of study collaborators (radiation therapy quality assessment identifying on 18% of major deviations from radiotherapy protocol).[4] It also confirmed that the radiation program was minimally toxic and there were clear palliative benefits of improved local control, and beneficial delay to time of recommencement of chemotherapy.[10]

Conclusion

Locally advanced pancreatic cancer has a poor outlook. Advances in radiotherapy technique and expertise in locally advanced pancreatic cancer have resulted in improved tolerance and benefits in palliation, such as improved local control and increasing time off chemotherapy. Furthermore, in a small but not insignificant number, the potential for long-term survival has been observed. With the introduction of more effective systemic treatments, more studies are needed to identify the optimal integration of radiotherapy and further define the most effective sequencing strategy to improve quality of life and survival.

* In the Will Rogers Phenomenon, stage migration and new diagnostic techniques are recognised as a source of misleading statistics for survival in cancer. Patients who previously would have been classified in a "good" stage migrate to a "bad stage" with the new identification of metastases with improved techniques. The prognosis of those migrated (although worse than those in the good-stage group) is better than those in the bad-stage group; thereby improving the survival rates of both groups without improvement of individual outcomes.

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THE CHANGING LANDSCAPE OF SYSTEMIC THERAPY IN ADVANCED PANCREATIC CANCER

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Abstract

Pancreatic cancer is a highly lethal disease due to its late presentation and its innate resistance to treatment. Although much research has been conducted in order to discover and develop new therapeutic targets to combat this disease, the survival gains for patients have been modest. This review aims to synopsize the current literature which has framed the approach to first and second line therapy of advanced disease. We look at the evolution of targeted therapies and briefly discuss current trials evaluating the role of immunotherapy. Finally, we cover the future of pancreatic cancer, in particular the essential role that predictive and prognostic biomarkers need to take in order to change the way we approach clinical trial design and management of patients.

Pancreatic cancer is a major cause of cancer related morbidity in Australia. In 2011, 2748 patients were diagnosed with pancreatic cancer in Australia, making it the 5th most common cause of cancer related death.[1] Although survival rates for pancreatic cancer have increased over the past decade, they still remain disappointingly low, with the five year survival rate at around 5%.[1]

Surgery is the only treatment with a potential for cure, however 80% of patients with pancreatic cancer present with stage IV disease and are not amenable to surgical

resection.[2] Late diagnosis is a hallmark of this cancer as presenting symptoms are vague. Chemotherapy is an important treatment option for patients with metastatic pancreatic cancer. Gemcitabine has been the standard of care until recent two phase 3 trials showed a benefit of multi-drug regimens.[3,4] Although these trials represent a clear advance in the treatment of pancreatic cancer, the survival gains are modest.

The relative chemoresistance of this malignancy and data from explorative genome analyses suggest that pancreatic cancer is a genetically heterogeneous disease.[5] Efforts continue across the world to address this heterogeneity in an attempt to use clinical, pathological and/or genetic factors to predict responses to treatment in order to personalise therapy to improve outcomes for patients. This review aims to summarise the pivotal studies and the evolving landscape of systemic treatment for advanced pancreatic cancer and future directions of research into this devastating disease.

First line treatment

Unlike many other cancers, where increased understanding of the molecular biology has led to improvements in treatment and management, pancreatic cancer management has shown minimal progress over the past decade. Chemotherapy remains the mainstay of systemic treatment for advanced pancreatic cancer, with gradual improvements made over time and targeted therapies showing small, incremental survival benefits (figure 1).

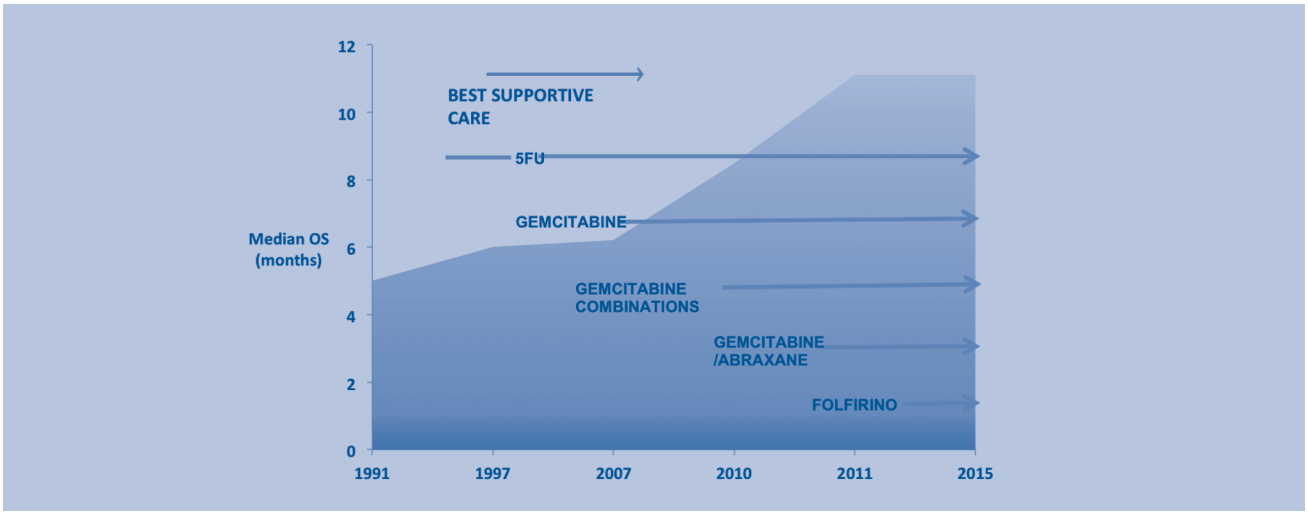
median overall survival (OS) was 6.2 months, however the overall response rate was only 7%. Alterations in dosing and frequencies have not resulted in a significant improvement in efficacy.[6,7,9]

A meta-analysis of randomised control trials published in 2007, compared combination chemotherapy including 5-FU to best supportive care alone.[10] Six trials between 1980 and 2001 involving 385 patients were included and demonstrated that OS was significantly better in patients who received chemotherapy compared with patients who received best supportive care, with a relative risk reduction of 36% (HR 0.64).[11-15]

Gemcitabine became the new standard following the results of a study in 1997. Burris et al randomised 126 patients to either gemcitabine or 5-FU and demonstrated an improvement in median survival (5.6 months vs 4.4 months p=0.0025), as well as reduced toxicity in the gemcitabine arm.[17] Also, a rapid and sustained improvement in patient reported outcomes was seen, including pain, analgesic requirements and Karnofsky performances status in the gemcitabine arm.[17]

Over the next decade, multiple trials were conducted trying to improve the efficacy of gemcitabine, using it as a backbone to add novel chemotherapeutic agents and targeted therapies. A meta-analysis comparing gemcitabine combination therapy to gemcitabine alone demonstrated a small benefit with the addition of 5-FU to gemcitabine, with an improvement in OS (HR .89[0.81-0.97] p=0.008) and progression free survival (HR 0.78[0.7-0.87] p<0.00001.[18]

***Figure 1**: Overall Survival: progress over time. Demonstrates the gradual improvement of survival over time and the timing of when new treatment options became available, most recently with combination treatments including FOLFIRINOX or Gemcitabine/nab-paclitaxel.*



In the early 1990s, 5-fluorouracil (5-FU) was one of the first chemotherapeutic agents to be used in the management of solid tumours. In 1991 Decaprio et al conducted a single arm, phase 2 study looking at the efficacy of 5-FU in patients with metastatic pancreatic cancer.[6] A total of 43 patients were enrolled, and the

Two major advances in chemotherapy for advanced disease were made after 2010. Firstly, Conroy et al randomised 342 French patients to FOLFIRINOX (5-Fluorouracil/Irinotecan/Oxaliplatin) and gemcitabine.[20] The primary endpoint of OS was met with a median OS of 11.1 months reached with FOLFIRINOX treatment

compared to 6.8 months with gemcitabine (HR 0.57 p<0.001). Response rates were also higher at 31.6% vs 9.4%. Not surprisingly, toxicities were significantly higher in the FOLFIRINOX group, with a higher rate of febrile neutropenia, thrombocytopenia, diarrhoea and sensory neuropathy. Despite these increases in adverse events, quality of life at six months was superior in the FOLFIRINOX group, (66% vs 31% HR 0.47 p<0.001).[20] The second study performed by Von Hoff et al randomised 861 patients to either gemcitabine plus nab-paclitaxel or gemcitabine alone.[21] Median OS was 8.5 months compared to 6.7 months (HR 0.70 p<0.001), confirming the superiority of gemcitabine plus nab-paclitaxel.[21] Adverse effects including peripheral neuropathy were higher, as was the incidence of fatigue and neutropenia in the gemcitabine/nab-paclitaxel combination arm. Interestingly, despite the increased incidence of side-effects experienced by the patients receiving gemcitabine and nab-paclitaxel, this did not reduce the number of doses of chemotherapy received compared to the control arm. The peripheral neuropathy was rapidly reversible when the treatment was stopped or doses reduced.

The results of both these studies have provided two new options for patients. The best option remains unclear as there have not been any randomised trials comparing these regimens. The von Hoff study included patients more typically seen in community practice in Australia (median age 63) and included patients with an ECOG of 2 (8%).[21] In contrast, the Conroy study was run in France only, excluded patients older than 70 years of age and only patients with excellent ECOG performance status of 0-1 were eligible. The high toxicity rates described in this study limit its applicability for all patients with advanced pancreatic cancer.

Gemcitabine and nab-paclitaxel has now become a standard of care in Australia. There is currently a neoadjuvant study looking at the tumour response of combination gemcitabine and nab-paclitaxel pre-operatively in patients with localised, potentially resectable pancreatic cancer. (ClinicalTrials.gov Identifier: NCT01783054)

Targeted therapies

Targeted therapies have led to significant advances in other cancer types, most notably with trastuzumab in HER2 breast cancer, however to date this strategy has had limited benefit in advanced pancreatic cancer. A variety of targeted therapies, including antibodies to vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), and KRAS have been assessed. The results of these trials have mostly been disappointing. The single positive study by Moore et al, published in 2007, assessed the addition of erlotinib to gemcitabine compared to gemcitabine alone.[19] A total of 569 patients were randomised and there was a small, but statistically significant OS benefit seen in the treatment arm (6.24 months vs 5.91 months (HR 0.82 p=0.038)).[19] Although this combination is approved in Australia, it is not currently funded by the Pharmaceutical Benefit Scheme due to the small clinical benefit and high cost. Importantly, no relevant biomarker has been identified to aid patient selection for this targeted therapy.[19]

Erlotinib was not the first targeted therapy to be studied in advanced pancreatic cancer. Among the first targeted agents studied in pancreatic cancer was celecoxib. Selective cyclooxygenase-2 (COX-2) inhibition was shown to be significantly upregulated in pancreatic cancer tissue compared with normal pancreatic tissue or benign lesions.[23] Furthermore, pre-clinical and clinical studies demonstrate that COX-2 inhibitors seem to work synergistically with 5-FU or cemcitabine.[23-25] A phase 2 study of 42 patients by Ferrari et al in 2006 using celecoxib and gemcitabine, showed a disease control rate of 71% (four patients had a partial response and 26 had stable disease). Median survival was 9.1 months.[25] Grade three neutropenia was the most common toxicity (19%) and no grade four toxicities were observed.[25] Although the survival seen looked promising, 38% of the patients had locally-advanced pancreatic cancer, which typically has a better prognosis than metastatic pancreatic cancer. Larger studies of this low toxicity and low cost therapy, especially in combination with the newer chemotherapy regimens, are warranted.

Oral EGFR receptor tyrosine kinase inhibitors (erlotinib and gefitinib) have also been investigated in the second line setting.[26] Combination erlotinib with capecitabine was studied in the advanced pancreatic cancer setting and published in 2007 by Kulke et al. Thirty patients with gemcitabine refractory advanced pancreatic cancer were included and a median OS of 6.5 months was observed.[27] To date, no correlation between EGFR expression, EGFR mutation or KRAS mutation and response to targeted therapies has been consistently seen.

As VEGF expression is frequent in this disease, it was hypothesised that VEGF inhibition would improve OS when added to standard line gemcitabine. Disappointingly, multiple studies of VEGF inhibition have shown a similar outcome to the other targeted therapies. A study by Kindler et al, comparing gemcitabine and bevacizumab in combination to gemcitabine alone, showed no survival benefit (5.8 vs 5.9 months) and increased rates of hypertension in the bevacizumab arm.[28] Similarly, aflibercept (a chimeric fusion protein of human VEGF receptor which competitively binds VEGF) was tested in combination with gemcitabine in a phase 3 trial conducted by Rougier et al, which was terminated for futility, demonstrating no survival benefit and significant adverse events, specifically hypertension in the aflibercept arm,[29] thus suggesting that targeting this pathway is an ineffective strategy in controlling this disease.

Overall, targeted therapies have not significantly impacted on the life expectancy of patients with advanced pancreatic cancer. Although erlotinib with gemcitabine has been shown to improve survival, its high cost and very limited benefit has resulted in minimal used of this therapy in Australia.

Second line therapy

Increasingly, clinicians are faced with patients who, after failing first line therapy, can be considered for second line chemotherapy. Without active treatment, it has been shown that the expected survival is likely to be poor. An observational study reported a median survival of 1.9 months after progressive disease following gemcitabine in 74 patients, the majority of whom received best supportive care (97%).[32]

Limitations of current evidence for second line therapy include the significant heterogeneity between small sample sized trials comparing chemotherapy to best supportive care, likely a reflection of the patients' poor performance status when at this stage of advanced pancreatic cancer, and their potential to deteriorate rapidly (table 1).

In 2011, Pelzer et al randomised 46 patients to 5-FU, leucovorin and oxaliplatin, or best supportive care. Although stopped prematurely, this study provided evidence of the benefit of this regimen as second line therapy (HR 0.50, p=0.031). Finally, based on the results of the CONKO-003 study, which randomised 160 patients to combination 5-FU and oxaliplatin, to 5-FU alone, showing a survival benefit of 2.6 months (5.9 vs 3.3 months (HR 0.66; p = .010),[33] this is the recommended second line treatment for advanced pancreatic cancer according to the National Cancer Care Network and European Society of Medical Oncology guidelines.[34,35] However, as FOLFORINOX is now being utilised as first line treatment, alternate second line agents are needed.

Multiple other agents have been investigated, predominantly in single arm phase 2 studies. Anti-mitotic agents including taxanes and topoisomerase inhibitors, demonstrate similar response rates and survival benefit.[37-41] Rubitecan, a convenient orally active topoisomerase I inhibitor studied in patients with advanced pancreatic cancer, demonstrated tumour growth control of 28% vs 13% with best supportive care only. Median progression free survival was also

***Table 1**: Selected second line studies in advanced pancreatic cancer.*

Study	Year	Study regimen	Number of patients	Median age	ECOG 0-1 (%)	Median PFS (mo)	Median OS (mo)
Rothenberg et al	1996	Gemcitabine 1000mg/m2 Week 1-7 q8weeks, then D1, D8, D15 q28days	63	62	27	2.53	3.9
Oettle et al	2000	Paclitaxel 50 mg/m2 weekly for 6 weeks with a 1 week break	18	59	NR	3.2	4
Jacobs et al	2004	Rubitecan 1.5mg/m2 D1-D5 q7days	198	NR	NR	1.9	3.6
Burris et al	2005	Rubitecan 1.5mg/m2 D1-5 q7days for 8 weeks	58	62.5	NR	1.9	3
Androulakis et al	2005	Oxaliplatin 130 mg/m2 q3weekly	18	61	75	NR	3.5
Demols et al	2006	Gemcitabine 1000 mg/m2 D1, Oxaliplatiin 100 mg/m2 D2 q14days	33	57	88	4.2	6
Stathopoulos et al	2006	Lipoplatin 25-125 mg/m2 D1, D15 and Gemcitabine 1000 mg/m2 D1, D15 q28days	24	66	50	NR	4
Kulke et al	2007	Capecitabine 1000mg/m2 BD D1-D14, Erlotinib 150 md daily q21days	32	60	100	3.4	6.5
Boeck et al	2007	Pemetrexed 500 mg/m2 q3weekly	52	62.5	94	1.6	4.6
Hosein et al	2013	nab-Paclitaxel 100 mg/m2 D1, D8, D15 q28days	19	61	79	1.7	7.3

significantly longer (58 vs 48 days; p=0.003), with minimal increase in the rate of adverse events.[37,38] Pemetrexed showed limited responses, but was shown to be safe to use in the second line setting.[41] Weekly paclitaxel demonstrated a 17.5 week median survival time with very rare grade 3-4 toxicities.[39,40]

The addition of platinum therapy to gemcitabine after progression on the latter has proved to be of benefit in a select group of patients. Two trials using gemcitabine in combination with oxaliplatin,[42,46] and three trials with cisplatin,[43] cisplatin/5-FU,[44] and cisplatin/5-FU/Irinotecan,[45] showed response rates of 8%-24% (median 23%) and a median PFS of four months (2.5-5 months) and OS of six months (4-10.3 months).[47] In a recent retrospective analysis of 20 patients who progressed on FOLFIRINOX, those who received gemcitabine had a median OS of 5.7 months. Although these results provide evidence of safety and tolerability in this setting, the lack of phase 3 data in the second line setting proves to be a challenging area warranting further research.

Immunotherapy

Cancer immunotherapy has recently emerged as a treatment modality in multiple advanced cancers including melanoma and non-small cell lung cancer. Over 20% of patients with metastatic melanoma show a sustained response of greater than two years when treated with agents targeting negative regulatory molecules on activated T cells, such as cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1).[48,49] However, the role of immunotherapy in pancreatic cancer is not yet clear. A phase 2 trial of ipilimumab (an anti-CTLA4 antibody) in an unselected population of patients with advanced pancreatic cancer as monotherapy revealed no responders, however one patient demonstrated a delayed response in Ca19.9. It is clear that predictive biomarkers are essential for appropriate patient selection for these therapies to be successful.[51] Similarly, studies have shown limited clinical response to vaccines.[50,51] This may be due to a combination of patient related immune factors or the inappropriate selection of tumour antigens.

The so far disappointing results with immunotherapy in advanced pancreatic cancer are currently in the process of being further investigated through the utilisation of combination treatment with existing immunotherapies, together with newer agents targeting different pathways. One of these trials, currently recruiting, is assessing the safety and tolerability of an anti-lymphocyte activation gene 3 antibody alone, and in combination with an anti PD1 monoclonal antibody in a phase 1 dose escalation study. (ClinicalTrials.gov Identifier: NCT01968109.)

Future directions

Initiatives including the Australian Pancreatic Cancer Genome Initiative continue to increase our understanding of the molecular and genomic alterations that lead to advanced pancreatic cancer and provide insights into reasons for the resistance to current therapies. As whole genome sequencing becomes faster and more affordable, identifying potentially actionable target mutations is closer to reality. Due to the rapidly progressive nature of pancreatic cancer, tests need to provide relevant information within a short timeframe to become useful in clinical practice.

Several potentially actionable mutations have already been identified and are currently being investigated to assist in directing treatment, including thymidylate synthase high intra-tumoral expression and topoisomerase expression.[52]

Identifying new therapies and new targets is vital for pancreatic cancer, but gaining a better understanding of the currently available treatments is also critical. Predictive biomarkers to select the most appropriate patient for treatment is an area of ongoing work. Currently there is mixed evidence for hENT1 expression being a positive predictive biomarker for adjuvant gemcitabine and evolving data to suggest there may be a relationship between markers of DNA damage repair and response to platinum agents.

Pancreatic cancer continues to be a devastating diagnosis. Despite decades of research into scores of novel therapies, most patients will die of their disease. What is clear is that pancreatic cancer is a heterogeneous disease and that genetic and molecular profiling must be expanded in order to stratify patients for clinical trials and ultimately to guide therapeutic choices.

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PATTERNS OF CARE – IMPROVING EQUITY OF ACCESS TO OPTIMAL CARE

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Abstract

People diagnosed with pancreatic cancer suffer the worst five-year survival of any cancer. Resection of the primary tumour currently provides the only potential for cure. Increasing the proportion of patients who undergo surgical resection and ensuring that this occurs in a high-volume setting may lead to population-level survival gains. Access to chemotherapy in both adjuvant and palliative settings may lead to further improvements. Worse survival has been reported for patients from lower socio-economic and rural areas than those who are wealthier and living in major cities. Management in higher-volume hospitals tends to be associated with higher survival. Differences in patient factors such as age, performance status and the presence of co-morbidities may partly explain the survival discrepancies. However, international and limited Australian data suggest that not all patients receive optimal treatment, and that variability in care may be related to socio-demographic factors. There is considerable investment in identifying new strategies for diagnosis and treatment. However, immediate improvements could be made by implementing policies and procedures that enable all patients to be managed by high-performing multidisciplinary teams, ensuring receipt of optimal curative and supportive treatment modalities. This will also enable full realisation of benefits expected to accrue from the development of new treatments over the coming decades.

Pancreatic cancer is the tenth most commonly occurring cancer in Australia, affecting over 2700 people each year. It has the worst five-year survival of any cancer at less than 5%, so takes the lives of over 2500 Australians annually and is the fourth-leading cause of cancer death in both men and women.[1] There has been little change in the mortality to incidence ratio since the early 1980s, in contrast with a number of other cancers. As a result, it has been estimated that within the next decade it will become the second-leading cause of cancer death in the United States and this is likely also to be the case in Australia.[2]

The dismal prognosis in patients with pancreatic cancer is due firstly to the late stage at which most people are diagnosed. Consistent with international estimates,[3] almost 60% of pancreatic cancer patients in Australia are diagnosed with metastatic disease which precludes resection of the tumour.[4] A further 20-30% of patients have locally advanced disease and, although surgical techniques have improved, the vascular involvement is frequently too extensive to permit resection. The second reason for the poor survival has been the lack of efficacious systemic treatments. Until recently, administration of gemcitabine was considered the standard of care in both adjuvant and palliative settings, despite only small improvements in survival. The use of new regimens such as FOLFIRINOX and albumin-bound paclitaxel for treatment of inoperable pancreatic cancer, and increased investment in discovery of new therapies, may lead to further improvements in pancreatic cancer survival in the next decade.

Ensuring all patients receive optimal treatment will help to realise potential survival gains. However, international data suggests that patients from lower socioeconomic and rural areas may have worse survival than their counterparts from wealthier and metropolitan areas[5,6] and similar trends for geographic location have been observed in Australia.[7,8] While differences in patient factors such as age and the presence of co-morbidities may partly explain the survival discrepancies, it is likely that differential access to treatment also plays a role.

Increasing the proportion of patients who undergo resection of the primary tumour

Surgical resection of the primary tumour improves five-year survival from less than 5% to up to 20%,[9] but consistent with international estimates, only 15% of patients in two states of Australia underwent resection between 2009 and 2011.[4] Population-level survival estimates would improve if this proportion could be increased. It has been estimated that increasing the proportion of patients diagnosed with stage one and two (i.e. operable) disease from 6% to 19%, with a concomitant decrease in the proportion of patients with metastatic disease, would double five-year survival.[3]

Earlier diagnosis might increase the proportion of patients diagnosed with operable disease. Some studies,[10,11] although not all,[12] indicate that diagnostic delay is associated with later stage disease and poorer outcomes. However, a substantial component of the delay occurs as a result of the non-specific nature of symptoms which do not prompt early presentation to

medical practitioners, and it is unlikely that this will be amenable to significant improvement. Implementation of screening programs has more potential to lead to a shift in the distribution of the stage of disease at diagnosis, but considerable challenges remain. Population-wide screening is not feasible due to the relative rarity of pancreatic cancer. Indeed, modelling studies suggest that such an approach would reduce life expectancy due to false positive results and unnecessary surgery.[13] Screening is therefore currently restricted to people with genetic predisposition to pancreatic cancer and is only occurring within the context of research studies. Attempts to identify other subgroups of the population that have sufficiently high risk to make screening viable have so far proven unsuccessful.[14] Further, current screening relies on either computed tomography or magnetic resonance imaging; these are insufficiently accurate for identifying small tumours, may not be easily accessible and are expensive. Until these issues are resolved and screening becomes a feasible option, it is doubtful that there will be any discernible increase in the proportion of patients diagnosed with early stage, operable disease.

A second approach to increasing the proportion of patients who undergo surgery is to ensure that this treatment option is offered to all patients with resectable tumours and acceptable performance status. International data show that there is currently inequitable access to surgical intervention, with patients who are black, unmarried, have low education or socioeconomic status, and who come from rural rather than metropolitan areas being less likely to undergo resection of the primary tumour.[15-18] This is most probably associated with the expertise of the facility at which patients are staged. Patients who are managed at high volume or accredited cancer centres have higher likelihood of undergoing surgery than those who are treated at lower volume centres, and there is evidence that centralisation of care can increase resection rates.[19] There is limited published Australian information about patient factors such as education which might influence access to surgical treatment, but our unpublished data suggests that remoteness of residential location is inversely associated with resection, and a Queensland report shows a slightly higher resection proportion in more affluent patients with cancers of the pancreas, biliary tract and small intestine combined.[20] Guidelines suggest that all patients without metastatic disease should be assessed for tumour resectability by a multidisciplinary team that includes a specialist hepatobiliary surgeon;[21] developing referral pathways or telehealth facilities that enable implementation of this guideline has the potential to increase the number of patients in Australia that are offered a resection of their tumour.

Surgical volume and mortality/survival

Pancreatic cancer surgery is challenging due to the anatomic location of the pancreas, with its close proximity to large blood vessels into which the tumour has frequently invaded. The experience of the hospital at which patients are treated is therefore an important determinant of outcomes. A meta-analysis of 11 studies, most from the United States and none from Australia, found that patients treated in higher volume hospitals had lower post-operative mortality and longer overall survival.[22] The cut points for high and low volume varied markedly however, so volume is likely to be a marker of expertise and multidisciplinary care, but there is little evidence upon which to base recommendations about the minimum number of surgeries that should be performed. This is reflected in the guidelines which are inconsistent, with the National Comprehensive Cancer Network recommending a minimum of 15 surgeries per year, the National Cancer Institute Guidelines recommending five and the British Society of Gastroenterology not specifying a particular number. There are no specific Australian guidelines. Between 2005 and 2008 in New South Wales pancreatic cancer surgery took place at 37 hospitals. Only six of these performed more than six pancreatic cancer surgeries annually, and 15 (41%) undertook fewer than two procedures each year.[23] Between 2002 and 2011 in Queensland, 23 hospitals performed pancreaticoduodenectomies; by 2011 this number had dropped to 13[20] indicating that centralisation of care has been occurring in some jurisdictions.

Adjuvant chemotherapy

There is a high risk of recurrence after resection of the primary pancreatic tumour, with median disease-free survival of less than one year.[24] Clinical practice guidelines therefore recommend adjuvant chemotherapy or chemo-radiotherapy,[21] although the type of therapy to be used is not specified, probably due to a lack of consensus about the interpretation of clinical trial data. As with surgery, international evidence suggests variable implementation of adjuvant therapy. A recent report from the Netherlands found that only about half of patients received adjuvant chemotherapy, but this was higher in patients who underwent their resection at a high-volume hospital.[25] Similarly, studies from the United States found that receipt of adjuvant therapy was higher among patients treated at high volume hospitals (vs low volume) and at academic rather than community hospitals[15] and in white rather than black patients.[16] In Australia, chemotherapy with gemcitabine has been the standard of care, particularly since the publication of the CONKO-01 trial in 2007.[24] Presumably as a result of this key publication, use of adjuvant chemotherapy increased from 47% in Victorian patients diagnosed in 2002-2003 to 76% in patients from Queensland and New South Wales diagnosed almost a decade later. Patients who did not receive adjuvant treatment had worse performance status or a complicated post-operative course (unpublished data). This suggests that most Australian patients who undergo surgery are now receiving appropriate multi-modality postoperative care in accordance with guidelines.

Chemotherapy in advanced pancreatic cancer

The majority of patients present with metastases or locally advanced inoperable disease. For these patients there have been limited curative treatment options and symptom control has been the primary aim of management. In 1997, a landmark study was published which showed that, although gemcitabine resulted in only a modest survival benefit over 5-flurouracil, it delivered substantial improvements in pain, performance status and weight.[26] It subsequently became the standard of care for first line treatment in patients with advanced disease. As with surgery and adjuvant chemotherapy, there is evidence from the United States that socioeconomic disadvantage is associated with lower use of palliative chemotherapy.[16,27] Elderly patients with advanced cancer are also less likely to receive chemotherapy than younger patients, even though there is evidence of benefit in older patients.[28,29] In our population-based study in Queensland and New South Wales, only 43% of people diagnosed with inoperable disease received chemotherapy[4] but there are currently no recent published data about determinants of receipt of therapy. Newer chemotherapy regimens with greater impacts on survival and quality of life are now used for treatment of advanced pancreatic cancer, including FOLRIRINOX and albumin-bound paclitaxel and Gemcitabine.[30-32] Ensuring equitable access to these and other novel systemic treatments as they become available will be an important contributor to improvements in survival in the coming decade.

Conclusion

Pancreatic cancer continues to have unacceptably high mortality and patients report extremely high supportive care needs throughout the course of disease.[33] International and limited Australian data suggest that not all patients receive optimal treatment, and that variability in care may be related to socio-demographic factors. There is considerable investment in new strategies for diagnosis and treatment and there now appears to be light at the end of the tunnel. However, immediate improvements could be made by implementing policies and procedures that enable all patients to be managed by high-performing multidisciplinary teams, ensuring receipt of optimal curative and supportive treatment modalities. This will also enable full realisation of benefits expected to accrue from the development of new treatments over the coming decades.

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PALLIATIVE CARE IN ADVANCED PANCREATIC CANCER

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Abstract

The management of patients with advanced pancreatic cancer often requires a multi-disciplinary approach with individualised therapy. Addressing the underlying causes of several of the troublesome symptoms that are relatively unique to the pathophysiology of pancreatic cancer is crucial in order to optimise the function and comfort of people diagnosed with this poor prognosis cancer. Early recognition and response is likely to improve outcomes later in the course of the disease, but more work needs to be done to compare expectant and reactive approaches to the most troublesome symptoms in advanced pancreatic cancer. Given such a poor outlook, referral to a palliative care service that has an active, team-based approach that includes dietetics, gastroenterology, interventional pain expertise and liaison psychiatry is likely to deliver the best possible outcomes. Such programs need to be in centres with sufficient caseload to ensure that meaningful outcomes can be measured prospectively and these teams are also best placed to incorporate new knowledge and approaches as the evidence base continues to evolve.

Pancreatic cancer is the fifth most common cause of death due to cancer in Australia, and the rest of the western world. In 2011, the overall five year survival was 5.2% in Australia for patients diagnosed with pancreatic cancer. If Australian trends of incidence and mortality in pancreatic cancer mirror the United States, the implication is that the incidence of pancreatic cancer will increase over the next few decades to become one of the leading causes of cancer-related mortality in Australia.[1] Approximately 80-85% of patients have unresectable disease at presentation,[2] and this group of patients can expect to have a five-year survival of 3% in Australia.[1] Therefore, patients with locally advanced pancreatic cancer may benefit from early referral to a palliative care service for symptom management.

Specific symptom management issues that relate to advanced prostate cancer

In the palliative care setting, patients with advanced cancer commonly experience symptoms such as pain, nausea and vomiting. However, advanced pancreatic cancer causes a number of other symptoms due to the anatomical location of the primary tumour and pattern

of metastatic spread, with infiltration of the liver and coeliac or splanchnic nodes. Advanced prostate cancer also predisposes patients to an increased risk of venous thrombo-embolism (VTE).

Venous thrombo-embolism in pancreatic cancer

A diagnosis of cancer carries a hundred-fold increased risk of venous VTE compared with the healthy population. Pancreatic cancer has an increased incidence of VTE compared with all other cancer populations. The rate of presentation with VTE has recently been reported to be 11.6% at three months and 21.3% at 12 months after diagnosis in advanced pancreatic cancer.[3] The increase in VTE risk is thought to be due to cancer cell over-expression of tissue factor and mucin, and this leads to a hypercoagulable state. Over-expression of tissue factor and mucin occur more frequently with primary tumours originating within the body and the tail of the pancreas than in the head. This may explain the increased incidence in VTE in body and tail tumours, and a worse prognosis in these patients.[4] Where patients with advanced pancreatic cancer present with abdominal pain, inferior vena cava or splanchnic vein thrombosis should be considered in the differential cause.

The CLOT study in 2003 demonstrated that low molecular weight heparin (LWMH) dalteparin produced better overall survival and fewer bleeding events than warfarin. LMWH has been the gold standard treatment of VTE in cancer.[5] Since then, rivaroxiban has been introduced to reduce the risk of stroke in atrial fibrillation. The advantages of rivaroxiban over LMWH and warfarin are that it is taken by tablet once a day and does not require any therapeutic monitoring. However, there have been no studies published to date that prove superiority of the use of rivaroxiban in the treatment of VTE in cancer patients. The role of primary prevention of VTE in advanced pancreatic cancer is being elucidated. The PROSPECT-CONKO 004 study showed that the greatest reduction in VTE events was in the first three months after patients commenced chemotherapy in combination with treatment with enoxaparin compared with chemotherapy alone.[3] As expected, there was also an increased risk of major bleeding in the enoxaparin group (8.3% in the enoxaparin group vs 6.9% in the observation group). The study was not powered to determine the safety of enoxaparin in the trial conditions. Further studies are awaited to determine the role of thromboprophylaxis in the management of patients with advanced pancreatic cancer who have supportive care alone.

Pancreatic exocrine insufficiency

Pancreatic exocrine insufficiency (PEI) occurs as cells, which synthesise pancreatic enzymes, are either progressively destroyed by pancreatic cancer cells, or the main pancreatic duct is blocked by a tumour within the anatomical head of the pancreas, where the majority of tumours occur.[6,7] This causes compression of the proximal pancreatic duct, and endoscopic stenting may be required. Consultation with a gastroenterologist will determine the role for investigation with endoscopic retrograde cholangiopancreatography and insertion of a biliary stent. Untreated blockage at the head of the pancreas causes progressive loss of exocrine function of the pancreas, and patients will experience symptoms of PEI resulting in deterioration in the patient's quality of life and overall survival.[8,9] The incidence of PEI is estimated to be around 85% when patients present with pancreatic cancer.[10]

PEI occurs in other disorders of the pancreas such as cystic fibrosis, chronic pancreatitis and following pancreatic resection. PEI has been extensively studied in these non-malignant conditions, but not in advanced pancreatic cancer. Symptoms arise due to malabsorption of fat, and these include weight loss, diarrhoea, steatorrhoea, flatulence, abdominal pain and bloating. PEI may also cause fat-soluble vitamin deficiencies.

The mechanism for treating PEI in pancreatic cancer with pancreatic enzyme replacement therapy (PERT) was elucidated in a small study from the Mayo Clinic in 1983.[11] Guidelines, based on studies with small numbers of patients, recommend the empiric treatment of symptomatic patients with PERT.[7,12,13] Patients who have undergone pancreatic resection are prescribed PERT based on their risk of PEI.[2] Yet patients who have advanced pancreatic cancer are not routinely evaluated for symptoms of PEI, referred to a dietitian or offered PERT.[14] There is evidence that patients often try dietary fat restriction or other therapies to manage their symptoms, and have a variable degree of success in managing of PEI.[15]

The most commonly prescribed PERT is an encapsulated form of pancreatic enzymes derived from porcine pancreas. Its safety profile has been established in cystic fibrosis and chronic pancreatitis.[16] Successful treatment with PERT requires education by a dietitian to explain the timing of medication with relation to meals. Individualised therapy may be required, including, for example, a change in dose or the addition of a proton pump inhibitor, which aids the activation of PERT if the gut pH is too low. Patients who are on treatment require monitoring and treatment algorithms have been published.[17] Data on the success of treatment with PERT in advanced pancreatic cancer have not been published to date. For patients who have treatment failure, further investigation can exclude the presence of bacterial overgrowth.[18]

Cachexia in advanced pancreatic cancer

Cachexia arises as a consequence of release of systemic cytokines and PEI in advanced pancreatic cancer, and is known to have an adverse effect upon overall survival of patients who present with resectable pancreatic cancer.[9] This study compared patients who had cachexia at presentation with pancreatic cancer and those who did not, and found that patients who

cachexia at presentation had poorer overall survival at 12 months post-operatively compared with patients who did not. It has been demonstrated that PERT can prevent weight loss in advanced pancreatic cancer,[19] but no definitive studies have established that there is a survival advantage with PERT. The hypothesis that treatment of cachexia and PEI in advanced pancreatic cancer may result in improvement of patient quality of life and prognosis is unproven in clinical trials.

Pain and pancreatic cancer

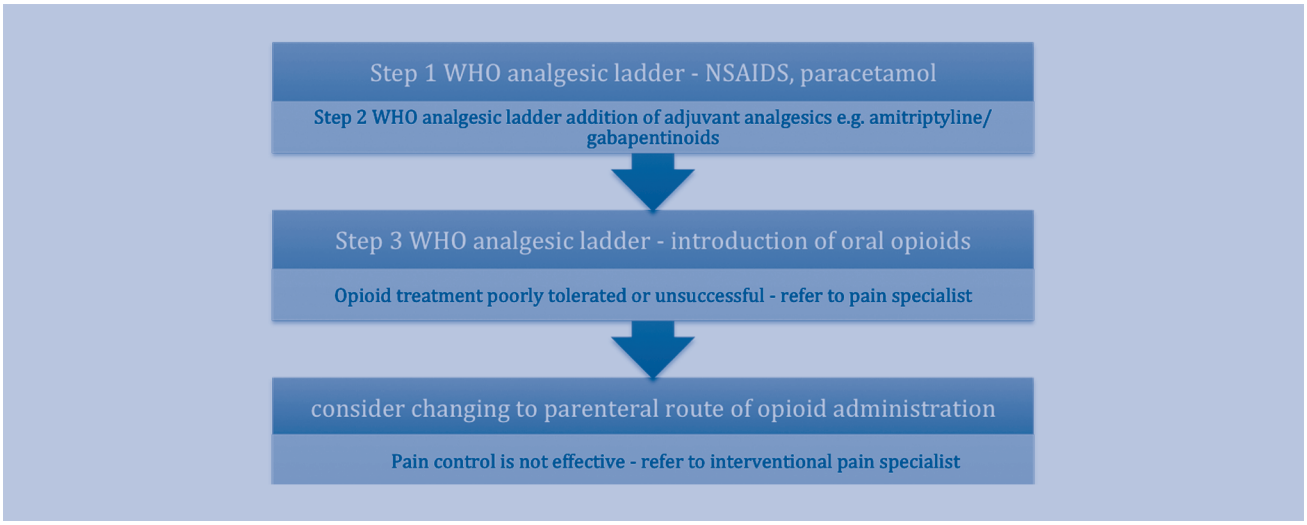
Pain management is a challenging issue and affects 50-70% of patients who are diagnosed with pancreatic cancer. The principles of management have not changed significantly since Russell Portenoy published an article on this area in 1996.[20] Pain caused by pancreatic cancer can be multi-factorial in aetiology and accurate diagnosis is essential in successful management. Perception of pain may be increased if depression coexists in advanced cancer. The incidence of depression in patients who have been diagnosed with pancreatic cancer has been reported to be as high as 41-71%.[21] Pain in pancreatic cancer can be neuropathic in nature, especially where there is infiltration of the coeliac plexus and may require treatment with a combination of opioid and adjuvant analgesics (see figure 1).

When there is treatment failure with oral opioids, alternative routes of administration can be considered, such as transdermal, subcutaneous or intravenously. Patients can also be referred for consideration of an interventional procedure such as a coeliac plexus block. There is considerable regional variation in access to interventional pain specialists within Australia, and patients in rural locations may travel to a major tertiary referral centre for assessment. A recent Cochrane Collaboration review of coeliac plexus blocks for pain in advanced pancreatic cancer did not demonstrate a durable benefit in analgesia with this technique. However, there was an objective reduction in oral opioids taken by patients who underwent the procedure compared with those who were managed conservatively and they experienced fewer side-effects from opioid administration.[24]

Liver metastases

Advanced pancreatic cancer commonly metastasises to the liver, causing progressive liver failure with jaundice, ascites, lymphoedema and hepatic encephalopathy. Biliary stenting may be complicated by ascending cholangitis and this can require treatment with intravenous antibiotics or replacement of the biliary stent. It is known from private billing data from the United States that chemotherapy is more commonly delayed for patients who have plastic endoprosthetic stents than metallic stents, as plastic stents are more frequently blocked and colonised by bacteria than metallic stents.[25,26] It is worthwhile to consider replacement of a stent if colonisation is suspected.[21,26] Pruritis occurs with jaundice, and treatment options with a variety of agents from different classes have been reported in clinical trials. These include rifampicin, cholestyramine and ondansetron.[27] However, due to the small numbers of participants in studies considered in a Cochrane review on pruritis in palliative care, it was only possible for the

***Figure 1**: Management of pain due to coeliac plexus infiltration.*



Recently the anticonvulsants gabapentin and pregabalin have been introduced in the management of neuropathic pain. Treatment failure with these agents may occur for different reasons. Pregabalin has been studied in pain due to chronic pancreatitis and its absorption profile is unaltered in this condition.[22,23] However, it is not known whether alteration in gastrointestinal motility caused by opioids, which are commonly co-prescribed in cancer pain, has an affect upon the absorption of adjuvant analgesics, or whether PEI and its treatment influences the absorption of orally administered analgesics.

authors to recommend that good quality further studies are needed in this area.

Ascites can be a difficult symptom to manage. Successful treatment with diuretics such as spironolactone is enhanced when the intra-abdominal volume of ascites is relatively small by clinical evaluation, which is more likely at an early stage in the illness. More established ascites is likely to be refractory to diuretics, even with a combination of class agents, and ascitic drainage may be required.[28] In some centres this is done under radiological guidance. Where repeated abdominal paracentesis is required, permanent drains such as Tenckhoff catheter (peritoneal dialysis catheter) or tunneled PleurX drains can be used. The insertion of a drain of this type means that patients can be managed successfully at home without attending a hospital appointment or being admitted as an inpatient to have a procedure.[29]

Conclusion

Patients with pancreatic cancer often present with advanced disease, for which there are no curative options. There is evidence that conditions which co-exist in pancreatic cancer such as pain, depression, cachexia and pancreatic exocrine insufficiency are under-treated. A multi-disciplinary approach to management can have a positive impact on quality of life in a condition that is predicted to increase in prevalence over the next few decades and currently has limited options for disease modification.

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INTEGRATED PSYCHOSOCIAL AND SUPPORTIVE CARE NEEDED FOR PATIENTS WITH PANCREATIC CANCER

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Abstract

Pancreatic cancer is acknowledged as one of the most challenging diseases in the 21st century. Despite the recent focus on research and novel therapies, by 2030 pancreatic cancer is projected to be the second leading cause of cancer death after lung cancer. With incidence and mortality rising against the trend in other cancers, the importance of a whole team approach to achieve best quality of life and care is critical. Recent Australian research has reported significant unmet needs for psychosocial and supportive care for people affected by pancreatic cancer. Nihilism has been identified as a problem in pancreatic cancer that affects clinicians, patients, carers and families. This can lead to loss of hope and people becoming disengaged from care, resulting in increased distress, poor quality of life and signs of demoralisation. Meaning-centred therapies can help with reducing demoralisation, improving existential wellbeing, increasing dignity and legacy building. Effective interventions can ease the existential distress that is often experienced at end of life and help family members during the grieving process. Essential in providing optimal care for patients and caregivers is timely and appropriate discussions about the importance of palliative care in managing symptoms and improving quality of life. Early integration of psychosocial and supportive care is recommended to achieve best quality of life and relieve suffering.

Pancreatic cancer is a challenging disease from both clinical and research perspectives.[1,2] The literature constantly reminds us that survival in pancreatic cancer has not improved in contrast to other cancers.[3] The relative five-year survival rate is the lowest of all solid cancers, at less than 5%.[4] The overarching burden of pancreatic cancer is expected to increase, with Australian and US data projecting a rise in incidence and associated mortality leading pancreatic cancer to becoming the second highest cause of cancer death by 2030, surpassing breast, prostate and colorectal cancers.[5,6] Individuals diagnosed with pancreatic cancer have poor quality of life and demonstrate a lower level of functioning across the five domains of the EORTC QLQ-C30 and a higher symptom burden, particularly for digestive symptoms (EORTC QLQ-Pan26).[7] The substantial literature on all aspects of pancreatic cancer research, treatment and care never fails to note that consequences for those diagnosed still remain grim.

Patients exhibit high levels of distress

Distress is recognised as the sixth vital sign in cancer, as a diagnosis of any cancer is associated with physical and psychological challenges.[8] Adjusting to and coping with the demands of treatment and the disruption to personal and occupational lives, for both the individual and their family, can place a significant emotional burden on all involved. Emotional distress associated with diagnosis can be a major factor that affects an individual's quality of life and the ability to make well informed decisions. A consistent finding from research is that a diagnosis of a poorer prognosis cancer produces the highest rates of distress.[9] In pancreatic cancer, people diagnosed often demonstrate the highest rates of anxiety and depression and record a higher percentage (27%) of psychosocial distress than those with other cancers (21%).[10] Because of the short survival time and the elevated levels of distress, it is imperative that assessment and intervention be prioritised, and psychological strategies appropriate for this population are identified and utilised to support patients and families early on in the care trajectory.

Psychosocial supportive care is recognised as a complex multidimensional construct that includes informational, emotional and physical support, social integration, esteem and support of others.[11] As is the case in pancreatic cancer, when cure is not an outcome, and treatment options are readily exhausted, psychosocial

and supportive care needs are likely to increase for both patients and caregivers. The benefits of psychosocial support have been linked to lower levels of distress and improved outcomes in other cancers. Lutgendorf and colleagues demonstrated in a recent study that psychosocial support conferred a significant survival benefit for women diagnosed with ovarian cancer.[12] For people affected by pancreatic cancer, awareness and early assessment of psychosocial distress and meeting supportive care needs are critical to help achieve best quality of life to end of life, and to relieve carer burden.

Communication difficulties predict high levels of unmet need

Evidence suggests individuals with pancreatic cancer and their carers have unmet needs in many areas, not only in psychosocial and supportive care, but also having unmet information needs. These findings are reported in both a recent qualitative study and also by the largest population-based study to date in Australia.[13,14]

Beesley and colleagues reported that along with high levels of physical need including pain, fatigue and difficulty managing daily activities, almost all participants reported having a psychological need that was currently unmet by services, half at moderate-to-high levels.[13] High levels of unmet need for information about managing the effects of pancreatic cancer were also identified, supporting the earlier finding by Gooden.[14] Both studies also reported perceived difficulties in communication with clinicians that led to people experiencing feelings of isolation and 'abandonment'. Communication difficulties were found to have contributed to distress in both patient and carer groups.[14] Maintaining good communication and managing perceived difficulties encourages continuity and engagement with care.[15] Australian guidelines are available to promote best practice regarding communicating prognosis in advanced illness and end-of-life discussions to minimise distress and ensure patients and families feel supported.[16]

Nihilism versus hope

The reputation and reality of pancreatic cancer projects a pervasive nihilism that can have a negative impact on clinicians, nurses, health professionals, patients and families. The problem of therapeutic nihilism, defined as the lack of belief in the value and/or efficacy value of therapy, has been flagged in the literature in relation to pancreatic cancer care.[1] What has not been acknowledged is the potential for this nihilism to inadvertently directly affect the provision of care. Experiencing nihilism leads to a loss of hope for patients and families.

A recent study found that in the face of hopelessness, communication between clinicians and patients/families was often less than ideal and as a result, continuity of care was disrupted.[14] This meant that opportunities were missed to have discussions around key issues such as supportive care needs and the importance of palliative care and timely referral into services. Typically the responsibility to introduce formal conversations around palliative care rests with clinicians. A new study has reinforced the key role of oncology nurses in continuing the conversations, negotiating futility and managing the emotions and tensions around transitioning to palliative care.[17] Delivering effective integrated person-centred care requires a shared approach, with the responsibility for monitoring and managing psychosocial or existential distress assumed by the whole cancer care team.

Though the ideal is early integration of palliative and psychosocial services, these services may not be available or easily accessible to all, particularly for those in regional areas. Phillip and Collins recently asserted that successful integration of palliative care relies on the importance of engagement with communication, a willingness to have these difficult conversations, rather than access to quality services.[18] Regardless of access to services, giving time to patients and families is critical. Checking-in with them regarding their existential feelings and fears can promote the demystification of palliative care, and reframe the conversation to one of providing hope for best quality of life to end of life.

Risk of demoralisation

The twin effects of lack of continuity of care and nihilism, in conjunction with a lack of hope, have been identified as key factors that make the daily struggle with pancreatic cancer much harder. In the face of hope destroyed, people have exhibited signs of demoralisation,[14] and it is critical to sustain hope in advanced cancer.[19] Hope can be reframed as hope for quality of life, hope for a pain-free death, hope for research to benefit future generations and hope for support to enable well-managed caregiving and importantly, to avoid demoralisation.

Demoralisation is defined in the oncology literature as a state beyond distress whereby the greatest risk is considered to be in people affected by advanced cancers.[20] Demoralisation is distinguished from depression in that it is characterised by hopelessness, helplessness and loss of purpose and meaning in life.[21] Social isolation may also intensify feelings of distress and this is exacerbated particularly in situations where people have low social support.[22,23] People affected by pancreatic cancer who are struggling with high unmet needs for psychosocial and supportive care become socially isolated, as efforts to maintain activities of daily living become more difficult. Caregivers who express feelings of isolation have also been found to demonstrate signs of demoralisation as they struggle with their carer burden.[14] Reducing social isolation, by ensuring continuity of care and providing social support by linking people affected by pancreatic cancer into support services, is critical to improve quality of life.

Existential wellbeing, increasing dignity and legacy building, are promising ways of reducing demoralisation and enhancing meaning in those with advanced cancer.[24]

A recent review of psychological interventions effective in the treatment of distress in cancer patients, found that meaning-centred therapies can have a significant and positive effect with relatively short-term interventions, whether delivered individually or in groups.[25] A 2007 study on family members' perspectives on dignity therapy found that not only did this intervention alleviate psychological and existential distress in the patient, it also helped family members during the grieving process.[26] These findings suggest that even in the most confrontational of situations, psychological wellbeing, meaning and hope can be positively influenced by certain interventions. Dignity therapy and meaning-centred therapies may be the most effective for those individuals with pancreatic cancer and their families, due to the benefits to be gained in a relatively short amount of time.

Importance of integrated psycho-oncology and palliative care

Clinical practice guidelines demonstrate strong evidence that end of life psychological interventions can improve mood, coping, sense of personal control, and physical and functional adjustment.[27] Very necessary in this population group is early referral and integration into palliative care, along with the provision of psychosocial support services. Although this is accepted as essential to manage physical, spiritual and psychosocial care in inevitably fatal disease, both studies cited previously found this did not happen for the majority of the people in their studies affected by pancreatic cancer.[13,14] This may be due to the stigma associated with palliative care and its association with the inevitability of death.

Studies have confirmed the negative connotations associated with the term 'palliative care' and demonstrated a preference by oncologists in the US for the term 'supportive care'.[28,29] The study by Rhondali and colleagues highlighted a name change alone did not strongly influence earlier referral patterns to palliative care. Communication difficulties were still acknowledged as a problem in discussing transitioning of care. Best practice is considered to be early integration of palliative care with emphasis on a whole team approach to support patients to achieve best quality of life and help their families manage and understand the care trajectory.

Australia, like many other countries, has a multi-cultural society where norms around death or discussions of death vary widely across cultures. The transition from active care to being supported to live with the dying process is a paradigm shift that is difficult for individuals and families in every cultural context. The risk for patients and families affected by pancreatic cancer, when palliative care is not appropriately engaged, is an undignified, distressing and painful experience of death that can result in ongoing and complex grief for families. The acceptance of palliative care is a key step in providing optimal care for many patients and families across all cultures, with sensitivity required to individual belief-systems. Indeed, it becomes even more important when evidence suggests that involving palliative care early in the care of metastatic cancer patients can increase mood, quality of life, and may actually extend life in some cases.[29] Conway advocates for working together to move beyond the confines of acute health care, within a broader health promotion approach, to create supportive environments around end of life.[30] The emphasis is on effectively delivering quality of life to end of life through the provision of coordinated cancer care.

Is quality of life an achievable goal in pancreatic cancer?

Quality of life to end of life is a goal that is achievable for people affected by pancreatic cancer. Providing phase-appropriate support helps to engage patients and their families with the medical and psychosocial support that will facilitate their adjustment process. In the long term it is hoped that genomic research and new biotherapies will achieve the breakthroughs that are needed to prolong disease-free survival and improve outcomes in this disease. In the short term, efforts need to be directed towards supporting best possible quality of life by promoting effective communication that fosters realistic hope for a managed disease process. This would ideally involve integrating psycho-oncology into multidisciplinary care and ensuring continuity of care throughout the disease trajectory, which may ameliorate feelings of isolation and abandonment. Initiating timely and appropriate discussions about the importance of palliative care in managing symptoms and improving quality of life is also an essential part of optimal care for all patients with metastatic cancer.

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2015 Tom Reeve Award
HOPES, WISHES AND TIME WELL SPENT

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The Tom Reeve Award for Outstanding Contributions to Cancer Care, offered annually by the Clinical Oncology Society of Australia (COSA), formally recognises a national leader who has made a significant contribution to cancer care. Since its inception in 2005, when the inaugural Award was presented to Professor Tom Reeve himself, there have been nine recipients from diverse cancer disciplines.

In its 10th year of this prestigious Award, the 2015 recipient of the Tom Reeve Award was Professor David Currow. Professor Currow is the Chief Cancer Officer, NSW and Chief Executive Officer, Cancer Institute NSW, the NSW Government's cancer control agency. He was appointed to the position in March 2010. Prior to that he was the foundation Chief Executive Officer of Cancer Australia, the Commonwealth's cancer control agency.

Professor Currow accepted the Award at the COSA Annual Scientific Meeting in Hobart on 18 November 2015 and delivered an inspiring and meaningful oration that challenged the audience to consider their personal and professional perspectives on end of life care.

"It's satisfying to see how far we have come, and to think about where we can go towards improving cancer patient care and treatment." Emeritus Professor Tom Reeve CBE, AC. Cancer Forum. October, 2013

Patients with life-limiting illnesses such as cancer are able to simultaneously hold hopes and wishes often even in the same sentence - hope for something that is likely to be achievable and wishing for things that are highly unlikely, yet still bear talking about. The level of insight this reflects and the level of courage to acknowledge both is remarkable at such a potentially traumatic time in a person's life. How do we honour patients' hopes and their wishes to ensure that they can make the most of whatever time people have?

To try and understand what this may look like, what would each of us change were we to learn that life was suddenly very finite? Priorities in this setting are interesting. For example, lots of people who are employed continue to work, but not because they need the money. In part, work defines who they are. Most people reprioritise to spending as much time as possible with family and friends.[1] For most people, good symptom control is a means to an end – quality time with the people who mean the most to them – and not an end in itself.

Many of us have been at the bedside of thousands of people facing death. What have our patients taught us about caring for people at the end of life in order to continually improve our care? How do we ensure that the care that they get is the best possible care, and that we focus on the things that will best support patients and their caregivers in order to optimise outcomes? Clinicians and the health system can learn a great deal about the care that we offer from people as they face the physical decline associated with late stage disease.

Professor David C Currow, Chief Executive Officer, Cancer Institute of New South Wales.

By carefully listening to people facing death, we can find key ways to improve the care that we offer and the way that it is delivered to all patients, not simply those at the end of life.

Don Berwick, now head of Institute for Healthcare Improvement, was formerly the head of the Center for Medicare and Medicaid Services, providing the funding to 95% of Americans over the age of 65 and a high proportion of the most socio-economically disadvantaged people in the rest of the population. With such a critical role in the health of the nation, it may have been surprising that he wrote an open letter when he was due to have a knee replacement in 2005.[2] In this article, he started to outline a patient-centred manifesto for a good health care system. In this personal plea, he was keen to ensure that avoidable mortality was addressed, that the things that were done in the name of clinical practice were likely to benefit him, that needless pain could be avoided, that people were not made to feel helpless, that his time was valued by not keeping him waiting and that resources were not wasted.

Subsequently, this manifesto was expanded and slightly reworded. Relief of pain was clarified to include both physical and emotional pain. Ensuring that people did not feel helpless was juxtaposed with the need for clinicians to actively share information. Waste appeared at a personal level ('don't do things that cannot help me') and at a systems level ('don't waste resources – mine or anyone else's'). This lecture focuses on concepts from Don Berwick: firstly 'don't hurt me' and 'relieve my physical and emotional pain'; and secondly 'don't make me feel helpless' and 'share information'.

Don't hurt me and relieve my pain

It is frightening that patients need to tell us that symptom control is important. The studies from the 1980s on post-operative analgesia when a regular prescription was compared with *pro re nata* prescribing are very telling – people after major surgery were provided with very little analgesia.[3] Yet even 30 years ago, it was known that good analgesia helped to improve patient outcomes directly - out of bed sooner, out of hospital sooner, few complications, quicker recovery.[4]

In 2015, people are still telling us that physical symptom control is poor and yet we have a strong evidence base that, when used, it ensures predictable and safe symptom control for almost all people. People's psychological wellbeing is also something which patients want to tell us is not looked after as well as they hoped.

Symptom control and the ability to look after oneself for as long as possible are important patient-centred goals.[1] How much effort across cancer services is focused on optimising people's physical functioning – during and after therapy or when physical decline is apparent at the end of life? Yet, patients consistently tell us that the ability to care for themselves is highly valued throughout their life, including at its end. Cancer and palliative care services have systematically under-invested in ensuring people's physical independence is a key goal of care. Rehabilitation services have often been difficult to engage in this process, often citing funding models that do not support better maintenance of current function in the face of predictable decline. With physical symptom control and physical independence optimised, people at the end of life can focus on the important work at the end of life - spending time with people they love and care for. Optimising function and physical comfort allows for people to be themselves and focus on things that they value – dignity, humour, being treated as a whole person – the things that make each of us who we are.[1]

But there are real challenges even in eliciting people's physical symptom burden. We were taught to ask open-ended questions, and we have (mostly) learnt that lesson very well. Yet the comparison between patients' responses when asked about symptom control with open questions and the use of a systematic symptom screening tool is dramatic.[5] One tenth as many symptoms are elicited when only open questions are asked compared to using a simple screening tool. Of great concern is that 69% of symptoms whose intensity was rated as 'severe' or 'very severe' were not reported in response to open-ended questions. The proportion was even higher for not reporting distressing symptoms – 79%. Together such figures challenge our current models of care and ask that we focus urgently on patient-reported measures every time we have contact with patients.[5,6,7]

In Australia, recent work paints a picture of less-than-ideal symptom control despite contacts with health services. A consecutive cohort of patients and caregivers were asked to fill out a questionnaire on current symptom control using the Palliative Outcomes Scale.[8] One thousand eight hundred respondents from 49 palliative care services nationally responded.[9] One in four patients reported 'severe pain' despite having contact with a specialist service, well above the rates of pain control that should be seen when guided by what can be achieved in the literature.[10] Likewise, one in five people have other symptoms that patients rated at 'severe' or' 'overwhelming'.[9] A high prevalence of distress was not limited to patients. One in five caregivers identified that they were experiencing 'severe' or 'overwhelming' anxiety. Such distress at such a challenging time of life suggests that there is much more to do to improve outcomes for patients and the people who provide almost all of their care.

At a national level, Australia is in a unique position in seeking to understand and improve its performance in

delivering palliative care.[11] The national initiative – the Palliative Care Outcomes Collaborative – has now been collecting point-of-care data since 2006 and coverage now includes more than 85% of all people referred to specialist palliative care services in the country. It spans direct inpatient care, inpatient consultations, outpatient clinics and community-based care. Most importantly, these data tell us that we are able to systematically improve the care that is offered, with significant improvements in all domains in the last three years (2012-14) building on significant improvements in all domains except pain in the previous three years (2009-11).[12] Continued improvements need to be made, but this program demonstrates that this can be achieved.

Don't make me feel helpless and share information

Some of the angriest patients I have ever seen were not angry because they had cancer, nor necessarily because their cancer was progressing. They were angry because they felt cheated. Clinicians they trusted had not outlined (or outlined in a way that they could hear) that their prognosis was now limited or, in some cases, very limited. These people felt that one of their most precious commodities – time – had been stolen from them. Most importantly, they were adamant that they would have used the time they lost very differently if only they had known that their life-expectancies were so limited. Of course, this is not to say that conversations about prognosis between treating clinicians and patients had not taken place – but we can say that these patients had not heard the message in a way that could inform really important decisions.

As clinicians working with people who have advanced cancer, we have really good signposts about how each person's disease is progressing and how the systemic changes help to inform their prognosis. Rate of change in functional status has been confirmed as a factor that adds to the accuracy of an individual's prognosis.[13] Along with consideration of the person's co-morbid conditions, evidence of the systemic manifestations of uncontrolled cancer (anorexia, weight loss and fatigue) and the natural history of that particular cancer, the rate of changing functional status, form a way of generating a prognosis with high levels of accuracy if the broad measures of time (days, days to weeks, weeks, weeks to months etc.) are discussed with the patient.[14]

The other factor that can assist in helping to refine estimates of prognosis is whether the person has a special event to which they are particularly looking forward. Evidence does exist that such occasions do influence the timing of death at a population level.[15] With all of these factors, a reasonable estimate of prognosis can be discussed with a patient and their family.

Providing a prognosis is not always about breaking bad news. Some people have a very pessimistic view of their life expectancy. Equally, at times, discussing a longer-than-expected prognosis is not always met with a positive response. Sadly, providing any prognostic information to patients with advanced cancer is not something that physicians who work daily with this population necessarily do well. One study from the United States reported that 28% of clinicians would provide a conscious over-estimate, 22% would disclose no prognostic information and only 37% of clinicians would provide a frank estimate.[16] How would any of us feel drawing on the expertise of another professional – architect, engineer, account, lawyer – if their most honest estimates were only conveyed one in three times? Any of us would walk away in disgust, but this is the approach of many practising clinicians. With knowledge of a likely prognosis, where is the intellectual honesty if that knowledge is not shared in a timely way in a language that the patient can understand and assimilate?

Caregivers remain the other group for whom discussions around the future care needs of the patient and the timelines for that care are really important. The impact of caregiving is seen during the role and in the years after the role has been completed.[17] Most notably, there is an association between improved caregiver survival at 18 months and the use of community-based palliative care supports.[18] Evidence exists at a population level of an association between better met informational needs for day-to-day hands-on caregivers and accessing palliative care services.[19] Outcomes suggest real differentials at a population level between caregivers who do and do not access specialist care services, with significantly higher rates of 'moving on' with life up to three years after care was completed in those who used specialised palliative care services.[19]

Australian data confirm that family and friends who provide care at the end of life are not always willing to provide that care again were the opportunity to arise once more.[20] Predictors of lower rates of being willing to provide this care again included lower educational levels and increasing age. Given the almost absolute reliance of the health and social system on family and friends to provide care for people with advanced cancer, and the fact that most of us will be asked to do this more than once in lifetime, this finding has far reaching implications.[21,22]

Ultimately, there is an opportunity systematically to improve the quality of care provided to patients and the level of support offered to the families and friends who provide care for them. This requires a vigilant approach to building a health care system directly around the needs of patients and their families – at every clinical encounter. This is currently aspirational, but it is the expectation of the people we serve. As

patient reported measures – experience and outcomes – are more widely collected and reported, the need for every clinician to focus on each individual person will become greater. The challenge is whether we as a clinical community can deliver this. The opportunity is that patients and their families know the difference when we get it right.

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BEHAVIOURAL RESEARCH AND EVALUATION UNIT (BREU), CANCER COUNCIL SA

Fear of recurrence and psychological wellbeing in women with breast cancer: The role of causal cancer attributions and optimism

Causal attributions or beliefs that people hold with regards to the cause of their own illness are associated with affective responses to cancer and subsequent choice of coping mechanisms. This study investigated the association between causal cancer attributions, fear of cancer recurrence (FCR) and psychological wellbeing, and the possible moderating effect of optimism among women with a previous diagnosis of breast cancer. Participants completed an online self-report assessment of causal attributions for their own breast cancer, FCR, psychological wellbeing, and optimism. Simultaneous multiple regression analyses were conducted to explore the overall contribution of causal attributions to FCR and psychological wellbeing separately. Hierarchical multiple regression analyses were also utilised to examine the potential moderating influence of dispositional optimism on the relationship between causal attributions and FCR and psychological wellbeing.

Results indicated that causal attributions of environmental exposures, family history and stress, were significantly associated with higher FCR. The attribution of stress was also significantly associated with lower psychological wellbeing. Causal attributions of lifestyle risks and chance were not associated with psychological outcomes measured. Optimism did not moderate the relationship between causal attributions and FCR or wellbeing. The observed relationships between causal attributions for breast cancer with FCR and psychological wellbeing among women highlight the need to improve awareness of evidence-based risk factors for breast cancer. Furthermore, health professionals may need to provide greater psychological support to women who attribute their cancer to non-modifiable causes and are less optimistic. Women who attributed the cause of their cancer to stress may be at most of risk of experiencing greater distress. As beliefs about lifestyle were not associated with poorer psychological outcomes, cancer prevention messages that are intended to help women meet necessary lifestyle recommendations may help improve their cancer-related self-efficacy, as opposed to exacerbating negative affective responses.

Sex differences in the relationship between socio-cultural norms and sun exposure behaviours

The tripartite influence model (Thompson et al. 1999) theorises that internalised appearance ideals mediate between socio-cultural norms and sun exposure. This study examined the extent to which socio-cultural norms lead to an idealisation of a toned physique and darker skin, which, in turn predicts sun exposure.

Adult males (N = 124) and females (N = 175) completed an online questionnaire measuring socio-cultural norms endorsing a tanned appearance, internalisation of mesomorphic and tanned ideals, and sun exposure. The internalisation of mesomorphic and tanned ideals mediated between norms and sun exposure in both sexes. A greater internalisation of a tanned ideal was associated with increased sun exposure in both sexes whereas, in males, a greater internalisation of a mesomorphic ideal was associated with increased sun exposure.

Evidently, people who internalise a tanned ideal based on the perceived attitudes of others are more likely to sun expose. Skin cancer prevention should aim to target the perceived norms of others, with possible education about the often unrealistic portrayal of appearance ideals in media. Furthermore, when creating an intervention to reduce risky sun exposure in males, some males may be better targeted through an internalised mesomorphic ideal. Targeting males with a high internalisation of the mesomorphic ideal could indirectly reduce risky sun exposure by challenging the ideal through addressing the bronzed, highly muscular males in media. Such an approach could be beneficial to males who may find interventions based specifically around a tanned ideal to be more feminine or not relatable to them, as they do not deliberately sun expose to the same extent as females. Overall, the results of this study support the need to address the perceived benefits of tanned skin in order to reduce skin cancer prevalence.

CENTRE FOR BEHAVIOURAL RESEARCH IN CANCER (CBRC), VICTORIA

Advocacy message framing study

Policies that encourage healthy behaviours are often met with strong opposition from well-funded industry lobby groups. Public health advocates need to be able to compete against the anti-policy messages communicated by these industry groups, so they can secure high levels of public support for important cancer prevention policies. Two approaches that may be useful to these public health advocates, based on message effect theories in communication research, are inoculation and narrative persuasion. Inoculation involves protecting people from future anti-policy messages by forewarning them and actively refuting the arguments typically made by the industry. Narratives involve short stories focusing on how a particular character will be affected by the policy. In collaboration with Dr Jeff Niederdeppe from Cornell University in the United States, we are conducting an online randomised experiment to test whether messages that include inoculation and/or narrative components are more effective at generating support for four different health policies (increased taxes on sugary drinks and alcohol; marketing restrictions on sugary drinks and alcohol) relative to no message or a standard pro-policy advocacy message. They will also examine whether these messages, delivered as mock radio interviews, can maintain policy support over time (at one or two week follow-up), even when participants are faced with a strong anti-policy message from the soft drink or alcohol industry. It is expected that results from this study will assist public health organisations in their efforts to advocate for policy changes to tackle obesity and alcohol-related harm in Australia.

Prevalence of smoking behaviours among Australian secondary students in 2014

The Australian Secondary Students' Alcohol and Drug survey, conducted triennially since 1984, is a collaboration between Cancer Councils in Victoria, Queensland, Tasmania and South Australia, as well as Commonwealth and state and territory health departments. In 2014 around 23,000 students aged 12 to 17 years from 352 schools participated in the study. Encouragingly, there has been a decrease in Australian students' involvement in smoking. When the survey started in 1984, 31% of students had never had a cigarette and in 2014 that proportion had increased to 81%. In 2014, the proportion of students reporting they had never had a cigarette was significantly higher than estimates found in 2011 and 2008. Only 5% of all 12 to 17 year-old students had smoked in the past week (current smokers). The percentage of current smokers increased with age, from 1% of 12 year-olds to 12% of 17 year-olds. While the proportion of 12 to 17 year-old current smokers appeared to have stabilised at around 7% between 2008 and 2011, the proportion of 12 to 17 year-old current smokers in 2014 was significantly lower than in 2011 and 2008. Winfield (33%), JPS (17%) and Peter Jackson (9%) were the three most commonly smoked cigarette brands for adolescent current smokers. JPS has now overtaken Peter Jackson as the second most popular brand among adolescents. The report is available from: http://www.nationaldrugstrategy.gov.au/internet/drugstrategy/Publishing.nsf/content/school11

NEWCASTLE CANCER CONTROL COLLABORATIVE (NEW-3C), NSW

Exploring experiences of medical errors among cancer patients

A cross sectional survey of 1136 medical oncology patients and 166 haematology patients was conducted to explore patients' perceptions of whether or not an error had occurred in their care, and if so, what steps were taken by the hospital or health care team. Eligible participants were aged 18 or older, English speaking and with a confirmed diagnosis of cancer. Participants completed one survey at the time of recruitment and a second survey approximately four weeks later. Preliminary analyses indicate that 148 (13%) of medical oncology and 42 (26%) of haematology patients report experiencing an error in their care. Of those who reported an error, one third (n=46) of medical oncology and six (14%) haematology patients reported that the error was associated with severe harm. For medical oncology patients, the proportion of patients reporting an error who reported perceiving that one of the following had occurred, ranged from one third to just

under half: an explanation for the error; an apology or; being informed that steps had been taken to prevent the error from reoccurring. For haematological cancer patients, more than two-thirds reported they were told about the adverse event as soon as it happened, and were given an explanation about why the adverse event occurred. Data indicate that a substantial minority of patients perceive that an error has been made in some aspect of their care. There also appears to be significant scope to improve communication following the experience of a perceived error in care.

Extending treatment centre opening hours to accommodate working medical oncology outpatients

A cross sectional survey was conducted to examine whether the opening hours of medical oncology treatment centres impacted on outpatients' ability to continue working. Participants were recruited from six major medical oncology treatment centres across five Australian states. Two survey items explored, whether: 1) extended treatment centre opening hours (e.g. weekends, evenings) would allow the patient to continue to work during cancer treatment; and 2) the patient had stopped working or reduced work hours as a result of the opening hours of the treatment centre. A total of 716 patients returned a survey (63% response rate) and 24% (n=174) indicated the items were relevant (e.g. not retired before diagnosis). Of these, 65% were women, average age 55 years (SD=11), 27% were within six months and 35% more than two years post-diagnosis. At the time of recruitment, 60% were employed, 13% retired, 11% disability pensioners, 7% unemployed, 7% home duties or other. Of those participants who indicated the items were relevant, 44% (n=76) reported that they stopped working or reduced work hours as a result of the opening hours of the treatment centre. The majority (74%) reported that extended treatment centre opening hours would allow them to continue to work during cancer treatment. Extending medical oncology opening hours for working cancer patients could potentially allow more patients to work, relieving financial burden, and maintaining social connectedness and identity.

WESTERN AUSTRALIAN CANCER PREVENTION RESEARCH UNIT (WACPRU), CURTIN UNIVERSITY

Healthy eating for everyone

In the face of heavily advertised, widely available and inexpensive processed foods, it can be difficult for people to prioritise healthy eating. In particular, those on constrained budgets with low levels of nutrition literacy can perceive unhealthy options as the most cost-effective and satisfying alternatives for them and their families. FOODcents is a community nutrition education program that is designed to provide low-income Western Australians with the knowledge and skills they need to overcome the marketing spin they encounter throughout the supermarket, assisting them to choose nutritious, affordable foods (see www.foodcentsprogram.com.au). FOODcents is delivered by a consortium of NGOs, including Cancer Council WA, Red Cross and Foodbank. During face-to-face FOODcents courses, participants learn how to shop according to the food pyramid, read food labels and use the price-per-kilo method of product selection. Many sessions also include a cooking component to demonstrate how tasty, healthy, inexpensive foods can be quick and easy to prepare.

WACPRU undertook a two year evaluation of FOODcents to assess whether the program was still performing as intended more than 20 years after its introduction. Much has changed in the supermarket environment, making it important to identify areas of program strength and opportunities for future improvement. More than 1000 Western Australians were involved in the evaluation, which included survey, focus group and observation components. The main finding of the evaluation was that course attendance resulted in significant improvements in knowledge, confidence and behaviour. In addition, very high levels of satisfaction with the course were recorded. The qualitative data indicated these outcomes were attributable to accessible and relevant content that is delivered in a friendly, non-intimidating manner. The results were especially promising among Aboriginal participants, with larger improvements found for this group across most of the evaluation outcomes. The evaluation outcomes have been recently published in *Public Health Nutrition* and *Social Science and Medicine.*

Which cancer would make you reconsider your alcohol consumption?

Alcohol consumption increases the risk of cancer, but this inconvenient truth is largely unknown to the drinking public. In collaboration with Cancer Council WA, WACPRU undertook a major study of the kinds of cancer warning messages that could be most effective in convincing drinkers of the alcohol-cancer link and encouraging them to reduce their consumption. More than 4000 adult drinkers across the country participated in online surveys featuring a range of messages designed to alert drinkers to the relationship between alcohol and (i) cancer in general and (ii) specific types of cancer (mouth, throat,

breast and bowel). Despite preliminary focus group research indicating that very few drinkers associate cancer with alcohol and many have an aversion to believing this information, the survey results were promising. Once they were exposed to the warning statements, a majority found the information believable, convincing and personally relevant. In addition, they reported lower intentions to drink heavily after exposure to the statements. These results suggest that policy makers should consider mandating warning statements on alcohol products.

CANCER COUNCIL AUSTRALIA

Public health priorities

Cancer Council Australia continues to develop and promote evidence-based public policy recommendations spanning the cancer control spectrum. Current public health priorities include measures to increase participation in the National Bowel Cancer Screening Program and to prepare for a change in cervical screening practice in 2017.

National Bowel Cancer Screening Program

By 2020, the National Bowel Cancer Screening Program will be available to all Australians aged 50 to 74 as a biennial screening program. This year, 72 and 64 year-olds are being added to the program, joining those aged 50, 55, 60, 65, 70 and 74. From 2017, all eligible age groups will begin the transition to biennial screening.

Participation has been steadily increasing, with the rescreening rate particularly high. Cancer Council is working closely with government to maximise program participation, with particular interest in preparing for the transition to biennial screening in 2017. Cancer Council also continues work on its health professional engagement strategy to support the program's effectiveness. GP support and engagement are critical to the program's success and are the subject of ongoing policy and communications activity.

Cervical screening renewal

Cancer Council is developing new guidelines to support the anticipated change in cervical screening practice next year, using HPV testing as the principal screening tool. Cancer Council will also be developing information resources to support the change, and will be working to ensure Australian women continue to participate in the Pap test based program until the changes are introduced.

Population attributable fraction analysis

Another key focus in public health is the ongoing promotion of Cancer Council's ground-breaking *Population attributable fraction analysis of cancer incidence and causal association in Australia.* The analysis is assisting in the prioritisation of Cancer Council's public policy recommendations aimed at reducing the impact of modifiable cancer risk factors.

Healthcare reform

In the clinical and patient care environment, Cancer Council continues to evaluate the evidence and develop recommendations on the provision of more equitable and sustainable specialist cancer services and improved access to high-cost cancer drugs.

Cancer Council is also engaged in the broader healthcare reform agenda, including ongoing reviews of the primary care sector and Medicare.

Study links processed and red meats to cancer

A new study by the International Agency for Research on Cancer has found that consuming processed meats (such as bacon, salami and ham) is a cause of bowel cancer and that red meat in general is probably carcinogenic to humans.

Chair of the International Agency of Research on Cancer working group and scientific adviser to Cancer Council Australia, Professor Bernard Stewart, said the review looked at more than 1000 studies in order to provide clear, evidence-based information to health organisations and the public.

Professor Stewart said the evidence did not support complete abstinence from red meat. "We aren't recommending a ban on bacon or taking the beef off the barbecue altogether," he said. "But this latest advice should help make Australians more aware of the cancer risks associated with long-term excess red meat and processed meat consumption."

Chair of Cancer Council Australia's Nutrition and Physical Activity Committee, Kathy Chapman, said red and processed meats were associated with around one in six bowel cancers diagnosed in Australia and Cancer Council supported the National Health and Medical Research Council's recommendation that people ate no more than 65 to 100 grams of cooked red meat, three-to-four times a week.

Research sheds light on skin cancer prevention challenges

After years of sun protection campaigns Australians are well aware of the need to be SunSmart at the beach

– however new research released by Cancer Council in November has highlighted two new skin damage hotspot frontiers to be tackled - outdoor work and the home/backyard.

New data from Cancer Council's National Sun Survey released in November showed that one in two Aussie sunburns on a weekend occur during everyday activities – like gardening, chores around the house or socialising in the backyard.

The survey also showed that there has been little improvement in sun protection provision in the workplace, with around one in two workers who spend time outside missing out on sun protection.

In response, Cancer Council and the Australasian College of Dermatology joined forces during National Skin Cancer Action Week (14 – 21 November) to remind Australians that when it comes to damage from UV radiation, 'it all adds up' – whether by accident or attempts to tan, increasing the risk of skin damage and skin cancer.

Cancer Council also called on employers to help protect their workers skin by having a sun protection policy in place, providing sun protective clothing and sunscreen, and providing shade where possible, particularly during the middle of the day.

Clinical Guidelines Network

Cancer Council Australia aims to produce concise, clinically relevant and up-to-date electronic clinical practice guidelines for health professionals, accessible on its wiki platform at wiki.cancer.org.au

For more information or to be added to the mailing list for notification of guidelines open for public consultation or guidelines launches, please email guidelines@cancer.org.au.

New guidelines

Clinical practice guidelines for PSA testing and management of test-detected prostate cancer received recommendation approval by the Chief Executive Officer of the National Health and Medical Research Council on 2 November 2015 and were released in January.

Guidelines in development

Guideline	Status
Clinical management guidelines for the prevention of cervical cancer	Public consultation (http://wiki.cancer.org.au/australia/Guidelines:Cervical_cancer/Prevention)
Clinical practice guidelines for the prevention, diagnosis and management of lung cancer	Systematic reviews in progress
Clinical practice guidelines for the diagnosis and management of melanoma	Systematic reviews in progress
Clinical practice guidelines for the prevention, early detection and management of colorectal cancer	Systematic reviews in progress
Clinical practice guidelines for the management of sarcoma in AYA	Systematic reviews in progress

Cancer Council Australia guidelines

Guideline	Last updated
Clinical practice guidelines for PSA testing and management of test-detected prostate cancer	August 2015
Clinical practice guidelines for the diagnosis and management of Barrett's oesophagus and early oesophageal adenocarcinoma	September 2014
Clinical practice guidelines for the treatment of lung cancer	December 2012 (update in progress)
Management of apparent early stage endometrial cancer	March 2012
Clinical practice guidelines for surveillance colonoscopy	December 2011
Clinical practice guidelines for the management of adult onset sarcoma	February 2015
Clinical practice guidelines for the management of locally advanced and metastatic prostate cancer	April 2010

Clinical Oncology Society of Australia guidelines

Guideline	Last updated
Clinical practice guidelines for teleoncology	December 2015
Diagnosis and management of gastroenteropancreatic neuroendocrine tumours guidance	August 2012
Evidence-based practice guidelines for the nutritional management of adult patients with head and neck cancer	August 2013
Early detection of cancer in AYAs	May 2012
AYA cancer fertility preservation	September 2012
Psychosocial management of AYA cancer patients	June 2012

Other guidelines

Guideline	Last updated
Cancer pain management	August 2013

CLINICAL ONCOLOGY SOCIETY OF AUSTRALIA, COSA

COSA Annual Scientific Meeting (ASM)

The 42nd COSA ASM was held in Hobart, from 17-19 November, at the Hotel Grand Chancellor.

The ASM week began with the COSA Public Forum. Each year COSA hosts this free information forum for people who have been affected by cancer on the Sunday prior to the ASM. Seventy five members of the general public attended the forum at the Hotel Grand Chancellor. Guest speakers included: Poulam Patel on new cancer therapies; Prue Cormie on the role of exercise in the management of cancer; Jeremy Couper on using mindfulness during cancer treatment; Angelica Pearce talking about oral chemotherapy medication safety; and Christine Edwards discussing communication between GPs and oncologists. Feedback from the day was excellent. It's not often that the public have an opportunity like this to hear from leading cancer experts.

On the Monday, COSA hosted a number of pre-conference workshops. All had great feedback from delegates and most were sold out.

- 'Multi-disciplinary Supportive and Survivorship Care: models, methods and more' workshop, attended by 100 delegates, was co-hosted by five COSA Groups - Complementary and Integrative Therapies, Exercise and Cancer, Nutrition, Psycho-oncology and Survivorship. This workshop provided a unique opportunity for members to develop practical skills, debate clinical scenarios and hear in depth discussion of current research.
- Molecular biology workshop, 'Precision medicine starts here', discussed new approaches to tumour classification, with a focus on genetic reclassification. Delegates explored what this means for those diagnosing and treating cancer patients, with an overview of the principles of molecular diagnostics including next generation sequencing (the practicalities of testing – which tests for which cancers, what they mean, their limitations, FISH diagnostics, multigene tests in breast cancer), as well as how these may be used in the clinic.
- COSA Cancer Pharmacists Clinical Development Workshop, as always was sold out, and provided relevant and high-level advanced educational and development opportunities to cancer pharmacists. The program included sessions on: medication safety; the pros and cons of electronic chemo prescribing software; antibody-conjugates and other new drug delivery systems for chemotherapy; and the management of neuroendocrine tumours, including carcinoid crisis.

- COSA Clinical Trials Research Professionals Group Clinical Development Workshop focused on risk-based monitoring and GCP coordinators training. The workshop was highly interactive with case studies to support the theory covered.

The conference proper commenced on Tuesday 17 November. The COSA ASM had not been hosted in Hobart for 18 years, and with over 760 registrations was considered a very successful meeting. The opening ceremony, officiated by the Governor of Tasmania, the Honourable Professor Kate Warner AM, set the scene and reminded all delegates that the cancer patient and survivor is at the heart of our work.

The opening plenary 'What are rare cancers?' chaired by prominent COSA member Ray Lowenthal, cemented the importance of the rare cancers theme. Two of the invited international speakers, Paolo Dei Tos and Derek Raghavan, presented on classifying, diagnosing and managing rare tumours. Hugh Dawkins spoke about how other rare diseases can learn from rare cancers and David Kissane brought the psycho-oncology perspective to the fore.

The Tuesday program focused on some of the common rare cancers – melanoma, NETs and sarcoma. In addition to the various health professional experts, the patient's viewpoint was also heard. Luke Ryan – comedian, author and two-time sarcoma survivor – was honoured to share the stage with his surgeon and oncologist, and Simone Leyden from the Unicorn Foundation spoke about the patient and carer perspective of NETs.

The diverse Wednesday program included sessions on rare presentations and sub types, genetics, imaging, trial design and supportive care. One of the program highlights was a session on 'Pregnancy and cancer'. Expertly chaired by Rosemary Harrup, speakers included: Elizabeth Sullivan who spoke on her population study on gestational breast cancers; Kim Hobbs who dealt with the emotionally charged topic of termination decision making; Kelly Phillips who gave an informative update on fertility preservation; and Sally Brooks who presented on the safety of cancer therapies during pregnancy. COSA was delighted to include the personal perspectives of Rebecca O'Donnell and Pamela Cinquini, both diagnosed with, and treated for breast cancer, during their pregnancies. Both are doing very well now and continue to undergo surveillance.

All the sessions held in the plenary hall were recorded and will be made available exclusively to COSA members on a secure area of the COSA website.

2016 COSA ASM – Gold Coast

As previously reported, COSA is partnering with the ANZ Breast Cancer Trials Group to host a joint breast cancer focused conference, 15-17 November 2016 at the Gold Coast Convention and Exhibition Centre. At the time of writing this report, the Program Committee had held its first meeting and developed a first draft of the program. We plan to publish the draft program by March 2016.

Progress in regional and rural oncology

The COSA Regional and Rural Group has been very busy in the last few months with a number of their projects completed and endorsed COSA Council.

Teleoncology is becoming part of the core business of many cancer clinicians to enable them to provide care closer to home for rural and remote patients. In 2014, the Regional and Rural Group identified the need to pool together the evidence and make recommendations for use of teleoncology models. After a year of work, the draft COSA Clinical Practice Guidelines for Teleoncology were launched at the COSA ASM in Hobart. The guidelines were developed by a multidisciplinary working group led by Sabe Sabesan and assisted by COSA Project Manager Jessica Harris. The guidelines will continue to be updated on the Cancer Guidelines Wiki and can be found at: wiki.cancer.org.au/australia/COSA:Teleoncology

Development of an ANZ Teletrial Model is underway to enable the conduct of clinical trials closer to home for regional and rural patients. The model allows clinicians from larger centres (primary sites) to enrol, consent and treat patients on clinical trials at regional and rural centres (satellite sites) using teleoncology in collaboration with clinicians from satellite centres. This is a joint collaboration between COSA and the Cancer Institute NSW, with the model being endorsed by COSA Council at their August 2015 meeting. The next steps will be to seek feedback and endorsement from our affiliated organisations, especially the cooperative trials groups on the guide for implementation.

At the August 2015 meeting, Council also approved the Regional and Rural Group's proposal for COSA to endorse the Queensland Remote Chemotherapy Supervision Model (QReCS), so that this can be adopted Australia-wide by centres willing to embark on this model. Although teleoncology models have enabled the access to various chemotherapy regimens closer to home for patients from larger rural centres, patients from many small rural towns with low patient numbers continue to travel to larger centres for their chemotherapy. This is mainly due to limited availability and access to chemotherapy trained nurses in those towns. A teleoncology model incorporating telemedicine, telenursing and telepharmacy can enable selected chemotherapy delivery at rural centres. In Queensland, this model has been established under the title of 'QReCS' and as a result of this many rural and remote centres have begun administering chemotherapy. A recent study published in the *European Journal of Cancer Care* showed that this model is welcomed by nursing, medical and allied health staff in North Queensland. COSA will now advocate to the Queensland Government to approve COSA sharing the QReCS.

Working with Cancer Council Australia

In COSA's role as medical and scientific advisors to Cancer Council Australia, we often collaborate on submissions to government. Since the last report we have submitted the following joint submissions from CCA and COSA:

1. Chemotherapy Compounding Payments Scheme, Draft Operational Guidelines (August 2015), led by the COSA Cancer Pharmacists Group.
2. Primary Health Care Advisory Group consultation (September 2015), also in partnership with PC4.
3. Australian Commission on Safety & Quality in Health Care discussion paper on establishing national priorities in clinical practice guidelines (September 2015).
4. Biosimilar Awareness Implementation Framework (October 2015).
5. IP Australia's proposed change in patent examination practice (November 2015).

For more information about COSA activities please visit www.cosa.org.au

Marie Malica
Executive Officer, COSA

FACULTY OF RADIATION ONCOLOGY (RANZCR)

Funding for radiation oncology

Advocacy for sustainable, appropriate funding for radiation oncology has been a priority work area for the Faculty this year.

The review of the Medicare Benefits Schedule (MBS) is underway. The Faculty has nominated representatives for a number of relevant MBS Review Taskforce clinical committees, and submitted a response to the MBS consultation paper. The submission is available on the College website.

In parallel with the commencement of the MBS Review, an audit of the Radiation Oncology Health Program Grants Scheme was undertaken by the Australian National Audit Office and changes to the Medicare Safety Net were introduced.

The Faculty has actively participated in these activities, providing input from the profession's perspective. However, at the time of writing, the outcomes of these initiatives were not yet known – causing the Faculty much concern over the potential impact of any significant changes on affordable and timely access to radiation therapy in Australia.

Radiation Oncology Targeting Cancer Campaign

Raising the profile and presence of radiation oncology remains a major priority for the Faculty, given radiation therapy in Australia is still very much underutilised.

The Targeting Cancer campaign website was revamped and relaunched in late October 2015. The website now contains more tumour site-specific content and videos, and information targeted at GPs. We hope the website will become the most trusted source of information about radiation therapy for cancer patients and their families, as well as for GPs and other health professionals.

GPs play a crucial role at every stage in the management of a patient diagnosed with cancer. Through Targeting Cancer GP oncology education evenings, GPs have the opportunity to learn about the role of radiation therapy for their patients. Hundreds of GPs have attended these events held in several departments across Australia, and have reported significant improvements in their understanding of radiation therapy.

A number of GP-focused articles, covering advances in radiation therapy and indications for localised prostate cancer, brain metastases and skin cancers have been published in *Australian Doctor* and *Australian Family Physician*, and are available for download from the Targeting Cancer website.

Quality assurance for radiation therapy services

The Faculty is committed to quality, continuous improvement and best practice, and we published a number of key position papers in 2015, including:

- Quality Guidelines for Volume Delineation in Radiation Oncology
- Position Paper on Particle Therapy
- Position Paper on Imaging Guided Radiation Therapy (IGRT) 2015

The position papers are available from the College website.

Radiation oncology techniques and technologies: 2015 Horizon Scan

The aim of the Faculty's regular Horizon Scan is to inform cancer professionals, health professionals, health administrators, consumers and interested individuals about the techniques and technologies used for safe delivery of high quality radiation therapy. The Horizon Scan was updated in 2015 with the latest

data and evidence, the format has been simplified and the two versions for Australia and New Zealand were merged into one. The final document is available from the College website, with the next update planned for 2017.

Faculty of Radiation Oncology Annual Industry Roundtable and Innovation Summit

The Faculty's annual Industry Roundtable was held on 9 October, with over 20 attendees representing industry, consumer organisations and radiation oncology professions. This annual event provides an opportunity for industry stakeholders to meet and discuss current issues in radiation oncology.

The Faculty also convenes a regular Innovation Summit with key stakeholders, with the most recent Summit held on 6 November at Old Parliament House in Canberra. Representatives from federal and state governments, cancer peak bodies, consumer organisations and medical professions attended to discuss key issues around the profile of radiation oncology, technologies and techniques, research and innovation in our sector.

We will continue to actively engage with governments and stakeholders in the broader cancer arena to advocate for radiation oncology as an essential pillar of cancer control.

Dr Dion Forstner
Dean, Faculty of Radiation Oncology, RANZCR

MEDICAL ONCOLOGY GROUP OF AUSTRALIA INCORPORATED, MOGA

The 2016 Annual Scientific Meeting (ASM), Implementation + Innovation in Immunotherapy (Surfers Paradise Marriott Hotel, Gold Coast, 3-5 August followed by Best of ASCO® Australia, 6 August) will present a challenging and far-reaching scientific program. The program will have a strong focus on immunotherapy and genomics, as well as innovations and implementations in research and clinical practice across major cancer streams. Over the last five years, the ASM has grown exponentially in scope and quality. It is very much our intention to continue to grow the meeting as the peak national gathering for our profession by incorporating a wide range of top-line, international and national speakers, focusing on current and emergent themes that have high relevance to oncology research and practice, as well as the introduction of new meeting partners to strengthen the Association's positioning nationally, regionally and globally.

More than 120 MOGA consultants and trainee members participated in MOGA's inaugural Immuno-Oncology Forum 'Insights and Advances' in Melbourne in late October. The planning committee, led by Convenor, Professor Michael P Brown, was able to bring together a group of international and Australian experts to provide insights on advances in the rapidly developing field of immuno-oncology. The scientific program featured presentations on: the cancer immunity cycle and cancer immuno-editing; infiltrating lymphocytes and PD1-PDL1 interactions; mutational load and tumour neoepitopes; good and bad actors in the immune system and immunogenomics. The program also included presentations on immuno-oncology advances in melanoma, breast, genitourinary, lung, head and neck, and other cancers. A highlight was the forum dinner with international immuno-oncology experts, Professor Kim A. Margolin and Professor Alan J. Korman, presenting on their ground-breaking research. The Future Treatment Landscape session allowed delegates to learn about the pipeline plans of the event platinum sponsors Bristol Myers Squibb and Merck Sharp and Dome. To round out the forum, a 'Stump the Professors' panel discussion provided an opportunity for presenters and delegates to engage each other in open case-based discussion. The program brought together an impressive group of thought-leaders and MOGA hopes to present this important program in future years to ensure that Australian clinicians can stay abreast of global developments in this rapidly expanding area of oncology. International presenters: Professor Alexander Eggermont, Institut Goustave-Roussy, France; Dr Matthew D. Hellman, Memorial Sloan Kettering Cancer Center, US: Professor Alan J. Korman, Bristol-Myers Squibb Biologics Discovery, US; Professor Kim A. Margolin, Seattle Cancer Care Alliance, US; and Assistant Professor Tanguy Seiwert, The University of Chicago Medicine, US. Australian presenters: Professor Stephen Clarke; Professor Ian Davis; Professor Jonathan Cebon; Dr Thomas John; Associate Professor Sherene Loi; Dr Alexander Menzies; Professor Mark Smyth; Associate Professor Ben Solomon; and Professor David Thomas.

It is planned that the next two-day Immuno-Oncology forum will be held in 2017 and a half day Forum will be organised as part of this year's ASM.

The 2016 Australia and Asia Pacific Clinical Oncology Research Development Workshop (ACORD) is being convened by Professor Martin Stockler (http://acord.org.au/). The workshop, to be held at Magenta Shores on the New South Wales Central Coast, is a seven day residential educational program (11-17 September) in clinical trials design and development. Around 72 junior clinicians and early stage researchers from the Asia-Pacific and a world

class faculty of international leaders in cancer research, will come together for this unique oncology training program to develop clinical trials expertise and build professional networks. A record number of applications have been received across all oncology and allied health disciplines in the Asia–Pacific region for a place on this career-enhancing education program in clinical trials design and development.

In early April, the Young Oncologists Group of Australia (YOGA) will present 'Walking the Talk: Communication Skills for the Early Career Oncologist', a 1.5 day educational and professional development program designed for young Australian medical oncologists (within five years of receipt of fellowship) developed in collaboration with the Pam McLean Centre, University of Sydney. Good communication is core to our profession as medical oncologists at all levels. This innovative educational initiative will provide young oncologists in Australia with a challenging and valuable learning opportunity that will enable them to build their professional communications skills. Dr George Au-Yeung, President, YOGA, and his team of Dr Deme Karikios and Dr Felicia Roncolato are to be congratulated for this valuable new addition to MOGA's educational portfolio.

Associate Professor Rosemary A Harrup
Chair, Medical 0ncology Group of Australia

RESEARCH ON RELOCATION FOR SPECIALIST TREATMENT

Leukaemia Foundation of Queensland and Griffith University

Recent state-wide qualitative research examined the psychosocial and financial impact of relocation for specialist treatment on patients diagnosed with a haematological malignancy residing in Queensland. The study, funded by Leukaemia Foundation of Queensland and conducted by Associate Professor Pam McGrath, Griffith University, was based on in-depth interviews with a purposive sample of patients representing a diversity of haematological diagnostic groups, localities, age and gender, selected from the Leukaemia Foundation of Queensland client database.

The findings document the emotional vulnerability of patients who are experiencing the shock of diagnosis or relapse and are forced to leave the comfort of home to travel, often long distances, to a metropolitan treating centre. During treatment the distance is not only a barrier to returning home, but can prevent family from visiting the hospital.

The major financial impacts of relocation were also detailed, including out of pocket costs, the high cost of parking, for many the loss of work income from disruption caused by the disease, travel to treatment, and for some, reliance on credit cards or informal financial assistance. For those who are forced to leave work and/or do not have the buffer of savings, long-service leave, sufficient superannuation, home ownership, or assets to sell, there can be a spiral into poverty. There were special problems documented for farm and cattle property owners who, because of the inescapable responsibilities of running the farm or property, found it difficult to leave. The lack of finances to outsource daily maintenance, especially in times of drought, compounds the problem. Knowledge of, and access to formal financial assistance was explored in the study.

Leukaemia Foundation of Queensland's free accommodation was not only valued because it helped reduce the financial hardship caused by relocation, but also because of the welcoming atmosphere, the sense of security, the cleanliness and the closeness to the treating hospital. The purpose-built accommodation was appreciated for its food preparation and washing facilities the opportunity for family and friends to stay, entertainment technology available in the units, the closeness to public transport, and the availability of parking spaces.

Some of the patients living within the 50km radius of specialist treating hospitals not presently provided with government travel and accommodation assistance, were also shown to share many of the financial and physical hardships associated with extensive travel to and from hospital, especially those living on the islands at the periphery of the metropolitan area.

Importantly, the study explored the use of technology-based patient consultations as a new direction in patient care that can provide solutions to the challenges associated with relocation for regional, rural and remote patients. Although still in its infancy, initial indications show that haematology patients are keen to embrace the assistance of technology in order to reduce the distress of travel and disconnection with home life. Other trends towards the decentralisation of treatment, which include specialist outreach and capacity building for clinical care in regional centres, were greatly appreciated as means to overcome the profound difficulties associated with travelling to the metropolitan hospitals for specialist treatment.

To obtain peer-reviewed publications detailing the findings from the study please contact the investigator at: pmcgrathgu@gmailcom.

AUSTRALIA AND NEW ZEALAND

Date	Name of Meeting	Place	Secretariat
March			
3	PaCCSC 7th Annual Research Forum	Sydney, New South Wales	PaCCSC Website: http://www.caresearch.com.au Email: paccsc@flinders.edu.au Phone: +61 8 8275 1926
11-16	Australian Pain Society 36th Annual Scientific Meeting	Perth, Western Australia	DC Conferences Pty Ltd Website: http://www.dcconferences.com.au/aps2016/ Email: aps2016@dcconferences.com.au Phone: +61 2 9954 4400
14-17	TROG Annual Scientific Meeting	Brisbane, Queensland	TROG Website: http://www.trog.com.au/ASM-2016 Email: dean@cmnzl.co.nz Phone: +64 4479 4162
April			
12-14	World Indigenous Cancer Conference	Brisbane, Queensland	Menzies School of Health Research Website: http://www.menzies.edu.au Email: admin@ccm.com.au Phone: +61 7 3368 2644
13-16	8th General Assembly and International Conference of the Asian Pacific Organisation for Cancer Prevention	Brisbane, Queensland	Carillon Conference Management Pty Ltd Website: http://www.apocp8.org Email: admin@ccm.com.au Phone: + 61 7 3368 2644
13-15	ANZGOG Annual Scientific Meeting	Sydney, New South Wales	ANZGOG Website: http://www.anzgog.org.au/ Email: anzgog@yrd.com.au Phone: +61 7 3368 2422
May			
2-6	Royal Australasian College of Surgeons Annual Scientific Meeting 2016	Brisbane, Queensland	Royal Australasian College of Surgeons Website: http://asc.surgeons.org/ Email: asc.registration@surgeons.org Phone: +61 3 9276 7431
3-6	ALLG Scientific Meeting	Adelaide, South Australia	ALLG Website: http://www.allg.org.au Email: dilupa.uduwela@allg.org.au Phone: +61 3 8373 9702
6	Fertility Preservation Summit	Melbourne, Victoria	MIVF Website: www.mivf.com.au Email: TBC Phone: +61 3 9473 4570
12-14	CNSA 19th Annual Congress	Cairns, Queensland	CNSA Website: www.cnsa.org.au Email: info@cnsa.org.au Phone: +61 4 1982 2969
26-28	Asian Pacific Lymphology Conference	Darwin, Northern Territory	Australasian Lymphology Association Website: http://www.lymphoedema.org.au Email: admin@lymphoedema.org.au Phone: +61 3 9586 6030
June			
23-26	MASCC/ISOO Annual Scientific Meeting	Adelaide, South Australia	Kenes International Website: http://mascc2016.kenes.com Email: reg_mascc16@kenes.com Phone: +41 22 908 0488

23-25	ANZCHOG Annual Scientific Meeting	Cairns, Queensland	ANZCHOG Website: http://www.anr2016.org/anzchog/ Email: TBC Phone: TBC
July			
10-12	ANZUP Annual Scientific Meeting	Brisbane, Queensland	ANZUP Cancer Trials Group Limited Website: http://www.anzup.org.au Email: info@anzup.org.au Phone: +61 2 9562 5033
August			
3-5	MOGA Annual Scientific Meeting	Gold Coast, Queensland	MOGA Website: http://www.moga.org.au Email: projects2@moga.org.au Phone: +61 2 9256 9656
6-9	HGSA 40th Annual Scientific Meeting	Hobart, Tasmania	HGSA Website: http://www.hgsa.org.au Email: secretariat@hgsa.org.au Phone: +61 (0)2 9669 6602
18-20	6th Australian Lung Cancer Conference	Melbourne, Victoria	Lung Foundation Australia Website: http://www.alcc.net.au Email: info@alcc.net.au Phone: +61 (0)7 3251 3600
21-26	International Congress of Immunology	Melbourne, Victoria	Arinex Pty Ltd Website: http://ici2016.org/ Email: ici2016@arinex.com.au Phone: +61 3 9417 0888
September			
11-17	ACORD Workshop 2016	Magenta Shores, New South Wales	MOGA Website: http://acord.org.au Email: projects2@moga.org.au Phone: Phone +61 2 9256 9656
11-15	9th COGNO Annual Scientific Meeting	Sydney, New South Wales	COGNO Website: http://www.cogno.org.au Email: cogno@cogno.org.au Phone: +61 (0)2 9562 5000
14-16	AGITG 18th Annual Scientific Meeting	Melbourne, Victoria	AGITG Website: http://agitg.org.au Email: agitg@ctc.usyd.edu.au Phone: 1300 666 769
22-23	Sydney Cancer Conference	Sydney, New South Wales	Arinex Pty Ltd Website: http://sydneycancerconference.com.au/ Email: scc2016@arinex.com.au Phone: +61 2 9265 0700
October			
10-11	Australian Gastroenterology Week Satellite Symposium 2016	Adelaide, South Australia	GESA Website: http://www.agw2016.org.au/ Email: agw2016@gesa.org.au Phone: +61 3 9001 0279
11-14	ALLG Scientific Meeting	Sydney, New South Wales	ALLG Website: http://www.allg.org.au Email: dilupa.uduwela@allg.org.au Phone: +61 3 8373 9702

13-16	Royal Australian and New Zealand College of Radiologists' Annual Scientific Meeting	Gold Coast, Queensland	Waldron Smith Management Website: http://www.ranzcr2016.com Email: ranzcr@wsm.com.au Phone: +61 3 9645 6311
15-16	The Annual Sarcoma Conference	Sydney, New South Wales	Australasian Sarcoma Study Group Website: http://www.australiansarcomagroup.org Email: TBC Phone: TBC
25-27	ANZHNCS Annual Scientific Meeting and IFHNOS 2016 World Tour	Auckland, New Zealand	ANZHNCS Website: http://www.ifhnosauckland2016.org/ Email: anzhncs.asm@surgeons.org Phone: +61 3 9249 1273
November			
15-17	COSA's 43rd Annual Scientific Meeting	Gold Coast, Queensland	ANZHNCS Website: http://www.ifhnosauckland2016.org/ Email: anzhncs.asm@surgeons.org Phone: +61 3 9249 1273

INTERNATIONAL

Date	Name of Meeting	Place	Secretariat
March			
9-11	10th European Breast Cancer Conference	Amsterdam, The Netherlands	ECCO Website: http://www.ecco-org.eu Email: ipcra@libero.it Phone: +32 2 775 02 01
10-12	3rd St Gallen International Gastrointestinal Cancer Conference	St Gallen, Switzerland	St.Gallen Oncology Conferences Website: http://www.oncoconferences.ch Email: info@oncoconferences.ch Phone: +41 (0)71 245 68 05
21-23	14th International Congress on Targeted Anticancer Therapies 2016	Washington, USA	Congress by Design Website: http://tatcongress.org Email: tat@congressbydesign.com Phone: +31-88-089-8101
April			
13-16	6th European Lung Cancer Conference (ELCC)	Geneva, Switzerland	ESMO Website: http://www.esmo.org/Conferences/ELCC-2016-Lung-Cancer Email: esmo@esmo.org Phone: +41 (0)91 973 19 00
17-20	International Symposium on Oncology Pharmacy Practice	Santiago, Chile	Sea to Sky Meeting Management Inc. Website: http://www.isopp.org/isopp-symposia/isopp-2016/contact Email: symposium@isopp.org Phone: +1 604 984 6455
28-30	2nd World Congress on Controversies in Multiple Myeloma (COMy)	Paris, France	ComtecMed Website: http://www.comtecmed.com/comy/2016/ Email: info@comtecmed.com Phone: +972 3 5666166

CALENDAR OF MEETINGS

May			
6-7	1st International eCancer Symposium on Radiotherapy	Santiago, Chile	eCancer Website: http://www.ecancerchile.com Email: samantha@ecancer.org Phone: TBC
13-15	IASLC Asia Pacific Lung Cancer Conference – APLCC 2016	Chiang Mai, Thailand	VNU Exhibitions Asia Pacific Co., Ltd Website: http://aplcc2016.com Email: aplcc2016@vnuexhibitionsap.com Phone: +662 670 0900
26-28	ESTI 2016 Annual Scientific Meeting	Istanbul, Turkey	ESTI Website: http://www.myesti.org/ Email: office@myESTI.org Phone: +43(1) 5322165
June			
3-7	ASCO 52nd Annual Scientific Meeting	Chicago, USA	ASCO Website: http://am.asco.org/ Email: ascoregistration@spargoinc.com Phone: 888-788-1522
6-10	IARC 50th Anniversary Conference	Lyon, France	IARC Website: www.iarc-conference2016.com/ Email: iarc2016@inviteo.fr Phone: +33 825 595 525
12-15	17th International Symposium on Pediatric Neuro-Oncology	Liverpool, UK	Happening Conferences and Events Website: http://www.ispno2016.com Email: registration@happen.co.uk Phone: +44 (0) 151 558 0964
July			
16-20	AHNS 9th International Conference on Head and Neck Cancer	Seattle, USA	AHNS Website: http://www.ahns2016.org/ Email: registration@ahns.info Phone: 310-437-0559
September			
16-20	16th Biennial Metastasis Research Congress	Chengdu, China	Metastasis Research Society Website: http://www.2016mrsmeeting.org Email: mrs_secretariat@sina.com Phone: +86 28 86298147
29-1	15th International Workshop on Multiple Endocrine Neoplasia and Other Rare Endocrine Tumours	Utrecht, Netherlands	Congress by Design Website: http://worldmen2016.org/ Email: worldmen@congressbydesign.com Phone: TBC
October			
7-11	ESMO Congress 2016	Copenhagen, Denmark	ESMO Website: http://www.esmo.org Phone: +41 (0)91 973 19 26
13-16	9th China Conference on Oncology & 15th Cross-strait Academic Conference on Oncology	Tianjin, China	Medcon Website: www.cco2016.org Email: cco2016@126.com Phone: +86 (0)27 8767 0019

17-21	18th IPOS World Congress	Dublin, Ireland	IPOS Website: http://www.iposdublin2016.com/ Email: Iposdublin2016@abbey.ie Phone: +00 353 1 648 6278
29-31	16th Biennial Meeting of the International Gynecologic Cancer Society	Lisbon, Portugal	TWT Events and Tours Planner Website: http://igcs2016.com Email: gfrontani@twt-team.it Phone: +0039 06 44249321
31-3	UICC World Cancer Congress	Paris, France	UICC Website: http://www.worldcancercongress.org Email: congress@uicc.org Phone: +41 22 809 1834
November			
14-16	AICR Research Conference on Nutrition, Physical Activity, Obesity and Cancer	North Bethesda, USA	AICR Website: http://www.aicr.org Email: research@aicr.org Phone: +1 202 328 7744
17-19	SIOG 2016 Annual Conference	Milan, Italy	SIOG Website: http://www.siog.org Email: info@siog.org Phone: +41 22 552 3305
17-20	Society for Neuro Oncology (SNO) Annual Meeting	Arizona, USA	SNO Website: http://www.soc-neuro-onc.org Email: linda@soc-neuro-onc.org Phone: TBC
December			
4-7	17th World Conference on Lung Cancer	Vienna, Austria	ICS Website: https://www.iaslc.org Email: wclc2016@icsevents.com Phone: +1604 681 2153
6-10	40th Annual San Antonio Breast Cancer Symposium	San Antonio, USA	Website: https://www.sabcs.org/ Email: sabcs@uthscsa.edu Phone: +1 210 450 1550

CANCER COUNCIL AUSTRALIA

Cancer Council Australia is the nation's peak independent cancer control organisation.

Its members are the leading state and territory Cancer Councils, working together to undertake and fund cancer research, prevent and control cancer and provide information and support for people affected by cancer.

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CLINICAL ONCOLOGY SOCIETY OF AUSTRALIA

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

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

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INFORMATION FOR CONTRIBUTORS

Cancer Forum provides an avenue for communication between all those involved in cancer control and seeks to promote contact across disciplinary barriers. To this end, articles need to be comprehensible to as wide a section of the readership as possible. Authors should provide sufficient introductory material to place their articles in context for those outside their field of specialisation. *Cancer Forum* is primarily a review journal, with each issue addressing a particular topic in its 'Forum'. The Forum topic and appointment of Guest Editor(s) are determined by the Editorial Board, which welcomes suggestions. Proffered papers containing primary research findings will be considered for publication in *Cancer Forum* in limited circumstances. Articles will be considered by the Editorial Board and then published subject to two peer-reviews. Generally speaking, authors are encouraged to submit their primary research findings to established cancer research or clinical oncology journals. The following information is provided for contributors invited to prepare manuscripts for *Cancer Forum*.

Format

Prospective authors are encouraged to examine recent editions of *Cancer Forum* for an indication of the style and layout of Forum papers (cancerforum.org.au). All manuscripts should be submitted by email to the Forum's Guest Editor(s) and Executive Editor (rosannah.snelson@cancer.org.au) as MS Word documents.

Length: 2000-2500 words.

Font: Arial - 20pt and bold for title, 12pt and bold for headings, 12pt and italics for subheadings and 10pt for text.

Following the title, include your full name, organisation and email address. Include introductory headings and sub-headings that describe the content. Number pages in the footer.

Abstract

All manuscripts must include an abstract of approximately 200 words, providing a summary of the key findings or statements. No references or abbreviations should be included in the abstract.

Abbreviations and acronyms

Abbreviations and acronyms should only be used where the term appears more than five times within the paper. They must be explained in full in the first instance, with the abbreviation in brackets. The Editorial Board reserves the right to remove the heavy use of abbreviations and acronyms that may be confusing to the diversity of our readership.

Photographs, tables and graphs

Photographs and line drawings can be submitted via email, preferably in jpeg format. If images are not owned by the author, written permission to reproduce the images should be provided with the submission. A maximum of five illustrations and figures and three tables can be submitted with the manuscript. Inclusion of additional items is subject to approval by the Editorial Board. Unless otherwise specified by the authors or requested by the Editorial Board, all images, graphs and tables will be printed in black and white. All figures – including tables and graphs – will be reproduced to *Cancer Forum's* style. Figures containing data (e.g. a line graph) must be submitted with corresponding data so our designers can accurately represent the information. Figures and images should be labelled sequentially, numbered and cited in the text in the correct order e.g. (table 3, figure 1). Tables should only be used to present essential data. Each must be on a separate page with a title or caption and be clearly labelled.

Referencing

Reference numbers within the text should be placed after punctuation and superscripted. The maximum number of references is 75. Only papers closely related to the subject under review should be quoted and exhaustive lists should be avoided. Only one publication can be listed for each number. Citation of more than one reference to make a point is not recommended. The Editorial Board prefers a focus on more recent references (in the last 10 years). The list of references at the end of the paper should be numbered consecutively in the order in which they are first mentioned and be consistent with the National Library of Medicine's International Committee of Medical Journal Editors' Uniform Requirements for Manuscripts Submitted to Biomedical Journals. i.e. Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002 Jul 25;347(4):284-7.

The Editorial Board will make the final decision on inclusion of manuscripts and may request clarifications or additional information.

For further information or confirmation of the above, please contact:

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Cancer Council Australia

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