CONTENTS

This Issue in the Journal
3 A summary of the original articles featured in this issue

Editorials
5 Cancer services to 2025 in New Zealand—investing in research-driven quality care
Christopher Jackson, Bridget Robinson, Michael Findlay

10 Surgery for cancer: less and less for more and more patients
Jacob McCormick, Frank A Frizelle

Original Articles
12 Twelve years' experience of sentinel lymph node biopsy for melanoma at a rural New Zealand hospital
Magdalena M Sakowska, Nicole Smith, Richard J Coutts

23 Screening for colorectal cancer and prostate cancer: challenges for New Zealand
Ann K Richardson, John D Potter

31 Influence of age and site of disease on lymph node yield in colorectal cancer
Omid Ahmadi, Mark D Stringer, Michael A Black, John L McCall

41 Paediatric ovarian lesions—the experience at Starship Children’s Hospital, New Zealand
Benjamin Cribb, Naveen Vishwanath, Vipul Upadhyay

52 Thyroid cancer in Pacific women in New Zealand
Ineke Meredith, Diana Sarfati, June Atkinson, Tony Blakely

Viewpoint
63 Rectal cancer: future directions and priorities for treatment, research and policy in New Zealand
Christopher Jackson, Nieves Ehrenberg, Frank Frizelle, Diana Sarfati, Adrian Balasingam, Maria Pearse, Susan Parry, Cristin Print, Michael Findlay, Ian Bissett

Clinical Correspondence
73 Anorectal melanoma: not a haemorrhoid
Greg Turner, Sarah Abbott, Tim Eglinton, Chris Wakeman, Frank Frizelle
82 Pseudotumours and IgG4-related disease: a case report
Paul Tan, Graeme Taylor, Rennae Thiessen, Lutz Beckert

Letters
86 Missed melanomas
Peter A Foreman

88 Update from the NZ Familial GI Cancer Service
Chris Wakeman, John Keating, Susan Parry, Teresa Chalmers-Watson

91 Measurement of cigarette butt litter accumulation within city bus shelters
Jane Oliver, George Thomson, Nick Wilson

94 Does one size fit all? National elective operation hospital discharge rates may not be a good fit for all New Zealand district health boards
Mazin Ghafel Almurrani

100 Years Ago in the NZMJ

96 Hospital fees

Proceedings
97 Proceedings of the 222nd Scientific Meeting of the Otago Medical School Research Society, Wednesday 14 May 2014

Methuselah
104 Selected excerpts from Methuselah

Erratum
105 Timely cholecystectomy for acute gallstone disease: an ongoing challenge in a New Zealand provincial centre
NZMJ
In this Issue of the Journal

Twelve years' experience of sentinel lymph node biopsy for melanoma at a rural New Zealand hospital
Magdalena M Sakowska, Nicole Smith, Richard J Coutts

For those patients undergoing sentinel lymph node sampling for melanoma at Palmerston North, a high false negative-negative rate was observed in this study. The reasons for this are unknown. For those with a positive SLN sampling for melanoma, a further 20% have further nodal involvement on completion lymph node dissection, which is seen in other parts of the world.

Screening for colorectal cancer and prostate cancer: challenges for New Zealand
Ann K Richardson, John D Potter

Prostate cancer and bowel cancer are the most commonly registered cancers in New Zealanders and among the five most commonly registered cancers worldwide, but the balance of benefits and harms, and therefore appropriate screening policies, for these cancers differ. The balance of potential benefits and harms of screening is better for bowel cancer screening than for prostate cancer screening. For bowel cancer, the balance of benefits and harms is better for flexible sigmoidoscopy screening than for faecal occult blood screening. In New Zealand, bowel cancer screening should be a priority. Challenges include colonoscopy capacity, and decisions about the most appropriate screening test.

Influence of age and site of disease on lymph node yield in colorectal cancer
Omid Ahmadi, Mark D Stringer, Michael A Black, John L McCall

For adequate staging of colorectal cancer and its treatment, it is recommended by multiple international guidelines that at least 12 lymph nodes are harvested during surgery and examined. However, this study shows that lymph node retrieval and examination is influenced by a number of variables. The most important factors are patient age (with younger patients having a higher number of lymph nodes), location of tumour (tumours in the right side of the colon have higher lymph nodes) and size of the tumour (the bigger the tumour the higher the number of lymph nodes).
Paediatric ovarian lesions—the experience at Starship Children’s Hospital, New Zealand
Benjamin Cribb, Naveen Vishwanath, Vipul Upadhyay

This study provides important insight into the range of ovarian pathology encountered in a New Zealand paediatric population. Most of the ovarian lesions in this paediatric population are benign. This case series highlights the management of these lesions at Starship hospital and suggests that the prognosis of children with ovarian masses is excellent. In paediatric patients with ovarian masses it can be difficult to assess if ovarian lesions are benign or malignant. Therefore, in the acute setting the authors of this article favour ovary sparing and minimally invasive surgery where possible.

Thyroid cancer in Pacific women in New Zealand
Ineke Meredith, Diana Sarfati, June Atkinson, Tony Blakely

Pacific women have had the highest rates of thyroid cancer in New Zealand between 1981 and 2004. It is not clear which ethnic group is driving these rates but the risk is highest for women over 45 years of age.
Cancer services to 2025 in New Zealand—investing in research-driven quality care

Christopher Jackson, Bridget Robinson, Michael Findlay

Cancer is the leading cause of death in New Zealand, and is likely to be the defining health issue of the next decade. Cancer incidence increases with age and with our ‘baby boomers’ now turning 70 the total number of people with cancer is moving higher than ever.

In 2010, the Ministry of Health predicted that incident cancers would rise by 29% for males and 12% for females—by 2016. Primary prevention and well health strategies that are generally common to cardiovascular disease, diabetes and cancer are vitally important, but will not begin to impact on the age-related burden cancer will bring over the next 30 years.

As a country, we need to think clearly about how we can most effectively diagnose and treat patients with cancer over the next 3–5 decades, until we are beyond the ‘baby boomer’ effect and (hopefully) enjoying the longer term benefits of policy, education and public health interventions aimed at reducing the incidence and impact of cancer. With the looming challenges of modern cancer medicine we not only need to be responsive, we need to be innovative in our approach.

New Zealand’s health services are predominantly funded from the public purse. As a small country we have less to spend on health as a proportion of GDP and so have always had to be positioned at the cutting edge of value-for-money health care. This is sometimes politically unpalatable when access, affordability or the quality of outcomes are significantly compromised, however the overarching principle of equitable access to a ‘fair’ level of health care for all is also deeply valued by most New Zealanders.

How therefore does cancer diagnosis and treatment fit in this paradigm? Until now the issues have been largely divided into: improving existing services within current budgets; adopting new, better and often unfunded diagnostic and treatment technologies; maintaining equity of access to all members of the community; and staying within allocated funds.

In an attempt to improve current service provision within existing budgets, the government introduced a series of policies under the “Better, Sooner, More Convenient” plan that required cancer diagnostic services to be delivered more quickly, and for treatment to start within 62 days of referral for evaluation of suspicious symptoms.

Recent audits in colon and rectal cancer from different areas of New Zealand however have shown as few as 45% of colon and 22% of patients with rectal cancers received their first treatment within the idealised time frames. These targets will undoubtedly result in improvements as without the centrally-led process of measuring and
publishing targets there would be less organisational incentive to improve on the status quo.

Whilst these targets are welcomed, these strategies however need to be carefully monitored for perverse outcomes such as inappropriate reallocation of resource or worse still, gaming to meet required goals.

These time-based targets for evaluation and treatment are only the first step in a range of quality initiatives that have been launched, including the ten standards of service provision for common cancer areas. These standards are being developed with the intention of better defining what patients should expect of the diagnostic and treatment pathway and how each contributing practitioner must perform individually and collectively. These standards are an entry-level step towards reporting against performance criteria for each District Health Board (DHB), although are not as detailed in their requirements as some standards from comparable jurisdictions.

With an increased requirement for fast diagnosis and first management, coupled with an increase in the number of patients at risk of cancer and with symptoms, the burden on diagnostic services will grow.

Despite one of the highest rates of bowel cancer, New Zealand has been one of the slowest countries to implement the scientifically sound push for faecal occult blood screening. A key concern has been capacity of colonoscopy services, bringing a risk of diversion of diagnostic resource to screened false-positives and away from patients with symptoms highly suggestive of cancer.

If, however, New Zealand had been in a position to be involved in the original clinical trials of population screening then such capacity issues would have been better anticipated. The solutions would have been scalable and likely would have enabled screening and its population benefits a decade earlier.

Improvements in technology such as PET/CT, MRI, endoscopically-assisted biopsy and device placement services have reduced the number of futile and costly operations being performed, but come at their own cost – the cost-benefit equation for each are likely challenging. We now have specialised units tackling liver resection, pelvic exenteration and peritonectomy, offering high quality (but high cost) radical intervention for diseases previously considered incurable.

The processes around introduction of new devices, diagnostics and surgical interventions in cancer have until recently, been much less well regulated compared to cancer pharmaceuticals. Their implementation is driven by the relevant clinicians’ understanding of the results of clinical trials, often conducted at least in part in the New Zealand health setting by them and their colleagues.

The field of medical oncology embodies the cost-benefit crisis facing medicine as a whole, with an increasing number of active but extremely expensive cancer drugs being used to often only prolong median life expectancy by a matter of months.

As we develop a greater understanding of cancer genomics however, we will be able to increasingly identify those who will derive greatest benefit based on their molecular characteristics, rebalancing the cost-benefit equation, as well as sparing people futile treatments. Such advances are incremental and in each study there may only be a small handful of people with genomic changes who are found to benefit.
If we prospectively collect, sequence, and monitor each patient’s cancer and its treatment we have a powerful potential to discover previously hidden associations in a timely manner without the same reliance on large phase 3 trials. This however will require tissue collection and analysis infrastructure and an acceptance that such research is integral to future cancer service delivery.

This complex field of genomic medicine is moving at significant pace and will reshape the roles of cancer specialists of all types. Significantly, clinicians will need to have a greater understanding of basic science and bioinformatics principles along with their established clinical research knowledge.

Whilst PHARMAC provides an evaluation and purchasing process for new pharmaceuticals, the impending wave of expensive new cancer treatments and indications is going to challenge even the most efficient and robust of systems. Similarly their recent allocated responsibility for technology evaluation will exact the same challenges.

These challenges may undermine political resolve and lead to ad hoc approvals in response to interest-group lobbying and then disengagement by cancer care practitioners from the process, such as happened in the UK with the establishment of the Cancer Drugs fund. But more so than previously, at least in cancer, there is a need for a forward-thinking relationship with those that generate evidence (for drugs, technologies, companion diagnostics and predictors/prognostics), clinicians at the coal face who apply the evidence, funders and service providers to get the best value out of these agents for New Zealand.

We need a new approach.

Growth in services will require additional clinicians. With the increasing complexity of cancer care driven by genomic medicine, there will be a need for significant sub-specialisation and with this identification of appropriately trained generalists for the more protocol-driven aspects of care. Nurses and radiation therapists are likely to have an expanded role assessing patients, running outpatient clinics, and undertaking follow-up; hospitals are likely to divest follow-up to General Practice, and strong debates about the value of follow-up are still to be had. As practice shifts, we must be in a position to understand its impact.

Additionally, our current cancer screening programmes will need to be reviewed. As mentioned a national bowel cancer screening program is overdue however the increased uptake of HPV vaccination will undoubtedly impact on the utility of cervical cancer screening for younger vaccinated cohorts of women. Breast cancer screening continues to be contentious internationally with concerns raised about overtreatment, and the effectiveness of screening women aged 45-50.8

With expanding demand and changes in models of provision as well as regional variation in implementation of newer technologies, we need to be able to assure the public that we are still providing quality care. Our regionally led ad hoc audit of individual tumour standards will not provide this.

Without a rigorous focus on quality with the resources to measure and deliver this, the growth in demand will result in chaotic service delivery with inevitable corner
cutting, and many will be short changed by an over-burdened, inconsistent, and amblyopic system.

There are some hints that we are moving in the right direction. Work continues to develop national minimum data sets, although the detail of this work is to come. Regional data repositories for non-surgical cancer services are being developed, such as the South Island Clinical Information Systems project which should capture much of what is delivered by non-surgical cancer services. In order to realise its potential, it should be linked with surgical databases and perhaps primary health databases completing a comprehensive dataset.

We still lack the ability to capture whether treatments work, whether people relapse, and what toxicity and morbidity they suffer, aside from inference from admissions data. We have no ability to measure quality of life. We are poor at even recording the impact of comorbidity on treatment decisions and outcome. Our ability to measure the benefits or harms of our systems-based interventions is almost absent. Whilst there is collaboration with the private sector, data collection systems are still largely separate.

There are lessons we can learn from overseas. Measuring outcomes must go hand in hand with genuine efforts at training and quality improvement. The Dutch experience with rectal cancer demonstrates that a coordinated national approach to training, supervision and audit results in measurable reductions in local recurrence rates decade by decade, simply by teaching everyone best practice, and monitoring progress at a national level. This has been upscaled with the European collaborative cancer audit – the EURECCAA project – reportedly delivering QALY improvements at a cost of €750 per life year gained. Could we do better than this?

As we build our national minimum data sets and as our data collection tools are nationalised, we must have robust quality and outcome measures embedded. We have an opportunity to couple tissue collection and genomic analysis at a national level with high-grade clinical data rendering a fearsomely powerful quality and research tool of direct relevance to New Zealanders and of international interest.

We would need to invest in data collection by manual means as well as using routine collection systems to ensure data integrity, and completeness of response and toxicity data. For the meantime we would need to accept as a (not very large) leap of faith that genomics is going to be increasingly important in predicting outcome, as well as toxicity and response to treatment. We would need to invest in tissue collection and bioinformaticians. This would produce a resource that would be able to identify which patients benefit from treatment, those that do not, and relate this to both cancer biology and treatment-effect, and help us understand the linkages between the two.

The lessons from overseas are that nationalised quality efforts result in meaningful (and cost-effective) gains in outcome. With modern data systems and the complexity of genomics, we will be faced with far more information that we can easily handle, so investment in sophisticated analytic tools is paramount. We must embed rigorous measures of quality and outcome as part of routine service provision.
If we are ever to realise the benefits that genomics can deliver we must move towards building national tissue collection, storage and analysis alongside our current investment in clinical data systems.

By partnering research and treatment together with detailed, prospective evaluation of outcomes we can be assured that we are building an infrastructure that will deliver evidence based, high-quality, cost-effective and equitable care in 2025.

Competing interests: Nil.

Author information: Christopher Jackson, Consultant Medical Oncologist, Southern DHB and Dunedin School of Medicine, University of Otago, Dunedin; Bridget Robinson, Medical Oncologist and MacKenzie Chair in Cancer Medicine, University of Otago Christchurch and Oncology Service, Christchurch Hospital, Christchurch; Michael Findlay, Medical Oncologist and Director of Cancer Trials New Zealand, University of Auckland and Auckland Regional Cancer & Blood Service, Auckland

Correspondence: Professor Michael Findlay. Email: mp.findlay@auckland.ac.nz

References:


Surgery for cancer: less and less for more and more patients

Jacob McCormick, Frank A Frizelle

Surgery is often forgotten about as a cancer treatment, where the public and the media focus on oncology treatment as drugs, radiotherapy or immunotherapy. Surgery however, is the most common cancer treatment and it has the best results. For about 70% of solid cancers, surgery offers the best (often the only) chance of survival and cure. Whereas, in most such situations, chemotherapy and radiotherapy are palliative or adjunctive.

Targeted therapies are currently popular with researchers. The ability of a drug to target a specific line of cells is sexy and appealing, offering a treatment adjunct where previously one may not have existed. What should not be forgotten, however, is that surgery is the most targeted therapy. It is adjustable and focused, with the ability to expand resection to include other organs if required, or reduce the surgery in older, less fit patients whose life expectancy is limited more by comorbidities and whose quality of life is paramount. Surgery is not undertaken alone but as part of a team management—the multidisciplinary team (MDT). Indeed, many cancers will receive surgery as part of the arsenal of available therapies.

The place of surgery is always changing and in many ways we are doing less and less for more and more patients. In a few cancers, surgery is no longer required, such as the role of diagnostic laparotomy with splenectomy and lymph node biopsy for staging in lymphoma, which in the last 20 years has moved from current practice to historical interest.

Anal cancers are now usually treated with radical chemoradiotherapy, leaving resection to patients who require salvage. For most patients the chemoradiation is not about better survival, it is about a better quality of life. Patients are more likely to avoid a permanent stoma/colostomy bag (and therefore are understandably assumed to have a better quality of life)\(^1\) with radical chemoradiation. The treatment is no less difficult for the patients, and based on today’s costs, surgery would be cheaper.

Current surgery techniques have changed considerably with most becoming less invasive, however in a few specific uncommon situations, more radical. Indeed, the minimally invasive techniques such as laparoscopic colectomy are becoming more common but the data around these changes needs to be continually assessed.

The largest Australasian surgery technique trial looked at laparoscopic colectomy and clearly showed that while these techniques are equivalent in oncological terms, laparoscopic surgery is expensive with the biggest gain being a relatively small reduction in hospital stay.\(^2,3\)

With breast cancer surgery, the combined effect of smaller screen-detected cancers and large outcome studies has increased the frequency of multiple smaller surgeries (such as biopsy, wide excision, lymph node sampling) in the treatment of a single patient’s cancer.
In other cancer surgery, such as recurrent rectal cancer, more radical surgery (extended resection) is now undertaken more safely and with improved outcomes, albeit in very selected patient groups.\textsuperscript{4}

Surgical techniques have not always lent themselves towards randomised controlled trials,\textsuperscript{5} and may at times be better assessed in prospective audits (the argument by surgeons being ‘who needs to randomise parachutes’).\textsuperscript{6}

The introduction of national cancer standards by the present New Zealand Government will hopefully lead to better outcomes for patients. The emphasis on these standards has generally been about MDTs, equity of treatment and outcome, and data collection; however, the standards look at all aspects of cancer treatment and outcome including surgery. The difficulty with the standards, regardless of funding, will be their practical implementation and working out just where this data is and whether it can be collected in a meaningful and cost-effective manner.

Oncological surgery in New Zealand needs better data, not just mortality and morbidity, but also who does not get an operation and why. With this information patients can get appropriate surgery as part of their multidisciplinary management.

\textbf{Competing interests:} Nil.

\textbf{Author information:} Jacob McCormick, Surgeon; Frank Frizelle, Professor of Surgery. Department of Surgery, Christchurch Hospital, Christchurch

\textbf{Correspondence:} Professor Frank Frizelle, Department of Surgery, Christchurch Hospital, PO Box 4345, Christchurch, New Zealand. Email: FrankF@cdhb.health.nz

\textbf{References:}

Twelve years’ experience of sentinel lymph node biopsy for melanoma at a rural New Zealand hospital

Magdalena M Sakowska, Nicole Smith, Richard J Coutts

Abstract

Aim To document the false-negative sentinel lymph node biopsy (SLNB) rate for melanoma patients at a rural NZ hospital and the likelihood of further nodal involvement on completion lymph node dissection (CLND).

Methods All patients undergoing SLNB for melanoma at this centre were identified from the study period. Basic demographics along with histological data of both the primary lesion and SLNB were collated. Local and regional recurrences were recorded as was mortality.

Results Between January 2000 and July 2012, 95 patients underwent SLNB for melanoma. Ten patients (11%) underwent CLND after positive SLNB. A further two patients had a median of two additional nodes involved (range 1–3). After a median follow-up period of 65 months (range 47–112), 6 patients suffered nodal recurrence where previously a negative SLNB had been harvested, giving a false-negative rate of 38%. Recurrence occurred a median of 16 months after WLE and SLNB.

Conclusion A high false negative-negative rate was observed in this study. For those with a positive SLNB, a further 20% have further nodal involvement on CLND.

Melanoma is the fourth most common cancer in New Zealand with an estimated incidence of 10.8%. The Breslow thickness of melanoma is prognostic and the likelihood of developing lymph node (LN) metastases in patients with invasive melanoma increases with the primary tumour thickness.

Current standard of care in New Zealand is to discuss sentinel lymph node biopsy (SLNB) with patients whose primary tumour measures 1.2–3.5 mm in depth or, in patients whose tumours are thinner (0.75–1.2 mm) but have poor prognostic features such as ulceration, Clark level IV or V or a high mitotic rate.

The likelihood of a SLN containing metastatic melanoma can be calculated using a nomogram. This tool can help the patient make an informed choice whether to proceed with a SLNB.

If metastatic cells are found, completion lymph node dissection (CLND) is offered. However, the benefit of undergoing this morbid procedure is still to be fully elucidated as the majority of patients with a positive SLNB will have no further nodal involvement in the same nodal basin; therefore, gaining little clinical benefit at the expense of significant procedural morbidity.

Furthermore, CLND has been shown only to improve disease-free survival but not melanoma-specific survival when compared to those who undergo treatment with wide local excision (WLE) of the primary lesion, nodal observation and CLND only if delayed metastases occur.
Until the outcomes of the MSLT II and other similar trials are available, all patients at this rural centre with stage III disease, on the basis of a positive SLNB, are still offered CLND.4

If disease recurs in a regional lymph node basin where previously a negative SLNB has been undertaken, the SLNB is considered falsely negative. False-negative rates for SLNB in patients with melanoma have been documented in many trials, with some rates as low as 2%.11 False-negative rates of <10% are recommended by the National Tumour Standards Draft for Melanoma.12 Anecdotally, at this centre, a higher proportion of patients than would be expected have been observed to have regional recurrence following a negative SLNB.

The aim of this study was to document the local rates of falsely negative SLNB and the likelihood of further nodal involvement on CLND following a positive SLNB over a 12-year period, and to see how clinical practice measures up to the National Tumour Standards Draft for Melanoma12 as well as internationally.

**Methods**

SLNB for melanoma at this centre has been offered to patients whose primary tumour had a Breslow thickness of >1 mm, or in patients whose tumours were thinner (<1 mm) but had poor prognostic features such as ulceration, regression, Clark level IV or V or a high mitotic rate.3,4 Prior to the publications of these guidelines, SLNB was offered at the discretion of the individual treating surgeon in accordance with the then available evidence.

At this centre, SLN localisation and biopsy were carried out with a combination technique using both intradermal injection of blue dye and radioactive colloid around the primary tumour site. One or more sentinel nodes in one or more draining lymph node basins were located using pre-operative lymphoscintigraphy aided by intraoperative localisation with a hand held gamma probe, as well as, visualisation with blue dye.

All blue nodes and all nodes with radioactivity were considered as sentinel. No further nodes were harvested once the background activity of that draining lymph node basin recorded <10% of the radioactivity of the ‘hottest’ node and no further blue nodes could be located. This technique was introduced to Palmerston North Hospital in 1999.

Sentinel lymph nodes were examined according to a standard protocol:13 In brief, a sentinel node is received, described, measured and sectioned then cassetted up into a block and processed for paraffin sections. No coarse trimming occurs; superficial sections are taken followed by sections every 250 microns. The block is cut until extinction (i.e. no tissue remaining). The section with the fullest profile also has an extra section cut for MelanA (melanocyte marker) immunostaining. The remainder of the sections are H&E stained. The threshold for sentinel node positivity is any amount of metastatic tumour within the node.

To ensure all patients who underwent SLNB for melanoma were captured from this centre between January 2000 and July 2012, all patients with malignant melanoma (ICD-10 C43), who had undergone any of the following procedures, were queried from clinical coding: excision of lymph node, radical excision of lymph nodes, regional excision of lymph nodes, SLNB or biopsy of lymphatic structure of any site (neck, groin, axilla, other).

Those who had a diagnosis of other malignancy of the skin (ICD-10 C44) were also queried to ensure no patients were missed. In total, individual notes for 181 patients identified had their files reviewed as well as their histology reports. Ninety five patients were included in the final analysis (see Figure 1).

The following information, if described, was collected from histology reports of the original lesion: site of primary lesion (trunk, upper or lower limb, head and neck), Clark level, Breslow thickness in mm, presence of ulceration, regression, lymphovascular invasion (LVI), satellite lesions, rate of mitotic activity and completion of excision.

Where a punch biopsy had been initially obtained, the final histology of the entire lesion was documented rather that the punch biopsy given that this was likely to be an under-representation of the
final pathology and an underestimate of prognosis. The pathology of all wider local excisions was also noted.

Where SLNB was offered, the location, the number of lymph nodes harvested and the number that were positive for metastases were noted. If CLND was performed, the number of lymph nodes harvested and the number positive for metastases were again recorded.

Recurrences were documented including the date and location of recurrence. For patients with local recurrence, pathology specimens (original lesion and wider local excision) were recalled and reviewed again for Clark level, Breslow thickness in mm, presence of ulceration, regression, LVI, satellite lesions, and rate of mitotic activity.

Particular attention was given to the surgical excision margins of the originally excised lesions (deep and radial). Operating notes for these patients were also recalled to correlate these surgical excision margins and note was made of any difficulty that had been encountered in achieving their adequacy (for example, margins may have been limited by the location of the primary lesion). Date and cause of death were also recorded.

All values presented are medians (range) unless otherwise specified. Percentages are shown if the denominator is >50. Continuous variables were compared using Mann Whitney U test, categorical variables were compared using Chi-squared or Fisher’s exact test where appropriate.

Ethical approval was not required as this study met the definition of an audit and quality assurance-related activity as defined by the New Zealand National Ethics Advisory Committee guidelines.

Results

Patients—Between January 2000 and July 2012, 181 patients were identified for analysis. Of these 86 were excluded (Figure 1). Patient demographics and tumour characteristics are shown in Table 1.

Figure 1. Flow diagram showing reasons for exclusion from analysis

181 patients
melanoma

Metastatic disease at presentation
- 16 known primary, metastasis at presentation
- 14 unknown primary, metastasis at presentation
- 14 primary excised pre-2000
- 2 primary excised at another centre

SLNB not done (but ended up with nodal disease)
- 28 not offered/discussed
- 4 offered but declined
- 2 did not meet criteria for SLNB
- 1 palpable nodes excised (but not as SLNB)
- 5 other reasons

95 patients
included for analysis
Table 1. Patient demographics by sentinel node status

<table>
<thead>
<tr>
<th>Variables</th>
<th>SLNB negative n=85</th>
<th>SLNB positive n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at diagnosis (range)</td>
<td>60 (20–84)</td>
<td>63 (19–73)</td>
</tr>
<tr>
<td>Gender female</td>
<td>55%</td>
<td>4/10</td>
</tr>
<tr>
<td>Site of primary lesion excised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Leg</td>
<td>33</td>
<td>6</td>
</tr>
<tr>
<td>Trunk</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Head &amp; neck</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Median Breslow thickness (range) in mm</td>
<td>1.4 (0.5–18.5)</td>
<td>4 (0.8–15) *p=0.005</td>
</tr>
<tr>
<td>Clark’s level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>IV</td>
<td>64</td>
<td>6</td>
</tr>
<tr>
<td>V</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Not recorded/other</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Other pathological prognosticators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Regression</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Satellite lesions</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Excepting median Breslow thickness, there were no significant differences between those who had a negative SLNB compared to those who had a positive SLNB.

Primary lesion—Initial excision of the primary lesion was incomplete for 22 patients; 12 of these patients had undergone an initial diagnostic punch biopsy. All patients underwent subsequent WLE. Where initial excision had been histologically complete, subsequent WLE showed that three patients still had residual melanoma. One patient had undergone laser excision of their primary lesion (located on the thigh) and although the primary lesion was completely excised, it was fragmented and therefore an estimate of Breslow thickness or Clark level could not be documented.

Other histological features absent from pathological reports were as follows; Clark’s level: four patients (one had extensive regression and one was an extremely exophytic lesion thus the Clark’s level was deemed to be less meaningful and not reported); ulceration: 12 patients; mitotic activity: 89 patients; regression: 39 patients; LVI: 9 patients; and satellite lesions: 13 patients. Anatomical distribution of the primary lesion is summarised in Table 2.

Table 2. Anatomical distribution of primary lesion by gender, p=0.001

<table>
<thead>
<tr>
<th>Location of primary lesion</th>
<th>Female (n=51)</th>
<th>Male (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trunk</td>
<td>8 (16%)</td>
<td>20</td>
</tr>
<tr>
<td>Lower limb</td>
<td>27 (53%)</td>
<td>10</td>
</tr>
<tr>
<td>Upper limb</td>
<td>15 (29%)</td>
<td>13</td>
</tr>
<tr>
<td>Head and neck</td>
<td>1 (2%)</td>
<td>1</td>
</tr>
</tbody>
</table>
**Sentinel node biopsy**—Blue dye and colloid were used for all SLNB localisations. The proportion of patients who had a SLN successfully mapped was 100%, in other words, there were no patients in which a sentinel node could not be located using this technique.

Sentinel node biopsy was carried out at a median of 42 days (range 0–1143) after the initial histological diagnosis. Three patients underwent a SNB after their WLE had been carried out (at 28, 31 and 98 days post); one had their SLNB done 31 days prior to WLE, the remainder underwent concurrent WLE with SLNB.

The median number of nodes harvested with SLNB were two (range 1–9) with 10/95 (11%) patients having a median of one (range 1–2) node showing evidence of metastatic spread on histology. Only one patient had more than one LN basin sampled (both axillae, primary lesion of trunk).

All patients with positive SLNB then underwent subsequent CLND, and a further two out of ten had additional metastatic nodal involvement (figure 2). The median number of nodes harvested in CLND were 15 (range 1–31) with a median of 2 (range 1–3) further nodes involved.

**Recurrence**—Recurrence is summarised in Figure 2. In patients with a negative SLNB, there were 11 loco-regional recurrences. All six (7.5%) patients with regional LN recurrence were in the same lymph node basin where a previously negative sentinel node had been harvested. The one patient who had both right and left axillary LN sampling had recurrence in the right axilla. Their re-presentation was a median of 16 months after WLE + SLNB (range 7–39 months) with a median follow-up period of 65 months (range 21–112).

**Figure 2. Summary of sentinel lymph node biopsy outcomes**

```
95 SLNB
   ↓
85/95 (89%) 10/95 (11%)
       ↓     ↓
10/85 (12%) CLND
          ↓
       2/10
               ↓
6/85 (7.5%) Further nodal involvement
          ↓
5/85 (6%) nodal recurrence
          ↓
local/in transit recurrence
```
There was one death from metastatic melanoma in this group twelve months post WLE and SLNB. Local or in transit recurrence was suffered by 5/85 (6%) patients after a median of seven months (range 2–24 months) after WLE. Median follow up for these patients was 34 months (range 10-104).

There were two deaths in this group due to metastatic melanoma at 12 months and 32 months after WLE + SLNB. Retrospective review of the histology for patients who had local and in transit recurrence showed that these patients had adequate radial and deep surgical margins (data not shown).

Adjuvant treatment—No patients had adjuvant radiotherapy if they underwent a CLND after a positive SLNB. In those who had a negative SLNB and subsequent recurrence, radiotherapy was offered to one patient, and isolated limb infusion was performed for another.

Discussion

In 2009, melanoma was the fourth most common cancer registered in New Zealand and the sixth most common cause of cancer deaths. For melanoma, sentinel lymph node biopsy provides important prognostic information in addition to the histological features of the primary lesion.

The role of SLNB in management of melanoma in New Zealand is still investigative rather than therapeutic and relies on the patient being able to make an informed choice. The new National Tumour Standards Draft for Melanoma sets the uptake of SLNB at greater than 90% so it is reassuring that that at this centre only four patients declined a SLNB of the 181 that were offered it.

A full discussion of SLNB should include the likelihood and ramifications of a falsely negative SLNB. This includes both the failure to harvest the node with synchronous metastatic cells or, disease recurring in a regional lymph node basin where previously a negative SLNB has been undertaken.

A SLN is the first lymph node that receives draining lymph from the location of the primary lesion and therefore potential metastatic melanoma cells. At surgery, definitions of SLN include the ‘hottest node’ or any ‘hot’ node, a node with radioactive count or a given count ratio to the background count or any blue nodes. None of these definitions are absolute and tumour cells may still be left behind. There are several reasons why this may occur.

Tumour cells themselves may obstruct lymphatic flow directing the markers to a neighbouring node or a node may be too full of tumour cells to uptake any tracers (although these nodes are often palpable or visible in preoperative ultrasound scan).

Technical issues of node depth will yield different counts despite two nodes having similar amounts of tracer in them. Blue dye may even pass entirely through a sentinel node without being retained and onto successive nodes by the time surgical exploration takes place.

More than one node may be the ‘sentinel’ LN, either within the same lymph node basin or at different locations. This is particularly the case for truncal melanoma due to the overlapping lymphatic drainage areas.
For this reason lymphsyntigraphy is used to help locate these and all ‘sentinel’ nodes need to be harvested as early tumour metastases may be missed. Studies validating SLNB for melanoma have shown that the likelihood of leaving a positive node behind using this technique is 5%. The second scenario giving rise to a falsely negative SLNB is when disease occurs where previously a negative SLNB has been obtained. The preferred method of calculating this false-negative rate is obtained by dividing the number of false-negative patients by the total number of node-positive patients, in other words, the sum of false-negatives and true-positives: for this study this equates to 6/(6+10)=37.5%. However, commonly published values are obtained by calculating the number of false-negative patients/number of patients with a negative SLN (6/79=7.6%) or the number of false-negative patients/total number of patients with a negative SLN added to the number of false-negative patients (6/[79+6]=7.5%).

The latter two calculations give a lower value and are better described as failure rates. When calculated appropriately, published values of false-negatives for SLNB in patients with melanoma vary between 0–35%. The National Tumour Standards for Melanoma sets the false negative rate at less than 10%.

The reason for the high false-negative rate observed in this study is unclear. Others have discussed the technical contribution for a high false-negative rate with failures arising from the nuclear medicine technician, the surgeon and the pathologist, plus the learning curve associated with the technique for all three specialists. Valsecchi et al showed that the proportion of successfully mapped sentinel nodes increased over time reflecting the learning curve associated with the technique. The Draft National Tumour Standards suggest that an accepted learning curve for SLNB for melanoma is 30 cases. It is likely that at this hospital, staffed by six general surgeons, this may not have occurred prior to the audit period given the low numbers of SLNB performed for melanoma at this centre. The prior experiences and training of these surgeons is not quantifiable from this study, however, all surgeons at this centre perform SLNB for breast cancer and the skill set required for SLNB for breast cancer translates to treating melanoma patients.

Stewart et al showed that if fewer than three sentinel nodes are harvested, the risk of recurrence is higher than for those who have more than two nodes examined. Here the median number of nodes harvested were two which is not dissimilar to recent publications, all of which have shown lower false negative rates than that seen here. Additionally, the overall nodal basin status has been shown to be established with either the first or second SLNB. If the third or subsequent SLNB are positive, metastases are also found in the first or second node examined. In their meta-analysis of 71 similar studies, Valsecchi et al showed that the false-negative rate was inversely related to the proportion of patients which have a successfully mapped sentinel node. In this study, there were no patients in which a sentinel node could not be located thus the ‘proportion’ is 100%.

Conversely, the yield of positive nodes (in other words the number of positive nodes detected from all SLNB), is 11%. Elsewhere the yield for positive nodes ranges between 8–33%, with a median of 19%. When graphed, the false-negative rate looks to be inversely proportional to the yield of positive nodes (Figure 3). The yield
of positive SLNs may act as a performance marker and act as a predictor of a high false-negative rate.

**Figure 3. Relationship between the percentage yield of positive nodes and the false-negative rate**

![Figure 3](image_url)

**Note:** Figure generated using data from Valsecchi at al 2011 and subsequent publications⁵⁻²⁷

- denotes this study
- The trend line is indicated

Very few patients had more than one lymph node basin sampled in this study when compared to other trials.⁶⁻²⁷,²⁹,³² Even in trials of a similar population size, the number of patients where more than one lymph node basin was sampled was 3.5–6%.²⁷,³²

The reason for this is uncertain; lesions that are located on the trunk are more likely to drain to multiple lymph node basins and similar anatomical distributions of primary lesions are seen in this trial to elsewhere.⁶⁻²⁷,²⁹,³²⁻³⁶ Notably, no patients suffered recurrence in a lymph node basin not originally sampled.
Unsurprisingly those with a positive SLNB had thicker primary lesions (by Breslow thickness) than those who didn’t: median Breslow thickness 1.4 versus 4 (p=0.005). This has also been noted by others.\textsuperscript{2,26,29,33}

From the tumour-positive SLNB group, those who underwent CLND (10 patients), a further two patients had a median of one additional pathological node. Although the numbers are small, this figure is comparable.\textsuperscript{25–28}

Five of 85 patients with a negative sentinel lymph node suffered local recurrence defined as either at the site of the previous primary excision or in transit. This is a similar rate of recurrence seen in other studies.\textsuperscript{7,27} On review, all surgical histological margins were adequate and recurrence was due to poorly prognostic primary tumours.

Obvious criticisms of this study are the small sample size, heterogeneity of the group and the fact that this audit spans many years and may include changes in surgical practice and guidelines. One contributor to the heterogeneity of this population is the Breslow thickness range of 0.5–18.5 mm.

By comparison, patients included in the MSLT I trail had melanomas 1.2–3.5 mm thick—undoubtedly a much more pathologically homogenous group. Thus comparison of the results seen here to those from such large trails may be less meaningful than simply ensuring that national monitoring criteria for treatment of patients with melanoma are met\textsuperscript{12} at smaller centres such as this one.

**Conclusions**

A high false negative-negative rate was observed in this study. For those with a positive SLNB, a further 20\% have further nodal involvement on CLND.

**Competing interests:** Nil.

**Author information:** Magdalena M Sakowska, General Surgical Registrar, Department of General and Vascular Surgery, Palmerston North Hospital, Mid-Central District Health Board, Palmerston North; Nicole Smith, Pathologist, Medlab Central, Palmerston North Hospital, Mid-Central District Health Board, Palmerston North; Richard J Coutts, General Surgeon, Palmerston North Hospital, Mid-Central District Health Board, Palmerston North

**Correspondence:** Magda Sakowska, Department of General and Vascular Surgery, Palmerston North Hospital, Mid-Central District Health Board, PO Box 2056, Palmerston North 4440, New Zealand. Email: magda.sakowska@xtra.co.nz

**References:**

4. NCCN Clinical Practice Guidelines in Oncology. At \url{http://www.nccn.org/professionals/physician_gls/f_guidelines.asp}
5. Melanoma Nomogram: Sentinel Node Metastasis – Memorial Sloan-Kettering Cancer Center. At \url{http://nomograms.mskcc.org/Melanoma/PositiveSentinelNode.aspx}


13. American Joint Committee on Cancer. Available at http://www.cancerstaging.org/


Screening for colorectal cancer and prostate cancer: challenges for New Zealand

Ann K Richardson, John D Potter

Abstract

Aim Prostate cancer and colorectal cancer are the most commonly registered cancers in New Zealanders and among the five most commonly registered cancers worldwide, but the balance of benefits and harms, and therefore appropriate screening policies, for these cancers differ. We aimed to compare the potential benefits and harms of screening for prostate cancer and colorectal cancer to aid prioritisation in New Zealand.

Method Relevant reports from randomised controlled trials and systematic reviews of prostate cancer and colorectal cancer screening were reviewed to obtain estimates of the potential benefits and harms of screening for prostate cancer and colorectal cancer.

Results The balance of potential benefits and harms of screening is better for colorectal cancer screening than for prostate cancer screening. For colorectal cancer, the balance of benefits and harms is better for flexible sigmoidoscopy screening than for faecal occult blood screening.

Conclusion In New Zealand, colorectal cancer screening should be a priority. Challenges include colonoscopy capacity, and decisions about the most appropriate screening modality.

Prostate cancer and colorectal cancer are the most commonly registered cancers in New Zealand. Colorectal cancer is the second most common cause of cancer deaths in New Zealand (after lung cancer), followed by breast cancer and then prostate cancer.

Worldwide, prostate and colorectal cancers are among the top five most commonly registered cancers, with colorectal cancer also among the top five causes of cancer death (Figure 1).

Both prostate cancer and colorectal cancer are important causes of illness and death worldwide, but screening policies differ greatly for these cancers, in part due to differences in the available evidence about the benefits and harms of screening for these cancers. More than seventeen countries have national screening programmes for colorectal cancer and six countries have pilot screening programmes.

In contrast, no country in the world has a national prostate screening programme, and professional bodies such as the American Urological Association, the European Association of Urology, and the American College of Physicians—and organisations such as the UK Cancer Screening Committee and the US Preventive Services Task Force—do not currently recommend national screening programmes for prostate cancer because of concerns that the benefits of prostate cancer screening do not
outweigh the harms, with some actively recommending against prostate cancer screening overall or in specific age-groups.6,7

Figure 1. Worldwide cancer incidence and mortality (age-standardised to the World population) per 100,000

Although the benefits of screening tend to be well recognised, the potential harms of screening are not always acknowledged (Table 1).

Table 1. Potential benefits and harms of screening

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra years of life for some people diagnosed by screening</td>
<td>Earlier diagnosis but no extra years of life for some people diagnosed by screening</td>
</tr>
<tr>
<td>Less invasive treatment for some people with early cancer</td>
<td>Over-treatment for some people with early cancer, which may lead to complications, including mortality, and thus lost years of life</td>
</tr>
<tr>
<td>Reassurance for those with negative screen results</td>
<td>False reassurance for those with false negative results</td>
</tr>
<tr>
<td></td>
<td>Anxiety and sometimes damage for people with false positive screen results</td>
</tr>
</tbody>
</table>
Even in a screening programme for a common cancer such as colorectal or prostate cancer, the vast majority of people will not have the disease and so cannot benefit from screening; only a very small proportion can benefit from extra years of life. Thus, if the harms associated with screening cannot be kept to a minimum, across the population, these can readily outweigh benefits.

Further complicating the balance of benefits and harms is that, in any screening round, the benefits and harms do not accrue to the same individuals.

In Table 1, the people harmed as a result of false-positive and false-negative tests do not have these harms offset by gaining extra years of life (unless in a subsequent screening round). In this respect screening is very different from the treatment of sick individuals, who are often prepared to accept harms or unwanted effects of treatment in order to recover or live longer.

Even if a screening programme is beneficial, the harms of screening will still exist, because no screening test is perfect; hence the aphorism “All screening programmes cause harm; some do good as well”. If the benefits of screening do not outweigh the harms the net outcome of a screening programme will be to cause harm as well as to waste health resources.

Estimates of the benefits and harms of prostate-specific antigen (PSA)-based prostate cancer screening have been made by the US Preventive Services Taskforce. These estimates were calculated based on screening 1000 men for 10 years, and were presented in a table of benefits and harms. Similar estimates of the potential benefits and harms of colorectal cancer screening have not been published, although screening programmes and pilot programmes for colorectal cancer have been established.

**Method**

We reviewed relevant reports of randomised controlled trials and systematic reviews of colorectal cancer screening to obtain estimates of the potential benefits and harms of screening for colorectal cancer, in order to compare and contrast them with estimates of the potential benefits and harms of prostate cancer screening, and to compare modalities of colorectal cancer screening.

The “number needed to screen” quantifies the number of individuals that it is necessary to screen in order to achieve the desired outcome; for instance the number of people needed to screen for a disease in order to prevent one death from that disease.

To estimate the benefit of colorectal cancer screening with a faecal occult blood test (FOBT), we used the number needed to screen reported for two population-based randomised controlled trials of colorectal cancer screening (747 people screened over 7.8 years to prevent one colorectal cancer death in the Nottingham trial, and 470 over 10 years for the Funen trial) supplemented with an estimate for the Nottingham trial which took into account participation and selection effects (688 people screened over 7.8 years to prevent one death).

Together, these gave the estimate of extra years of life for 1–2 people as a result of screening 1000 people for 10 years (an earlier estimate of the number needed to screen of 1173, reported in a systematic review, was the number invited to be screened—rather than the number actually screened - to prevent 1 death from colorectal cancer).

The estimate of the benefit of colorectal cancer screening with flexible sigmoidoscopy came from the number needed to screen in a multicentre randomised controlled trial in the United Kingdom (489 people screened over 11 years to prevent 1 colorectal cancer death, and 191 people screened over 11 years to prevent 1 colorectal cancer diagnosis).

The estimates for diagnosis came from the Nottingham and Funen trials and the multicentre flexible sigmoidoscopy trial.
In the Nottingham trial, 60% of the intervention group were screened at least once (44,838 of the 75,253 randomised to screening) and 236 people were diagnosed with colorectal cancer as a result of screening (5.3 per 1000 over 7.8 years).

In the Funen trial, 20,672 (67% of those randomised) were screened at least once (over 90% accepted repeated screenings) and 120 people were diagnosed with colorectal cancer by screening (5.8 people per 1000 over 10 years).

In the multicentre flexible sigmoidoscopy trial 40,621 people (71% of those in the intervention group) were screened, and 140 people were diagnosed with colorectal cancer as a result of screening (3.4 per 1000 over 11 years).14–16

Information about the harms of colonoscopy and treatment was obtained from published data on the risks of screening from the Nottingham trial and published data on complications of flexible sigmoidoscopy screening.11,17

### Results

Estimates of the benefits and harms of colorectal cancer screening based on screening 1000 people for 10 years, compared with the benefits and harms of prostate cancer screening based on screening 1000 men for 10 years, are shown in Table 2.

For each screening programme, the benefits are expressed as the number of people per 1000 screened over a 10-year period who gain extra years of life as a result of screening (and, for flexible sigmoidoscopy, the number of people who avoid a diagnosis of colorectal cancer as a result of screening).

Similarly, for each screening programme, the harms are expressed as the number of people per 1000 screened over a 10-year period who are harmed as a result of being screened.

### Table 2. Benefits and harms of colorectal cancer screening compared with prostate cancer screening, for 1000 people screened over 10 years

<table>
<thead>
<tr>
<th>Benefits (per 1000 screened over 10 years)</th>
<th>Harms (per 1000 screened over 10 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate cancer screening</strong></td>
<td></td>
</tr>
<tr>
<td>Extra years of life for 0–1 man</td>
<td>At least 1 false positive result in 100–120 men</td>
</tr>
<tr>
<td></td>
<td>Biopsy complications in 30 men</td>
</tr>
<tr>
<td></td>
<td>Prostate cancer diagnosed in 110 men</td>
</tr>
<tr>
<td></td>
<td>Complications of treatment in 20–30 men</td>
</tr>
<tr>
<td></td>
<td>Mortality in &lt;1 man</td>
</tr>
<tr>
<td><strong>Colorectal cancer screening</strong></td>
<td></td>
</tr>
<tr>
<td><strong>FOBT (faecal occult blood test)</strong></td>
<td></td>
</tr>
<tr>
<td>Extra years of life for 1–2 people</td>
<td>False positive result in 35 people</td>
</tr>
<tr>
<td></td>
<td>Colonoscopy complications in 5 people</td>
</tr>
<tr>
<td></td>
<td>Colorectal cancer diagnosed in 5–6 people</td>
</tr>
<tr>
<td></td>
<td>Complications of treatment in &lt;1 person</td>
</tr>
<tr>
<td><strong>Flexible sigmoidoscopy (flex. sig.)</strong></td>
<td></td>
</tr>
<tr>
<td>Extra years of life for 2 people</td>
<td>False positive result in 1 person</td>
</tr>
<tr>
<td>PLUS</td>
<td>Flex. sig. complications in &lt;1 person</td>
</tr>
<tr>
<td>Colorectal cancer prevented in 5 people</td>
<td>Colonoscopy complications in 6 people</td>
</tr>
<tr>
<td></td>
<td>Colorectal cancer diagnosed in 3–4 people</td>
</tr>
<tr>
<td></td>
<td>High-risk adenomas diagnosed in 43 people</td>
</tr>
<tr>
<td></td>
<td>Complications of treatment in &lt;1 person</td>
</tr>
</tbody>
</table>
The comparison of the benefits and harms of colorectal cancer screening and prostate cancer screening in Table 2 shows why many countries have implemented national colorectal cancer screening programmes but none has a national prostate cancer screening programme.

First, the likelihood of benefit is lower for prostate screening (extra years of life for 0–1 man for every 1000 screened)\(^4,10,18\) than for colorectal cancer screening using FOBT (extra years of life for 1–2 people for every 1000 screened).\(^11,12\)

The benefits are even higher for colorectal cancer screening using flexible sigmoidoscopy, as these include prevention of colorectal cancer diagnoses as well as prevention of colorectal cancer deaths.\(^14\)

Over a longer period than the 10 years used in Table 2, it would be expected that even more colorectal cancer deaths would be prevented because flexible sigmoidoscopy detects pre-cancers (high-risk adenomas).

Secondly, the potential harms of screening are greater for prostate cancer screening than for colorectal cancer screening. The risk of a false positive test is higher for prostate cancer screening (100–120 men per 1000 screened)\(^4,10\) than for colorectal cancer screening with FOBT (35 per 1000 screened)\(^15,16\) or colorectal cancer screening with flexible sigmoidoscopy\(^14,17\) and the likelihood of complications resulting from investigations is higher.

Early death from prostate biopsy, while rare, is also a potential serious harm of prostate cancer screening due to the number of biopsies undertaken.\(^19\)

Complications of treatment are also more likely as a result of prostate cancer screening (20–30 men per 1000 screened)\(^4,10\) than colorectal cancer screening (<1 person per 1000 screened).\(^11\) This is partly due to the higher risk of overdiagnosis in prostate cancer screening. Colorectal cancer screening does not appear to carry the same risk of overdiagnosis.\(^20\)

Complications of treatment for prostate cancer include: chronic erectile dysfunction, chronic urinary incontinence, deep vein thrombosis, and pulmonary thromboembolism as temporary states are common after urological surgery, and chronic faecal incontinence is also an important side effect of radiotherapy for about 5% of those treated.\(^4,10\)

It has been estimated that up to half the cancers detected in a prostate-cancer screening programme would not have caused problems during a man’s lifetime\(^21\) but if treated, carry risks of these complications.

Although “watchful waiting” or “active surveillance” (defined as “an alternative initial management strategy that allows for definitive treatment for men with disease progression in addition to avoiding treatment-related morbidity in those without progressive disease”)\(^22\) is advocated for men with low-risk disease,\(^10,22\) 90% of US men and 70% of European men with low-risk prostate cancer undergo immediate surgical or radiotherapy treatment.\(^10,22\)
Discussion

Prostate cancer and colorectal cancer are the most commonly registered cancers in New Zealanders, but the balance of potential benefits and harms of screening is better for colorectal cancer screening than for prostate cancer screening.

The estimates of benefits and harms of colorectal cancer screening with FOBT in Table 2 are based on the Nottingham and Funen randomised controlled trials, which used guaiac FOBT (FOBTg) screening.

There have been no randomised controlled trials of colorectal cancer screening using immunochemical FOBT (which is being used in the pilot colorectal cancer screening programme in Waitemata). \(^{23}\)

Screening with immunochemical FOBT (FOBTi) is likely to result in more colorectal cancer diagnoses per 1000 screened, but at the expense of more people with false-positive results, because FOBTi has higher sensitivity and slightly lower specificity than FOBTg. \(^{24}\)

The participants in the UK trial of flexible sigmoidoscopy screening were a group who had indicated on a previous questionnaire that they would accept an invitation for screening \(^{14}\) and this may affect the generalisability of the results, but other randomised controlled trials using different recruitment methods have also shown that flexible sigmoidoscopy screening reduces colorectal cancer mortality. \(^{17,25,26}\)

Estimates of benefits and harms based on flexible sigmoidoscopy screening for colorectal cancer make the balance of benefits and harms even better for bowel screening. In part, this is because flexible sigmoidoscopy can detect pre-cancer as well as existing colorectal cancer, and thus has the potential to reduce colorectal cancer incidence as well as mortality.

This reinforces the conclusion that the balance of benefits and harms is better for bowel screening than for prostate screening.

Challenges for New Zealand in prioritising colorectal cancer screening include colonoscopy capacity and the need to determine the most appropriate screening modality.

Colonoscopy capacity in New Zealand is inadequate to meet the needs of a national colorectal cancer screening programme; it is estimated that such a programme using FOBTi would require 18,000 colonoscopies in the first year, rising to 27,000 by year 7. \(^{27}\)

From March 2013, the NHS colorectal cancer screening programme in the UK is piloting flexible sigmoidoscopy screening in six regions for people aged 55 years, \(^{28,29}\) and it has been recommended that New Zealand consider introducing flexible sigmoidoscopy screening rather than FOBT screening. \(^{30,31}\)

Decisions about colorectal cancer screening in New Zealand should be made urgently; over 3,000 New Zealanders are diagnosed with colorectal cancer every year and screening has been shown to reduce colorectal cancer mortality.
Competing interests: Nil.

Author information: Ann K Richardson, Professor, Wayne Francis Cancer Epidemiology Research Group, University of Canterbury, Christchurch, New Zealand; John D Potter, Senior Advisor, Fred Hutchinson Cancer Research Center, Seattle, USA—and Adjunct Professor, Wayne Francis Cancer Epidemiology Research Group, University of Canterbury, Christchurch, New Zealand

Correspondence: Ann Richardson, Wayne Francis Cancer Epidemiology Research Group, School of Health Sciences, University of Canterbury, Private Bag 4800, Christchurch 8140, New Zealand. Email: ann.richardson@canterbury.ac.nz

References:

5. UK National Screening Committee. The UK NSC policy on prostate cancer screening/PSA testing screening men over the age of 50. UK National Screening Committee 2010 http://www.screening.nhs.uk/prostatecancer (accessed on 8 April 2014)


Influence of age and site of disease on lymph node yield in colorectal cancer

Omid Ahmadi, Mark D Stringer, Michael A Black, John L McCall

Abstract

Aim Colorectal cancer (CRC) is the second-leading cause of cancer death in New Zealand. Lymph node yield (LNY) is an independent prognostic factor in CRC and 12 or more lymph nodes in the resected specimen is the current recommended standard, regardless of age or site of disease. The aim of this study was to examine the effect of age and site of the disease on LNY.

Method Patients undergoing elective surgery for CRC at Dunedin Hospital between 1995 and 2012, who enrolled in studies involving prospective data and tissue collection, were included in the current study. The relationship between LNY and demographic and pathological variables including age, sex, tumour location and stage were investigated.

Results 824 patients were included (mean age 70.5 years, 51% female). The mean (SD) LNY was 17.9 (10.1). There was a weak but significant negative correlation between age and LNY (r=-0.08; p=0.024) that was more evident in patients with right-sided tumours (r=0.18; p=0.001). Right-sided tumours also had a higher LNY (mean 20.5) than left colon (mean 16.8) and rectal cancer (mean 14.6) (p<0.001). Overall the mean LNY reduced by 1 for every 7 years advancement in age.

Conclusion LNY is higher in right-sided colon cancer and reduces with age. Further research should consider whether the recommended standard for LNY in the specimen should take account of age and tumour location.

Worldwide more than 1 million people are diagnosed with colorectal cancer (CRC) annually and nearly half of them will die of the disease. CRC is the fourth-leading cause of cancer death internationally. New Zealand has one of the highest incidences of CRC in the world where it is the second leading cause of cancer death.

One of the most important prognostic factors in CRC is involvement of regional lymph nodes (LNs), and this guides the decision for use of adjuvant therapy. En bloc surgical resection of the tumour which includes draining mesenteric (colon cancer) and mesorectal (rectal cancer) LNs is the gold standard of surgical treatment. International guidelines recommend examination of at least 10 to 14 LNs for adequate staging of CRC. Staging is done according to the Tumour Node Metastasis (TNM) system as described by the American Joint Committee on Cancer (AJCC).

Recently, lymph node yield (LNY), regardless of metastatic involvement, has been shown to have prognostic significance with a higher LNY being associated with improved survival. The prognostic value of LNY is thought to be independent of
other factors including the surgeon, the pathologist, patient age and sex, location of the tumour and T stage.

Surgeon factors include experience and adequacy of the en bloc resection and the proportion of patients with a LNY ≥ 12 has increased over time.

Pathologist factors include the use of fat clearing or LN revealing solutions and the experience of the pathologist in finding LNs. Since the association between LNY and survival seems to be independent of these factors it has been postulated that LNY may be a surrogate marker of host immunity against the cancer.

We have previously shown that the morphology and number of LNs is affected by senescence, which in turn may have implications for disease outcome.

In the current study we have examined the relationship between LNY and factors including age, site and stage of disease in a large prospectively gathered cohort of New Zealand patients with CRC.

**Method**

**Participants**—Patients included in the current study were those undergoing elective surgery for CRC at Dunedin Hospital between July 1995 and June 2012 who were recruited into a series of studies investigating the biology and outcome of CRC. All patients gave consent for data and tissue collection and long-term follow-up and ethical approval was granted by the Lower South Regional Ethics Committee.

Demographic and pathological data for each participant were retrieved including: sex, age at operation, location of tumour, AJCC (7th edition) staging, LNY, and use of neoadjuvant radiotherapy (RT) for rectal cancer patients.

Right-sided colon cancer was defined as a tumour proximal to the splenic flexure, left-sided colon cancer as a tumour between the splenic flexure and rectosigmoid junction and rectal cancer as a tumour distal to the rectosigmoid junction.

The following patients were excluded: duplicate entries, patients with a previous operation for CRC, non-adenocarcinoma CRC or non-CRC primary cancers, patients with incomplete data in whom there was no means of verifying essential information or those who received operations not suitable for lymph node count.

**Statistical analysis**—The relationship between LNY and demographic and pathological variables was investigated. Pearson’s and Spearman’s correlation were used to summarise the relationship between LNY and patient age, date of operation and number of positive LNs.

The relationship between patient age and number of positive LNs was also examined. To examine the relationship between LNY and sex or neoadjuvant RT, independent Student’s t-tests and Mann-Whitney U tests were used.

Finally, one-way ANOVA and Scheffé post-hoc tests and Kruskal-Wallis tests were used to examine the relationship between LNY and tumour site or AJCC stage (including tumour and node stage).

A linear regression model was constructed with LNY as the dependent variable and other demographic or pathological variables that either showed a statistically significant relationship with LNY or those that had a theoretical basis for a relationship with LNY as independent factors.

Statistical analysis was carried out using IBM SPSS Statistics software, version 20.0 (IBM Corporation, New York). Statistical significance was defined as a p-value of less than 0.05.

**Results**

Of the 856 patients recruited within the study period 32 patients were excluded for previous operation for CRC (n=13), incomplete data entry (n=8), duplicate entries (n=3), biopsy or local excision only (n=4), no evidence of primary CRC (n=2) or stage 0 CRC (n=2), leaving 824 patients for analysis.
The patient characteristics are shown in Table 1. Mean LNY was 17.9±10.1 (Figure 1) and mean age was 70.5±10.8 years.

Table 1. Demographic and clinicopathological features of 824 patients with CRC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>70.5 (10.8)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>401 (48.7%)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>423 (51.3%)</td>
</tr>
<tr>
<td><strong>Lymph node yield</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>17.9 (10.1)</td>
</tr>
<tr>
<td><strong>Year of diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>1995–1999 (%)</td>
<td>292 (35.4%)</td>
</tr>
<tr>
<td>2000–2004 (%)</td>
<td>284 (34.5%)</td>
</tr>
<tr>
<td>2005–2012 (%)</td>
<td>248 (30.1%)</td>
</tr>
<tr>
<td><strong>AJCC stage</strong></td>
<td></td>
</tr>
<tr>
<td>I (%)</td>
<td>158 (19.2%)</td>
</tr>
<tr>
<td>II (%)</td>
<td>301 (36.5%)</td>
</tr>
<tr>
<td>III (%)</td>
<td>289 (35.1%)</td>
</tr>
<tr>
<td>IV (%)</td>
<td>76 (9.2%)</td>
</tr>
<tr>
<td><strong>Primary tumour site</strong></td>
<td></td>
</tr>
<tr>
<td>Right-sided (%)</td>
<td>352 (42.7%)</td>
</tr>
<tr>
<td>Left-sided (%)</td>
<td>266 (32.3%)</td>
</tr>
<tr>
<td>Rectal (%)</td>
<td>206 (25.0%)</td>
</tr>
<tr>
<td><strong>Neoadjuvant radiotherapy (rectal cancer only)</strong></td>
<td></td>
</tr>
<tr>
<td>No (%)</td>
<td>125 (60.7%)</td>
</tr>
<tr>
<td>Yes (%)</td>
<td>81 (39.3%)</td>
</tr>
</tbody>
</table>

SD: Standard deviation
AJCC: American Joint Committee on Cancer – 7th edition
There was a weak but significant negative correlation between age at operation and LNY (Figure 2: $r=-0.08$; $95\%$ CI $-0.01 - -0.14$, $p=0.024$). The number of positive LN also decreased with advancing age ($r_s=-0.113$; $p=0.001$). Mean LNY was also evaluated according to other demographic and pathological variables and these results are summarised in Table 2.

Patients with AJCC stage I CRC had a significantly lower mean LNY than stage II (15.8 versus 18.9; $p=0.016$) but the difference in mean LNY between stages II, III and IV was not significant. Analysis of the relationship between LNY and T (tumour) stage revealed greater mean LNY with increasing T-stage. In addition, right-sided tumours had a significantly higher mean LNY than left-sided colonic and rectal tumours.

No relationship was found between mean LNY and sex, the date of operation, or N (node) stage or LNY and number of positive LNs. Furthermore, in rectal cancer patients, neoadjuvant RT ($n=81$) was not associated with a change in LNY.

The relationship between LNY and age in subgroups determined by the site of the primary tumour was also investigated. A statistically significant negative correlation was found between LNY and age in right-sided tumours ($r=0.18$; $95\%$ confidence interval: $-0.30$ to $-0.08$; $p=0.001$).
Figure 2. Scatter plot illustrating a decline in LNY with advancing patient age

Table 2. Univariate analysis of the association between demographic or clinicopathological variables and mean LNY

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean LNY</th>
<th>Mean difference</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17.4</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Female</td>
<td>18.3</td>
<td>-0.9</td>
<td>-2.27 to 0.50</td>
<td>0.212</td>
</tr>
<tr>
<td><strong>AJCC stage‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>15.8</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>II</td>
<td>18.9</td>
<td>-3.2</td>
<td>-5.97 to -0.42</td>
<td>0.016</td>
</tr>
<tr>
<td>III</td>
<td>18.1</td>
<td>-2.3</td>
<td>-5.14 to 0.45</td>
<td>0.137</td>
</tr>
<tr>
<td>IV</td>
<td>16.9</td>
<td>-1.2</td>
<td>-5.10 to 2.78</td>
<td>0.878</td>
</tr>
<tr>
<td><strong>T-stage§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>13.3</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>II</td>
<td>16.3</td>
<td>-2.9</td>
<td>-7.82 to 2.00</td>
<td>0.431</td>
</tr>
<tr>
<td>III</td>
<td>18.4</td>
<td>-5.1</td>
<td>-9.56 to -0.54</td>
<td>0.020</td>
</tr>
<tr>
<td>IV</td>
<td>19.5</td>
<td>-6.2</td>
<td>-11.46 to -0.90</td>
<td>0.014</td>
</tr>
<tr>
<td>**N-stage</td>
<td></td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17.9</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>1 (1-3 positive LNs)</td>
<td>17.7</td>
<td>0.1</td>
<td>-1.90 to 2.18</td>
<td>0.985</td>
</tr>
<tr>
<td>2 (&gt;3 positive LNs)</td>
<td>17.9</td>
<td>0</td>
<td>-2.42 to 2.41</td>
<td>1</td>
</tr>
<tr>
<td><strong>Primary tumour site§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right-sided</td>
<td>20.5</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Left-sided</td>
<td>16.8</td>
<td>3.8</td>
<td>1.81 to 5.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rectal</td>
<td>14.6</td>
<td>5.9</td>
<td>3.81 to 8.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>**Neoadjuvent radiotherapy (rectal cancer only)</td>
<td></td>
<td></td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14.7</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>14.5</td>
<td>0.2</td>
<td>-1.69 to 2.02</td>
<td>0.861</td>
</tr>
</tbody>
</table>

†: Mann-Whitney U test p-value: 0.108; †: Kruskal Wallis test p-value: 0.001; §: Kruskal Wallis test p-value: <0.001; ||: Kruskal Wallis test p-value: 0.861; ¶: Mann-Whitney U test p-value: 0.864.
A weaker negative correlation between LNY and age was evident for rectal cancers \((r=0.14, p=0.051)\) but there was no significant correlation in left-sided colon tumours \((r=0.07, p=0.243)\) (Table 3).

**Table 3. Site-specific correlation between LNY and age using parametric and non-parametric measures**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Right</th>
<th>Left</th>
<th>Rectal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson correlation</td>
<td>-0.18</td>
<td>-0.072</td>
<td>-0.136</td>
</tr>
<tr>
<td>P-value</td>
<td>0.001</td>
<td>0.243</td>
<td>0.051</td>
</tr>
<tr>
<td>Spearman’s correlation</td>
<td>-0.152</td>
<td>-0.079</td>
<td>-0.162</td>
</tr>
<tr>
<td>P-value</td>
<td>0.004</td>
<td>0.198</td>
<td>0.020</td>
</tr>
<tr>
<td>n</td>
<td>352</td>
<td>266</td>
<td>206</td>
</tr>
</tbody>
</table>

Finally, a linear regression model was constructed using LNY as the dependent factor and age, sex, tumour site, T stage, AJCC stage and date of operation as independent factors the results of which are summarised in Table 4.

This model indicates that for approximately every 7 years advancement in age at the time of operation mean LNY decreased by one LN (correlation coefficient \(\beta\): -0.14; \(p<0.001\)). The other variables that had a significant independent relationship with mean LNY were T-stage and site of the primary tumour.

**Table 4. Summary of multiple linear regression model for demographic and clinicopathological variables associated with LNY**

<table>
<thead>
<tr>
<th>Variable</th>
<th>(\beta)</th>
<th>p-value</th>
<th>lower bound</th>
<th>upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>&lt;0.001</td>
<td>21.432</td>
<td>34.159</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.136</td>
<td>&lt;0.001</td>
<td>-0.192</td>
<td>-0.063</td>
</tr>
<tr>
<td>Tumour site</td>
<td>-0.244</td>
<td>&lt;0.001</td>
<td>-3.940</td>
<td>-2.207</td>
</tr>
<tr>
<td>T-stage</td>
<td>0.133</td>
<td>0.002</td>
<td>0.753</td>
<td>3.203</td>
</tr>
<tr>
<td>AJCC stage</td>
<td>-0.043</td>
<td>0.303</td>
<td>-1.418</td>
<td>0.442</td>
</tr>
<tr>
<td>Sex</td>
<td>0.015</td>
<td>0.669</td>
<td>-1.066</td>
<td>1.663</td>
</tr>
<tr>
<td>Months since operation</td>
<td>-0.012</td>
<td>0.726</td>
<td>-0.014</td>
<td>0.010</td>
</tr>
</tbody>
</table>

\(\beta\): standardised beta coefficient

**Discussion**

This study shows that LNY does indeed decline with advancing age at a rate of one LN for every 7 years’ advancement in age. This was independent of sex, AJCC stage, T-stage and the date of operation. We have also shown, for the first time, that this association is strongest for right-sided colon cancers.

A decline in LNY with advancing age in colon cancer has also been reported by others. Wang et al (2010) investigated this relationship in 141,404 patients with AJCC stage I-IV colon cancer in the Surveillance, Epidemiology, and End Results (SEER)
They found that patients younger than 40 years of age were more likely to have at least 12 LNs in the resected specimen (67.6% under 40y vs 45.7% over 40y; p<0.0001). The mean LNY under 40 years was 19.2 compared to 12.7 in older individuals. Subsequently, Steele et al (2011) suggested that LNY is inversely correlated with age and supported this hypothesis from an analysis of 101,767 patients with AJCC stage I-III colon cancer from the SEER database. The decline in LNY with age was independent of sex and AJCC stage. A decline in the proportion of patients with LNY≥12 with advancing age was also reported by Patel et al (2012) who analysed 32,819 patients with AJCC stage I-IV colon cancer. Some authors have attributed this decline in LNY with advancing age to younger patients receiving a “more extensive” resection. However, we and others observed that the decline is continuous and begins at a relatively young age. Age-related decrease in lymph node numbers has also been reported in a variety of lymph node basins, even in the absence of disease. Age may therefore be a non-modifiable factor contributing to LNY in CRC.

The present study also found right-sided colonic cancers had a significantly higher LNY than left-sided cancers and rectal cancers, an observation consistent with other studies. Interestingly, we also found that right-sided colon cancers showed a greater decline in LNY with advancing age than left-sided colon or rectal cancers (Table 3). One theory to explain the higher LNY in right colon cancers is that right hemicolectomy specimens are generally longer and therefore contain a larger LN containing mesocolon but the evidence for this hypothesis is conflicting.

Another hypothesis is that right-sided colon cancers are biologically distinct from left-sided colonic and rectal cancers. Sporadic CRC with microsatellite instability or CpG island methylator phenotype are disproportionately more common in the right colon and tend to occur at an older age. Furthermore these right-sided tumours show a greater lymphocyte infiltration. It is hypothesised that this lymphocyte infiltration reflects the host’s anti-tumour immune response, which may explain the improved prognosis associated with microsatellite instability and why right-sided colonic cancers have a higher LNY. It is still not known whether the right colon mesentery contains more LNs than the left colon mesentery in normal subjects and we are currently investigating this.

The present study also found that LNY increased with increasing T stage, which is consistent with several other studies. It is possible that the locoregional immune response to the tumour is stimulated in proportion to the depth of tumour invasion. Reactive changes in the draining LNs leads to enlargement and this in turn makes them easier to detect.

In the present study younger patients were more likely to have node positive colon cancer. This phenomenon has also been described by others despite a paradoxically worse cancer specific survival with advancing age even after matching patients for stage and treatment modalities. This decline in the number of positive LNs may
reflect impaired lymph node filtering or intranodal shunting as consequent on LN senescence.\(^22\)

In other large studies, patients undergoing surgery in a more recent era, females, and patients receiving no neoadjuvant RT (in rectal cancer) were found to have a higher LNY.\(^4,16,20,35-37\) Our study found no significant difference in LNY based on date of operation, sex, or neoadjuvant RT.

There are several limitations to this study. Patient recruitment and data acquisition were carried out prospectively but the current study was not based on an *a priori* hypotheses. The findings may not be generalisable because the cases were not consecutive and acute cases were not represented. However, one study did not find a difference in LNY between acute and elective cases.\(^38\)

It would have been of interest to examine the relationship between long or short course neoadjuvant RT and LNY in rectal cancer, however this information was not recorded. Although our sample size was large, it was not as large as other studies that utilised national or regional databases.

In conclusion, we found that LNY is not constant and is influenced by both age and site of disease. LNY is higher in the right than left colon and declines with advancing age, more so in right-sided CRC.

**Competing interests:** Nil.

**Author information:** Omid Ahmadi, PhD student, Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin; Mark D Stringer, Paediatric Surgeon, Christchurch Hospital and Honorary Professor, Department of Anatomy, Otago School of Medical Sciences, University of Otago, Dunedin; Michael Black, Senior Lecturer, Department of Biochemistry, Otago School of Medical Sciences, University of Otago, Dunedin; John L McCall, General Surgeon and McKenzie Chair in Clinical Sciences, Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, Dunedin

**Acknowledgements:** Dr Ahmadi was supported by a Cancer Society of New Zealand Clinical Research Training Fellowship and a Dunedin School of Medicine Clinical Research Scholarship.

**Correspondence:** Professor John McCall, Department of Surgical Sciences, Dunedin School of Medicine, University of Otago, P.O. Box 913, Dunedin, New Zealand. Fax: +64 (0)3 4747622; email: john.mccall@otago.ac.nz

**References:**

Paediatric ovarian lesions—the experience at Starship Children’s Hospital, New Zealand

Benjamin Cribb, Naveen Vishwanath, Vipul Upadhyay

Abstract

Aim To review the experience of paediatric ovarian masses at Starship Children’s Hospital (Auckland, New Zealand). Primarily to assess the range of pathology, the presenting features, and the surgical management of these lesions.

Methods A search of the hospital surgical pathology database was carried out to identify patients less than 16 years in whom ovarian tissue was submitted for pathological analysis during the 12 year period from January 2000 to December 2011. A retrospective review of the medical records was carried out.

Results 244 ovarian masses in 219 patients were identified. 99 of these were neoplastic with 19 (7.8%) being malignant and an additional four (1.6%) borderline malignant lesions (borderline epithelial tumours). Mature cystic teratoma was the commonest neoplastic lesion (55.6%).

Patients who presented with acute abdominal pain were more commonly found to have non-neoplastic lesions than neoplastic lesions (71.5% vs 46.9%, p<0.0001), and those that presented with a palpable mass were more commonly found to have a neoplastic lesion (24.0% vs 3.3%, p<0.0001).

Laparoscopic surgery was performed in 41.6% of all patients. Ovary conserving surgery was performed in 56.6% of all patients, though only 32.3% of patients with neoplastic lesions.

Conclusion This study provides important insight into the range of ovarian pathology encountered in a New Zealand paediatric population. Most of the ovarian lesions in paediatric age groups are benign. Ovarian sparing surgery is recommended. In cases of ovarian torsion, malignancy in this series and in the literature is less than 2%. This review highlights that paediatric surgical units have vast experience to deal with ovarian pathology in paediatric age groups.

Background

Ovarian masses in children, whether solid or cystic, include a heterogenous group of lesions. Malignant neoplasms are rare in paediatric age groups with an estimated occurrence of 2.6 cases per 100,000 girls per year, and comprise approximately 1% of paediatric cancers.1,2

The presentation of ovarian masses can be variable and non-specific. Ovarian masses are commonly encountered during acute laparoscopy for suspected appendicitis or ovarian torsion. Best practice regarding the management of ovarian masses remains uncertain.
Due to the low rate of ovarian malignancy and the generally good outcomes observed in these patients, many surgeons are opting for minimally invasive and ovarian sparing operative management.

The primary aim of this study was to assess the range of ovarian lesions encountered at Starship Children’s Hospital and in particular to assess the range and volume of malignant lesions. We also set out to assess the presenting features and the management of these patients.

The authors reviewed the experience with paediatric ovarian masses at Starship Children’s Hospital over a 12-year period to provide a New Zealand perspective on this challenging clinical entity.

Materials and methods

Regional ethics approval was not required for this study, therefore following hospital board approval a search of the surgical pathology database at Starship Children’s Hospital was undertaken to identify all patients under 16 years, who had tissue submitted for pathologic analysis from the ovary or adnexa between 1 January 2000 and 31 December 2011. An extensive retrospective review of the patient’s clinical records was performed.

Age at surgery, clinical presentation, imaging and investigations, operation type, operative findings and follow up of all patients were recorded and analysed.

Results

A total of 247 patients were identified from the surgical pathology database. 28 patients were excluded from this review as they had undergone ovarian biopsies alone, or had no ovarian mass or cyst.

219 patients with 244 ovarian lesions underwent surgical procedures for ovarian masses in the period January 2000 to December 2011.

The age of patients ranged from 2 days to 15 years with a mean of 11 years at the time of surgery. In the patients over ten years, a higher proportion of the lesions were benign compared with those seen in the younger age groups (91.1% vs 87.1%).

As shown in Figure 1 the older age groups (10 to 15 years) accounted for the majority of the patients with ovarian masses in this series.

Figure 1. Age at surgery for different pathologic groups
**Histopathology results**—Neoplastic lesions accounted for 40.6% of the lesions (n=99). Mature cystic teratoma was the commonest neoplasm identified comprising 55.6% of the neoplastic lesions (n=55). Tumours of epithelial origin comprised 23.2% of the neoplastic group (n=23).

Nineteen patients had malignant tumours (8.7% of patients), two of which had metastatic disease at presentation.

Paratubal cysts accounted for the majority of the non-neoplastic lesions (42.1%), followed by corpus luteal cysts (21.4%) and simple follicular cysts (16.6%).

**Table 1. Pathologic findings from 244 ovarian lesions in 219 patients**

<table>
<thead>
<tr>
<th>Neoplastic lesions (n=99)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surface epithelial – stromal tumours (n – 23)</strong></td>
<td></td>
</tr>
<tr>
<td>Serous cystadenoma</td>
<td>10 (4.1%)</td>
</tr>
<tr>
<td>Mucinous cystadenoma</td>
<td>9 (3.7%)</td>
</tr>
<tr>
<td>Borderline malignant tumour*</td>
<td>4 (1.6%)</td>
</tr>
<tr>
<td><strong>Sex cord stromal tumours</strong></td>
<td></td>
</tr>
<tr>
<td>Juvenile granulosa cell tumour</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>Sertoli-leydig cell tumour</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Ovarian fibroma</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td><strong>Germ cell tumours (n – 68)</strong></td>
<td></td>
</tr>
<tr>
<td>Dysgerminoma</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Yolk sac tumour</td>
<td>5 (2.0%)</td>
</tr>
<tr>
<td>Mixed germ cell tumour</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>Immature teratoma</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>Mature cystic teratoma</td>
<td>55 (22.5%)</td>
</tr>
<tr>
<td><strong>Miscellaneous tumours</strong></td>
<td></td>
</tr>
<tr>
<td>Small cell carcinoma, hypercalcaemic</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>B cell lymphoma</td>
<td>1 (0.4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-neoplastic lesions (n=145)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Paratubal cyst</td>
<td>61 (25%)</td>
</tr>
<tr>
<td>Corpus luteal cyst</td>
<td>31 (12.7%)</td>
</tr>
<tr>
<td>Follicular cyst</td>
<td>24 (9.8%)</td>
</tr>
<tr>
<td>Haemorrhagic pseudocyst</td>
<td>12 (4.9%)</td>
</tr>
<tr>
<td>Para-ovarian cyst</td>
<td>9 (3.7%)</td>
</tr>
<tr>
<td>Broad ligament cyst</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>Tubo-ovarian cyst</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>Fimbrial cyst</td>
<td>2 (0.8%)</td>
</tr>
</tbody>
</table>

*Borderline epithelial tumours.

**Contralateral lesions**—Bilateral lesions were found in 24 patients (11.0%). Five patients had neoplastic lesions on contralateral ovaries. Two patients with serous cystadenomas later developed lesions in the contralateral ovary on follow-up. Only one patient in this series underwent bilateral oophorectomy for which histology showed a borderline serous tumour.
One mature cystic teratoma was excised from the contralateral ovary during oopherectomy for a mixed germ cell tumour. The other patient with a contralateral mature cystic teratoma was excised during an open salpingo-oophorectomy for a large paratubal cyst with associated ovarian torsion.

**Table 2. Pathologic findings from 28 contralateral ovarian lesions in 24 patients**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borderline serous tumour</td>
<td>1 (3.6%)</td>
</tr>
<tr>
<td>Serous cystadenoma</td>
<td>1 (3.6%)</td>
</tr>
<tr>
<td>Mucinous cystadenoma</td>
<td>1 (3.6%)</td>
</tr>
<tr>
<td>Mature cystic teratoma</td>
<td>2 (7.1%)</td>
</tr>
<tr>
<td>Paratubal cyst</td>
<td>10 (35.7%)</td>
</tr>
<tr>
<td>Follicular cyst</td>
<td>9 (32.1%)</td>
</tr>
<tr>
<td>Corpus luteal cysts</td>
<td>3 (10.7%)</td>
</tr>
<tr>
<td>Fimbrial cyst</td>
<td>1 (3.6%)</td>
</tr>
</tbody>
</table>

**Presenting features**—The presentation of patients with ovarian masses were variable. However, there were significant differences in the clinical presentation between the neoplastic and non-neoplastic groups of patients (see table 3 below).

The most common presenting symptom was acute abdominal pain (n=133, 60.7%). Presentation with acute abdominal pain was more common in patients with non-neoplastic lesions and this difference was statistically significant.

Presentation with an abdominal or pelvic mass was more common in patients with neoplastic lesions and this difference was also statistically significant.

Four children with non-neoplastic cysts presented with a palpable abdominal mass (two paratubal cysts, one corpus luteal cyst and one tubo-ovarian cyst).

All the infants in this study had non-neoplastic ovarian cysts which were diagnosed by antenatal ultrasound.

Patients presenting with endocrine disturbances were rare in this series. Four patients (1.8%) in our series presented with endocrine disturbances. Two patients with granulosa cell tumours and one with a serous cystadenoma presented with precocious puberty. One patient with a Sertoli-Leydig cell tumour presented with features of masculinisation.

One of the patients with an ovarian fibroma had clinical features of Gorlin-Goltz syndrome and is on surveillance for basal cell carcinoma.

Two patients (one 14 years old and the other 15 years old) had mature cystic teratomas that were found incidentally for investigation of encephalitis caused by anti-NMDA receptor antibodies.
Table 3. Clinical presentation of patients with ovarian masses

<table>
<thead>
<tr>
<th>Presenting symptoms / signs</th>
<th>Non-neoplastic lesions</th>
<th>Neoplastic lesions</th>
<th>Fisher’s exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(123)</td>
<td>(total 96)</td>
<td></td>
</tr>
<tr>
<td>Acute abdominal pain</td>
<td>88 (71.5%)</td>
<td>45 (46.9%)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Abdominal or pelvic mass</td>
<td>4 (3.3%)</td>
<td>23 (24.0%)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Chronic abdominal pain</td>
<td>9 (7.3%)</td>
<td>15 (15.6%)</td>
<td>p=0.08</td>
</tr>
<tr>
<td>Incidental finding</td>
<td>7 (5.7%)</td>
<td>9 (9.4%)</td>
<td>p=0.43</td>
</tr>
<tr>
<td>Antenatal ultrasound finding</td>
<td>18 (14.6%)</td>
<td>0</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Isosexual precocious puberty</td>
<td>0</td>
<td>3 (3.1%)</td>
<td>p=0.09</td>
</tr>
<tr>
<td>Masculinisation / deepening of voice</td>
<td>0</td>
<td>1 (1.0%)</td>
<td>p=0.45</td>
</tr>
</tbody>
</table>

Surgical management—91 patients underwent laparoscopic surgery (41.6%). The majority of patients with non-neoplastic lesions underwent laparoscopic surgery (60.2%, n=74). However, only 17.7% of those with neoplastic masses had laparoscopic surgery (see Table.4).

One borderline epithelial tumour and one malignant lesion were resected with laparoscopic surgery. This malignant lesion was an immature teratoma with associated ovarian torsion.

Table 4. Surgical procedures in 219 patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Non-neoplastic total=123</th>
<th>Neoplastic total=96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopic cystectomy</td>
<td>45 (36.6%)</td>
<td>12 (12.5%)</td>
</tr>
<tr>
<td>Laparoscopic salpingo-oopherectomy</td>
<td>12 (9.8%)</td>
<td>4 (4.2%)</td>
</tr>
<tr>
<td>Open cystectomy</td>
<td>31 (25.2%)</td>
<td>18 (17.8%)</td>
</tr>
<tr>
<td>Open Salpingo-oopherectomy</td>
<td>18 (14.6%)</td>
<td>61 (63.5%)</td>
</tr>
<tr>
<td>Laparoscopic de-roofing of cyst</td>
<td>17 (13.8%)</td>
<td>1 (1.0%)</td>
</tr>
</tbody>
</table>

Operative findings—83 (62.4%) patients had ovarian torsion as the cause of their acute abdominal pain. Non-neoplastic cysts were associated with 72.3% of these torted ovaries (n=60), while mature cystic teratomas were associated with 25.3% of these torted ovaries (n=21).

There was one case of an ovarian fibroma in a 13 year old that presented with abdominal pain secondary to ovarian torsion. One malignant tumour presented with ovarian torsion. This was a grade 1 immature teratoma in a 13 year old who presented with abdominal pain.

29.6% (8/27) of patients who underwent surgery for a palpable mass were found to have ovarian torsion.

66.7% (n=12) of neonates with ovarian cysts had torted ovaries.

Discussion

The experience with ovarian masses at Starship Children’s Hospital over a 12 year period from 1 January 2000 to 31 December 2011 comprises of 244 ovarian lesions in 219 patients.
A review of the literature revealed this case series to represent the largest published series of ovarian lesions in a paediatric population from a single hospital institution.

Table 5 below shows three other large published series’ of paediatric ovarian lesions from single institutions and table.6 demonstrates the pathological range of ovarian lesions reported in these studies.

To date there have not been any studies looking into the range of ovarian pathology seen in a New Zealand paediatric population. Therefore this series provides information which is important in the decision making process on the management of these lesions in a New Zealand context.

It has been reported in the literature that up to 64% of ovarian masses in children and adolescents are neoplastic. The majority of these tumours arise from germ cells. Other reports suggest that tumours arising from the surface epithelium comprise less than 20% of ovarian tumours in children and these are extremely rare before puberty.

In this series, neoplastic lesions accounted for only 40.6% of ovarian masses out of which 23.2% were of epithelial origin. The rate of malignancy in this series was 8.7% of patients (19.2% of the neoplastic lesions), which is similar to the published data from other institutions.

It is important to note that this study does not include patients with ovarian cystic lesions that did not have tissue submitted for pathological analysis, such as those patients who may have had laparoscopic de-roofing or drainage of a clinically benign cyst. Therefore, the true overall malignancy rate of ovarian lesions in this series is likely to be lower than the reported figure.

Mature cystic teratoma was the commonest tumour encountered and this was more than four times as common as all other malignant germ cell tumours (yolk sac tumour, mixed germ cell tumour, dysgerminoma and immature teratoma). Oophorectomy, salpingo-oopherectomy and ovarian cystectomy were performed for these lesions.

The current literature suggests that cystectomy only is the treatment of choice for patients with normal alpha-feto protein, a predominantly cystic appearance on ultrasonography, and no intraoperative features of malignancy (such as extracapsular extension and lymph node involvement).

As in other reports, most of the patients with malignancy had germ cell tumours. Age at presentation was not useful in distinguishing patients with benign from malignant lesions. The commonest presentation in those with malignant lesions was a palpable mass in the pelvis or abdomen. Also, two patients with juvenile granulosa cell tumours presented with precocious puberty, while one child with Sertoli-Leydig cell tumour presented with features of masculinisation.

In the adult population, imaging in malignancy predominantly shows an irregular or multilocular solid tumour. However, malignant ovarian lesions in children can be cystic. Gross cystic components are common in childhood with an incidence of 57% unlike in adults, where the quoted risk of malignancy in cystic ovarian lesions is only 2%.

All childhood ovarian malignancies should be treated with salpingo-oopherectomy. Although most of these present as stage I lesions, complete staging during surgery
including lymph node sampling, peritoneal washings and omental biopsy is the gold standard.\(^8\)

In this series there was one case of a grade I immature teratoma that presented with 360° torsion of the left ovary around a large ovarian cyst. Detorsion of the left ovary and excision of the left ovarian cyst was carried out laparoscopically. Malignancy was not suspected preoperatively.

Once the histology returned showing malignancy, an MRI was arranged. This showed no evidence of malignancy. A number of opinions were sought and following review by a multidisciplinary team a plan for observation, serial tumour markers and ultrasound imaging was made.

The commonest type of epithelial neoplasm in this series was benign cystadenoma (10 serous and 9 mucinous). Other studies have shown that epithelial tumours of the ovary are more commonly serous than mucinous.\(^9\)

The proportion of mucinous tumours is reported to be 40% in children (47.4% in this series) compared to 12% in adults\(^9\). Of the 19 cystadenomas, 8 underwent cystectomies while the remaining had oopherectomies done.

Adenocarcinoma of the ovary is a rare entity in children. Three cases reported by Shankar et al had a poor prognosis\(^10\). A 43-year review published in 1992 reported only two cases.\(^11\) There were no cases of adenocarcinoma in this series. Borderline epithelial ovarian tumours are defined as epithelial tumours with nuclear atypia without stromal invasion.\(^12\) These tumours are reported to be more common in children than in adults.\(^13\)

This series had four borderline epithelial tumours, all of which were serous. Unlike adenocarcinoma, which is managed aggressively according to the stage of the disease, borderline tumours can be treated by more conservative surgical procedures\(^9\).

Ovarian cysts have been reported to be seen in 30–68% of routine obstetric ultrasound scans.\(^14,15\) All neonatal ovarian masses are uniformly benign follicular cysts owing to maternal oestrogen stimulation\(^4\). Most of these resolve spontaneously, but can be complicated by ovarian torsion, intra-cystic haemorrhage or a mass effect.

Surgery has been advocated in cysts more than 5 cm in size or for those which increase in size after a 3-month follow up\(^15,16\). Twelve out of the 18 infants in this series had associated ovarian torsion. Early laparoscopy to evaluate for ovarian torsion with aspiration or de-roofing of the cysts may increase the chance of preserving ovarian function in infants with ovarian cysts. Further studies are needed in this regard.

Approximately two thirds of the patients with non-neoplastic ovarian lesions presented with acute abdominal pain. Also, almost all of the patients with corpus luteal cysts presented with acute pain. It is difficult to differentiate pre-operatively those patients with uncomplicated ovarian cysts from those with ovarian torsion or acute appendicitis.

Peritonism and an elevated white cell count can be seen with both ovarian pathology and acute appendicitis. Although ultrasonography can be helpful in differentiating
conditions like acute appendicitis from ovarian lesions, laparoscopy remains the only definitive method to differentiate these with certainty.\textsuperscript{17}

In this series, 29.6\% of patients who underwent surgery for an ovarian mass were found to have ovarian torsion. These patients usually have acute abdominal pain with vomiting. Right-sided ovarian torsion, being more common, can mimic acute appendicitis preoperatively.\textsuperscript{14}

An ovarian mass, solid or cystic, can result in a longer pedicle that predisposes the ovary to undergo torsion. Although preoperative ultrasonography plays a very important role in diagnosing ovarian torsion, false-negative results and delay in getting the imaging done emphasizes the role of diagnostic laparoscopy in the evaluation and management of these patients.\textsuperscript{5,17}

The recommended treatment for ovarian torsion is de-torsion and preservation of all ovaries, even those which appear frankly gangrenous. Cass et al has recommended simple de-torsion with aspiration of ovarian cysts followed by elective ovarian cystectomy if the cystic mass persists or alpha-feto protein levels remain high postoperatively.\textsuperscript{5} This recommendation has been based on the difficulty in assessing ovarian viability, potential damage associated with cystectomy in oedematous, friable tissue and also due to the very low rate of malignancy in these cases.\textsuperscript{18,19} Also, there have been reports of oophoropexy of the contralateral ovary.\textsuperscript{20}

Contralateral oophoropexy was not performed in any patients in this series. In this series there was one case of malignancy (immature teratoma) that presented with ovarian torsion. This equated to a 1.1\% rate of malignancy associated with ovarian torsion in this series. A study by Olmann et al in which they combined 14 series’ of ovarian lesions in the paediatric population reported a 1.8\% malignancy rate associated with ovarian torsion.\textsuperscript{21} Combining this large series with their study gives a malignancy rate of 1.7\% of cases of ovarian torsion.

Conservative ovarian surgery in children is important for the development of normal puberty and future fertility\textsuperscript{22}. In large ovarian cysts or mature teratomas there is very little or no tendency of malignant degeneration and with a bilateral incidence of 12\%, conservative surgery is more appropriate than salpingo-oopherectomy.\textsuperscript{23} Bilateral ovarian lesions were found in 11.0\% of our patients.

In this series, 60.2\% of non-neoplastic cysts were treated by laparoscopic surgery whereas 17.7\% of the neoplastic lesions were managed laparoscopically. Laparoscopic cystectomy with ovarian preservation in benign ovarian lesions has been documented to be safe in children and adolescents.\textsuperscript{24} The concerns of recurrence, spillage and malignancy seem to not be as significant as previously thought after laparoscopic surgery in children.\textsuperscript{24}

Two cases in this series (one borderline malignant tumour and one immature teratoma) were managed with laparoscopic surgery. No cases of malignancy recurrence were identified during data collection for this study.
Table 5: Summary of 4 large published series of ovarian lesions in paediatric patients from single institutions.

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of cases (n)</th>
<th>Length of study (years)</th>
<th>Age range (years)</th>
<th>Average cases per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Silva et al(^{25}) (Melbourne)</td>
<td>134</td>
<td>11</td>
<td>Up to 19</td>
<td>12.2</td>
</tr>
<tr>
<td>Cass et al(^{17}) (Texas)</td>
<td>106</td>
<td>15</td>
<td>Up to 19</td>
<td>7.1</td>
</tr>
<tr>
<td>Brown et al(^{26}) (Philadelphia)</td>
<td>91</td>
<td>11</td>
<td>Up to 18</td>
<td>8.3</td>
</tr>
<tr>
<td>Starship experience</td>
<td>219</td>
<td>12</td>
<td>Up to 16</td>
<td>18</td>
</tr>
</tbody>
</table>

Table 6. Summary of the case mix from the 4 published series in Table 5

<table>
<thead>
<tr>
<th>Authors</th>
<th>Non-neoplastic %</th>
<th>Neoplastic benign %</th>
<th>Neoplastic malignant %</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Silva et al(^{25}) (Melbourne)</td>
<td>59</td>
<td>32.8</td>
<td>8.2</td>
</tr>
<tr>
<td>Cass et al(^{17}) (Texas)</td>
<td>46.3</td>
<td>44.3</td>
<td>9.4</td>
</tr>
<tr>
<td>Brown et al(^{26}) (Philadelphia)</td>
<td>38.5</td>
<td>40.6</td>
<td>21</td>
</tr>
<tr>
<td>Starship experience</td>
<td>59.4</td>
<td>32.8</td>
<td>7.8</td>
</tr>
</tbody>
</table>

Summary—Ovarian lesions in children and adolescents include a wide array of pathologic diagnoses and these lesions have varied clinical presentations. Although neoplastic lesions are seen commonly in this group, the incidence of malignancy is less. This case series suggests that the prognosis of children with ovarian masses is excellent.

In benign lesions, future fertility should be the primary consideration when deciding the extent of surgery. A minimally invasive approach with cystectomy and ovarian salvage is safe and should be considered in children with benign lesions. Complete staging and complete resection should be the goal in those with malignant lesions. Bilateral oopherectomy is rarely necessary in children.

However, as is often the case with ovarian masses it is usually not known if the lesion is benign or malignant and clinical assessment of this is difficult. Therefore, in the acute setting of paediatric ovarian masses the authors of this article favour ovary sparing and minimally invasive surgery where possible.

For a population of girls aged 0–15 years, with acute abdominal pain, ovarian lesions should be part of the differential diagnoses. The authors also suggest that referral of these patients to a paediatric surgical unit is preferable. This paper shows that paediatric surgical units have vast experience to deal with this condition.

At our institution, all malignant tumours are discussed at a multidisciplinary oncology meeting and the authors recommend this practice.

Competing interests: Nil.

Author information: Benjamin Cribb, Paediatric Surgical Registrar; Naveen Vishwanth, Paediatric Surgical Registrar; Vipul Upadhya, Paediatric Surgeon and Paediatric Urologist. Department of Paediatric Surgery, Starship Children’s Hospital, Auckland
Acknowledgements: The authors thank Mike Watson and Daniel Wong from LabPLUS for their assistance with searching the Laboratory’s database as well as Peter Reed (Biostatistician, Starship Children’s Research Center) for assistance with the statistics.

Correspondence: Vipul Upadhyay, Department of Paediatric Surgery, Starship Children’s Hospital, 2 Park Road, Grafton, Auckland 1023, New Zealand. Fax: +64 (0)9 3078952; email: VipulU@adhb.govt.nz

References:

Thyroid cancer in Pacific women in New Zealand
Ineke Meredith, Diana Sarfati, June Atkinson, Tony Blakely

Abstract:

Aim To describe trends in incidence rates of thyroid cancer in New Zealand between 1981–2004 with a particular focus on Pacific women.

Method Linked census-cancer registration data was used to calculate age standardised cancer incidence rates for thyroid cancer. Both trends over time amongst Pacific women, and differences in rates between Pacific and European/Other women in New Zealand, were assessed.

Results Rates of thyroid cancer in New Zealand were higher for women than men. The highest rates of thyroid cancer in were observed amongst Pacific women with a pooled age-standardised incidence rate of 18.5/100,000 (95% CI 14.6–22.4/100,000) compared to 5.2/100,000 (95% 4.8–5.5/100,000) for European/Other; SRR 3.58 (95%CI 2.87–4.47). Sparse data mean it is difficult to clearly identify a trend over time for Pacific women but European women experienced a 73% increase from 4.0/100,000 (95%CI 3.3–4.6/100,000) in 1981–1986 to 6.9/100,000 (95%CI 5.9–7.8/100,000) in 2001–2004 (P trend=0.05).

Conclusions Pacific women in New Zealand have the highest rates of thyroid cancer among resident ethnic groups. Risk was highest for Pacific women over 45 years of age. More research needs to be done looking at which specific ethnicities are driving rates of thyroid cancer in New Zealand and whether the risk is influenced by birthplace and age at migration to New Zealand.

Thyroid cancer constitutes 1% of all cancers worldwide but is the most common malignancy of the endocrine system. Worldwide, the incidence of thyroid cancer between 1973–2002 has increased with an average rise of about 50% among males and about two-thirds among females, but there is large geographic variation with the greatest increases reported in South Australia (178% increase in men and 252% increase in females).

Thyroid cancer most frequently presents in the fourth or fifth decade of life and is two to four times more frequent in females than males suggesting that sex hormone elements may be involved in pathogenesis. With the exception of exposure to ionising radiation in childhood and female gender, risk factors for thyroid cancer are unclear, making it difficult to understand why there has been an observed increase in incidence rates or why this increase has varied by social group.

Potential risk factors for this disease that have been suggested include iodine deficiency, family history of thyroid cancer or personal history of benign thyroid disease, low consumption of fresh fruit and vegetables, and more recently, exposure to radiation associated with increasing computed tomography (CT) scanning.
An alternative explanation for the increasing trend is increased detection of subclinical tumours through the escalating use of ultrasonography and fine needle aspiration, but whilst this will account for an increase in small tumours, it does not explain the observed rise in incidence of larger tumours.

Most thyroid cancers arise from the thyroid follicular cell, are well differentiated and follow an indolent course with 10-year survivals in excess of 90%. The well-differentiated types include papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) and Hürthle cell carcinoma.

PTC is the most common type of thyroid cancer and is associated with exposure to ionising radiation, as evidenced by the increase in cases in Chernobyl. It comprises approximately 85% of all thyroid cancers and is the main driver of increasing incidence rates; rates of FTC and medullary thyroid cancer (MTC; a non-follicular type) have remained relatively stable over time.

The non-follicular types are responsible for a small proportion of thyroid cancers. MTC arises from thyroid C-cells and tends to pursue a more aggressive course. Thyroid lymphoma is rare. Anaplastic carcinoma accounts for <5% of thyroid cancers but is responsible for 50% of the mortality of thyroid cancer. Poor prognostic factors are tumour histology (high grade), extrathyroidal extension, metastases, age >40 years and male gender.

Women in New Caledonia, Hawaii and French Polynesia have the highest rates of thyroid cancer in the world with documented rates over five times greater than New Zealand Europeans. Such is the importance of this disease in French Polynesia that thyroid cancer was the second most commonly diagnosed malignancy for women in parts of this region whilst a relative rarity in most other populations.

High incidence rates have also been reported in Fiji, Vanuatu, Marshall Islands, Palau and the Northern Marianas. However, such high rates are not uniform for all Pacific nations.

Thyroid cancer is uncommon in Samoa with an incidence rate amongst Samoan women considerably lower than Polynesian women in Hawaii and Melanesian women in New Caledonia. Previous work in New Zealand has reported a higher incidence rate of thyroid cancer among Pacific than Māori or European people in New Zealand.

The aim of this paper is to describe trends in incidence rates of thyroid cancer, by age, in New Zealand between 1981–2004 with a particular focus on Pacific women living in New Zealand. Numbers were too small amongst men to examine trends over time.

**Methods**

The dataset was created by linking New Zealand Cancer Registry (NZCR) records to the 5-yearly New Zealand census of population and dwellings (the census) data, and is published in detail elsewhere. Briefly, five closed cohorts were created of the New Zealand usual resident population (all ages) on census night 1981, 1986, 1991, 1996, 2001, followed up for incident cancer(s) until the subsequent census or in the case of the 2001 cohort, until 31 December 2004 (the most recent data available at the time of the study’s record linkage). The NZCR is a population based cancer register that collects data on the full population of New Zealand, including all thyroid cancers (ICD code C73).
Between 71% to 82% of eligible thyroid cancers were linked to a census record. To avoid underestimation of rates due to linkage bias, weights were calculated for strata based on age, sex, ethnicity and small-area deprivation. For example, if 20 out of 30 cancer registrations for Pacific females aged 45–64 living in moderately deprived areas were linked, each of the 20 linked records was assigned a weight of 30/20=1.5, making the 20 records representative of the 30 eligible records. All analyses used these weights.

Approval was granted for this project under the Statistics New Zealand Data Integration Policy, and the Wellington Ethics Committee granted ethics approval for CancerTrends (Ref 04/10/093).

A modified total ethnicity approach was used for this work. Total ethnicity places an individual in all ethnic groups that they identify with. If individuals indicated any/all of Māori, Pacific and/or Asian ethnic affiliation they were placed in any/all of Total Māori, Total Pacific, Total Asian ethnic groups. The residual people who did not indicate any of the above ethnic affiliations were placed in the non-Māori/Pacific/Asian (referred to as European/Other hereafter).

Incidence rates and rate ratios (and 95% confidence intervals) were calculated after direct standardisation of the cohorts to the age structure of the 2001 WHO world standard population. Analyses were carried out for all adults (aged 15+ years), and by <45 years and ≥45 years for women. These age groups were chosen to parallel other studies that have suggested differential risk according to pre- and post-reproductive age.

Statistical tests of trend were conducted for rates, and of the log transformed rate ratios. All measures were also calculated for all five cohorts pooled. All these analyses were conducted in SAS v9.

**Results**

There were a total of 2541 thyroid cancers for the entire study period. Of these, 189 cancers were diagnosed amongst Pacific women (with 1.26 million person years), 261 cancers for Māori and 1407 for European/Other women (3.48 and 25.64 million person years respectively).

There were 33 cancers diagnosed amongst Pacific men (with 1,182,637 person years), 78 cancers for Māori and 573 cancers for European/Other men (3,249,289 and 23,977,590 person years respectively). Pooled standardised incidence rates (SR) for Pacific, Māori and European/Other men were 2.7/100,000 (95%CI 1.3–4.1/100,000), 3.2/100,000 (95%CI 2.5–4.3/100,000) and 2.2/100,000 (95%CI 2.0–2.4/100,000) respectively.

Corresponding rates for women were 18.5/100,000 (95%CI 14.6–22.4/100,000), 8.3/100,000 (95%CI 7.0–9.6/100,000) and 5.2/100,000 (95%CI 4.8–5.5/100,000). Table 1 shows the standardised incidence rates (to the 2001 WHO World Population) for males and females (ethnic groups pooled). Rates were clearly higher for females, with a pooled standardised rate ratio (SRR) of 2.71 (95%CI 2.45–3.01) for females compared with males.

Across time, Pacific women have had the highest rates of thyroid cancer (Figure 1a). Table 2 shows SRs and SRRs for females <45 years, 45+ years and total females (15+ years) by ethnicity. The pooled SRR across time for Pacific compared to European/Other females was 3.58 (95%CI 2.87–4.47). Māori rates were intermediary with a pooled SR for all women of 8.3/100,000 (95%CI 7.0–9.6/100,000), and an SRR compared to European/Other of 1.61 (95%CI 1.35–1.92).

Ethnic differences among males were less marked, with Pacific and Māori SRRs of 1.27 (95%CI 0.74–2.18) and 1.55 (95%CI 1.11–2.18) compared to European/Other (pooled over time and ages).
Over the time period, European/Other women experienced a statistically significant 73% increase from 4.0/100,000 (95%CI 3.3–4.6/100,000) in 1981–1986 to 6.9/100,000 (95%CI 5.9–7.8/100,000) in 2001–2004 (P trend=0.05). However, there was no apparent trend among Pacific women—although statistical imprecision at each time point renders the analysis ‘weak’ in terms of statistical power for detecting any trend for Pacific people.

Figure 1. Age-standardised incidence rates (with 95% confidence intervals) for all women (15+ years) by ethnicity

Thyroid cancer incidence rates were higher in those aged ≥45 years than <45 years for men and women alike. The pooled SR for total women <45yr was 4.7/100,000 (95%CI 4.3–5.1/100,000) and 8.1/100,000 (95%CI 7.5–8.7/100,000) for ≥45 years. For men, these values were 1.2/100,000 (95%CI 1.0–1.4/100,000) and 3.6/100,000 (95%CI 3.2–4.0/100,000) respectively.

By ethnicity, the pooled over time SR for Pacific females <45 years of age was 9.7/100,000 (95%CI 7.6–11.9/100,000) and for ≥45 years was 31.9/100,000 (95%CI 22.8–41.1/100,000) giving rate ratios for Pacific compared to European/Other women of 2.40 (95%CI 1.84–3.03) and 4.60 (95%CI 3.40–6.20) for younger and older women respectively.

Noting the non-overlap in the confidence intervals for the Pacific-European/Other SRRs, we can confidently conclude that the elevated Pacific female rates are more pronounced at older ages. For Māori women, pooled SRs were 5.3/100,000 (95%CI 4.2–6.4/100,000) and 13.0/100,000 (95%CI 10.0–15.9/100,000) for <45 years and ≥45 years respectively to give corresponding SRRs of 1.28 (95%CI 1.02–1.62) and 1.87 (95%CI 1.47–2.38).
Table 1. Age-standardised incidence rates (SR) among for 15+ years, 15–44 years and 45+ years (standardised to the 2001 WHO world population), pooled across ethnicity and by sex

<table>
<thead>
<tr>
<th>Sex</th>
<th>Cohort</th>
<th>SR (95% CI)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>15+yr</td>
<td>15–44yr</td>
<td>45+yr</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>1981-1986</td>
<td>1.9 (1.3–2.5)</td>
<td>1.0 (0.6–1.5)</td>
<td>3.4 (2.0–4.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1986–1991</td>
<td>1.7 (1.3–2.1)</td>
<td>1.2 (0.1–1.6)</td>
<td>2.4 (1.6–3.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1991–1996</td>
<td>2.3 (1.8–2.8)</td>
<td>1.0 (0.6–1.5)</td>
<td>4.0 (2.8–5.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1996–2001</td>
<td>3.0 (2.5–3.5)</td>
<td>1.7 (1.2–2.2)</td>
<td>5.1 (3.9–6.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2001–2004</td>
<td>2.7 (2.2–3.2)</td>
<td>1.3 (0.8–1.9)</td>
<td>5.1 (3.9–6.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P trend over time</td>
<td>0.07</td>
<td>0.29</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pooled</td>
<td>2.2 (2.0–2.4)</td>
<td>1.2 (1.0–1.4)</td>
<td>3.6 (3.2–4.0)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>1981-1986</td>
<td>5.7 (4.7-6.6)</td>
<td>3.8 (3.0-4.7)</td>
<td>8.4 (6.3-10.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1986-1991</td>
<td>5.3 (4.5-6.0)</td>
<td>3.3 (2.6-4.1)</td>
<td>8.4 (6.7-10.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1991-1996</td>
<td>5.0 (4.3-5.8)</td>
<td>3.6 (2.8-4.4)</td>
<td>7.2 (5.7-8.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1996-2001</td>
<td>8.8 (7.8-9.8)</td>
<td>7.5 (6.3-8.7)</td>
<td>11.6 (9.9-13.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2001-2004</td>
<td>8.1 (7.2-9.0)</td>
<td>5.9 (4.8-6.9)</td>
<td>11.8 (10.0-13.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P trend over time</td>
<td>0.15</td>
<td>0.18</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pooled</td>
<td>5.9 (5.6-6.2)</td>
<td>4.7 (4.3-5.1)</td>
<td>8.1 (7.5-8.7)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Age-standardised incidence rates (SR) and rate ratios (SRR) among women by ethnicity for 15+ years, 15–44 years and 45+ years (standardised to the 2001 WHO world population)

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Cohort</th>
<th>SR (95% CI)</th>
<th>SRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15+ yr</td>
<td>15–44 yr</td>
<td>45+ yr</td>
</tr>
<tr>
<td>European/Other</td>
<td>1981–1986</td>
<td>4.0 (3.3–4.6)</td>
<td>3.3 (2.5–4.1)</td>
</tr>
<tr>
<td></td>
<td>1986–1991</td>
<td>4.3 (3.6–5.0)</td>
<td>2.8 (2.0–3.6)</td>
</tr>
<tr>
<td></td>
<td>1991–1996</td>
<td>4.3 (3.6–5.0)</td>
<td>3.3 (2.4–4.3)</td>
</tr>
<tr>
<td></td>
<td>1996–2001</td>
<td>6.7 (5.7–7.7)</td>
<td>6.1 (4.7–7.5)</td>
</tr>
<tr>
<td></td>
<td>2001–2004</td>
<td>6.9 (5.9–7.8)</td>
<td>5.4 (4.1–6.7)</td>
</tr>
<tr>
<td>Pooled</td>
<td>5.2 (4.8–5.5)</td>
<td>4.1 (3.7–4.6)</td>
<td>7.0 (6.4–7.5)</td>
</tr>
<tr>
<td>Pacific</td>
<td>1981–1986</td>
<td>21.9 (10.2–33.7)</td>
<td>6.5 (2.2–10.8)</td>
</tr>
<tr>
<td></td>
<td>1986–1991</td>
<td>15.3 (7.1–23.4)</td>
<td>8.3 (3.8–12.9)</td>
</tr>
<tr>
<td></td>
<td>1991–1996</td>
<td>15.7 (7.3–24.1)</td>
<td>8.1 (4.1–12.1)</td>
</tr>
<tr>
<td></td>
<td>1996–2001</td>
<td>24.6 (17.5–31.8)</td>
<td>17.1 (10.7–23.4)</td>
</tr>
<tr>
<td></td>
<td>2001–2004</td>
<td>13.8 (8.7–18.9)</td>
<td>8.3 (4.1–12.5)</td>
</tr>
<tr>
<td>Pooled</td>
<td>18.5 (14.6–22.4)</td>
<td>9.7 (7.6–11.9)</td>
<td>31.9 (22.8–41.1)</td>
</tr>
<tr>
<td>Maori</td>
<td>1981–1986</td>
<td>8.5 (4.7–12.3)</td>
<td>5.1 (2.6–7.7)</td>
</tr>
<tr>
<td></td>
<td>1986–1991</td>
<td>6.8 (4.1–9.4)</td>
<td>4.6 (2.0–7.2)</td>
</tr>
<tr>
<td></td>
<td>1991–1996</td>
<td>5.2 (2.8–7.6)</td>
<td>2.3 (1.3–4.3)</td>
</tr>
<tr>
<td></td>
<td>1996–2001</td>
<td>10.6 (8.0–13.3)</td>
<td>8.1 (5.5–10.7)</td>
</tr>
<tr>
<td></td>
<td>2001–2004</td>
<td>11.1 (8.0–14.2)</td>
<td>6.0 (3.5–8.4)</td>
</tr>
<tr>
<td>Pooled</td>
<td>8.3 (7.0–9.6)</td>
<td>5.3 (4.2–6.4)</td>
<td>13.0 (10.0–15.9)</td>
</tr>
</tbody>
</table>

P trend over time: 0.05, 0.13, 0.05, 0.05, 0.64, 0.12, 0.06, 0.64, 0.12.
Discussion

Thyroid cancer is more common in females than males in New Zealand and this is consistent with a female preponderance observed worldwide. The highest rates of thyroid cancer in New Zealand are amongst Pacific women. Whilst this is in keeping with what is known about thyroid cancer in the Pacific basin, it is not clear why this is the case.

Between 1966 and 1974, France conducted 41 atmospheric nuclear tests in French Polynesia but the high rates of thyroid cancer here cannot be completely attributed to nuclear fallout because rates of thyroid cancer have remained stable since the 1950s and it does not explain the high rates of thyroid cancer across multiple Pacific Islands at a considerable distance from the nuclear testing areas.

The predominance of this disease amongst women worldwide has supported a role for hormonal and reproductive factors. In fact, in the same way that breast cancers express oestrogen receptors, it has been observed that thyroid tumours also have a high level of oestrogen receptor expression.

In New Caledonia, where Melanesian women have the highest rates in the world, a population-based study found an association between parity and thyroid cancer risk but the evidence in support of this is mixed. A pooled analysis of case-control studies found a non-significant 20% increase in risk for multiparous compared to nulliparous women. Notwithstanding this, if parity were related to risk, it would not explain the apparent low rates in Samoan women, or the variation between Pacific Island nations.

Artificial menopause increases the risk of thyroid cancer by 80% compared to women who have a natural menopause and in contrast to known risks for breast cancer related to oestrogen exposure, later age at menarche and age at first birth are only weakly associated with thyroid cancer risk.

The relationship between iodine and thyroid function is complex. Both iodine deficiency and excess can inhibit thyroid hormone synthesis and cause goiter. Goiter and benign thyroid nodules/adenomas are the strongest risk factors for thyroid cancer apart from radiation in childhood with pooled ORs of 5.9 (95%CI 4.2–8.1) and 29.9 (95%CI 14.5–62.0) respectively.

Due to such high rates of thyroid cancer in the Pacific, where seafood consumption is high and consequently iodine intake, it has been proposed that iodine excess is contributory. However, this hypothesis was not supported in an international pooled analysis of case-control studies that looked specifically at fish and shellfish intake. Nonetheless, it is possible that there is a differential effect depending on iodine status.

When examining only those studies from areas with an iodine rich diet (e.g. Hawaii, Japan, Norway), there was a non-significant mild increase in risk for the highest (≥3 times/week) compared to the lowest (<1 times/week) intake of fish or shellfish (OR 1.13, 95%CI 0.85–1.5).
Conversely, for low iodine and goiter endemic areas (e.g. Sweden, Switzerland), a high intake was protective with an OR of 0.65 (95%CI 0.48–0.88) for the highest versus the lowest intake groups. A high intake of butter and cheese has been found to be associated with thyroid cancer and this is likely related to BMI. In a systematic review examining risk of cancer with a 5kg/m^2 increase in BMI, the risk of thyroid cancer was found to increase by 14% in women (RR 1.14, 95%CI 1.06–1.23) and 33% in men (RR 1.33, 95%CI 1.04–1.70).

Whilst this may account for some of the disparity in thyroid cancer incidence rates between Pacific and European/Other women in New Zealand, it does not explain the very large disparity nor the variation between women in different Pacific Island nations.

In the United States, Southeast Asian migrants (largely Filipino and Vietnamese) have high rates of thyroid cancer compared to United States Caucasian women and Northern Asian women living in the United States (largely Chinese and Japanese). However, this relationship is complex, with Phillipine-born men and women living in the United States having incidence rates of thyroid cancer exceeding both their US-born counterparts and white men and women. This effect by birthplace was not seen for Chinese men or women.

A study examining thyroid cancer risk amongst Asian women living in the United States found that for Asian women <50 years, a large proportion of the difference in thyroid cancer rates when compared to white women was due to goiter/nodules and dietary differences (i.e. low consumption of isoflavones). For older women (≥50 years), whilst these were also contributory, recent migration was important with a risk over 2.5 times higher for Asian women who had spent <30% of their lifetime in the United States compared to Asian women who had spent ≥30% (OR 2.7, 95%CI 1.2–6.0). This suggests an early life exposure amongst these migrant populations which may affect thyroid cancer risk.

Increased diagnostic scrutiny is unlikely to be the reason for the higher rate seen in Pacific women. Evidence from New Zealand is that, if differences are present, Māori and Pacific people are likely to be under-served in relation to diagnostic and other services relative to the New Zealand European population.

**Conclusion**

Although thyroid cancer is a relatively rare disease in developed countries, it continues to be of importance in the Pacific and amongst Pacific women in New Zealand. Given that rates in Samoan women have been reported to be low, more work needs to be done to identify which Pacific groups are driving the incidence rates observed in New Zealand and whether thyroid cancer risk is affected by birthplace and migrant status.

Finally, we hypothesise that thyroid cancer rates among Pacific women will be largely among those born in the Pacific, due to the high iodine diets among children and young people living in the Pacific. The finding of larger relative differences in thyroid cancer between Pacific and European/Other women at older ages in this study is consistent with this hypothesis (older Pacific women living in New Zealand are more
likely to have been born in the Pacific than younger women), and sufficiently large datasets to test this hypothesis may be available following further linkage of census and cancer registration data.

Further work is required to investigate dietary iodine in the Pacific, including seaweed consumption, and monitoring iodine excess by way of urinary iodine and serum TSH and T4.

**SNZ disclaimer:** Access to the data used in this study was provided by and sourced from Statistics New Zealand under conditions designed to give effect to the security and confidentiality provisions of the Statistics Act 1975. The results presented in this study are the work of the authors, not Statistics New Zealand.

**Competing interests:** Nil.

**Author information:** Ineke Meredith, Surgical Registrar and Visiting Scholar; Diana Sarfati, Senior Lecturer, Director of Cancer Control and Screening Research Group; June Atkinson, Senior Analyst, Health Inequalities Research Programme (HIRP); Tony Blakely, Research Professor, HIRP and the Burden of Disease Epidemiology, Equity and Cost-Effectiveness Programme (BODE3). Department of Public Health, Wellington School of Medicine and Health Sciences, University of Otago, Wellington

**Acknowledgements:** We acknowledge the support of the Nikau Foundation and the CancerTrends study was funded by the Health Research Council of New Zealand (06/256).

**Correspondence:** Dr Ineke Meredith, Department of Public Health, Wellington School of Medicine and Health Sciences, University of Otago, PO Box 7343, Wellington, New Zealand. Fax: +64 (0)4 3895319; email ineke.meredith@otago.ac.nz

**References:**


Rectal cancer: future directions and priorities for treatment, research and policy in New Zealand

Christopher Jackson, Nieves Ehrenberg, Frank Frizelle, Diana Sarfati, Adrian Balasingam, Maria Pearse, Susan Parry, Cristin Print, Michael Findlay, Ian Bissett

Abstract

New Zealand has one of the highest incidences of rectal cancer in the world, and its optimal management requires a multidisciplinary approach. A National Rectal Cancer Summit was convened in August 2013 to discuss management of rectal cancer in the New Zealand context, to highlight controversies and discuss domestic priorities for the future.

This paper summarises the priorities for treatment, research and policy for rectal cancer services in New Zealand identified as part of the Summit in August. The following priorities were identified:

– Access to high-quality information for service planning, review of outcomes, identification of inequities and gaps in provision, and quality improvement
– Engagement with the entire sector, including private providers
– Focus on equity
– Emerging technologies
– Harmonisation of best practice
– Importance of multidisciplinary team meetings

In conclusion, improvements in outcomes for patients with rectal cancer in New Zealand will require significant engagement between policy makers, providers, researchers, and patients in order to ensure equitable access to high quality treatment, and strategic incorporation of emerging technologies into clinical practice. A robust clinical information framework is required in order to facilitate monitoring of quality improvements and to ensure that equitable care is delivered.

Colorectal cancer (CRC) is a major health burden in New Zealand, with over 2980 incident cases per annum and over 1200 deaths each year.1 Along with Australia, New Zealand has the highest incidence of colorectal cancer of any country in the world.2

See Figure 1.

In 2010 colorectal cancer and prostate cancer were equally the most common category of new cancer registrations; each accounting for 14.1% of registrations.

Colorectal cancer was the second most frequent cause of death from cancer in 2010. In most Western countries the male:female ratio is 2:1, whereas in New Zealand it is closer to 1:1 due to an excess of female cases. The reasons for this difference in New Zealand are not clear.
Rectal cancer accounts for approximately one-third of new CRC diagnoses. Note that the precise burden of rectal cancer is unable to be established from routine data sets due to inconsistent definition of rectal cancer, and the subsequent inconsistency of reporting to the NZ Cancer Registry (NZCR).

Rectal cancer is one of the few cancers for which incidence rates are lower among Māori, but rates among Māori are tending to increase towards those of non-Māori.
Māori patients tend to be younger at diagnosis and have a higher prevalence of comorbidity than non-Māori.\(^4,5\) Data on stage-specific outcomes by ethnicity are limited.\(^6\)

The management of rectal cancer is challenging and requires multidisciplinary collaboration. Specialists involved can include radiologists, pathologists, surgeons, gastroenterologists, medical and radiation oncologists, palliative care physicians, stoma therapists, familial GI cancer service and nurse specialists.

Due to the complexity of management, the overall health burden and an increasing number of available therapeutic options, a National Rectal Cancer Summit (‘the Summit’) was convened. The Summit took place in Wellington, New Zealand on 9 August 2013 and was attended by over 165 practitioners involved with the treatment of colorectal cancer.

International keynote speakers delivered addresses on neo-adjuvant radiotherapy in rectal cancer, management of locally recurrent rectal cancer, optimal imaging methods in diagnosis and staging, and systemic approaches to potentially resectable metastatic disease.

The final session of the Summit focused on domestic priorities and policy initiatives. These included discussion of the (then) proposed Standards for Service Provision for Patients with Bowel Cancer,\(^7\) the Ministry of Health’s Faster Cancer Treatment and Bowel Cancer initiatives, the work plan of the National Bowel Cancer Working Group, and inequalities of treatment and outcome in New Zealand. A facilitated discussion was then held.

In order to summarise themes and outcomes of the Summit, and to inform this paper, a sub-group made up of convenors and other interested experts held a meeting following the Summit.

**Summit session on the future of rectal cancer management in New Zealand**

Summit participants identified the following top priorities for the future of rectal cancer services in New Zealand:

- *Access to high-quality information* for service planning, review of outcomes, identification of inequities and gaps in provision, and quality improvement
- *Engagement with the entire sector, including private providers*
- *Focus on equity*
- *Emerging technologies*
- *Harmonisation of best practice*
- *Importance of multidisciplinary team meetings*
Access to high-quality information—Summit participants identified a need for access to robust, high quality information on rectal cancers.

In alignment with the draft Standards for Service Provision for Patients with Bowel Cancer in New Zealand, Summit participants supported the Ministry of Health work around developing a national cancer database. Multiple disparate databases currently exist, including routinely collected national collections (the New Zealand Cancer Registry, the National Minimum Database, and the National Mortality database) and a number of regional or ad hoc databases including the Colorectal Surgical Society of Australia and New Zealand, the Otago Surgical Audit, and the METRIQ database (South Island).

While the nationally collected databases are recognised as valuable, there are important gaps that limit their usefulness in evaluating the stage, patterns of care and outcomes for rectal cancer patients. In particular, data on the extent of disease at diagnosis for rectal cancer patients are often missing, and access to data on treatment occurring in the private sector is limited. Some of the data in the regional databases are high quality but the systems are not integrated and collect separate information.

Participants highlighted the importance of systematically collecting information on patients with rectal cancer on databases that are consistent on a national level, to monitor, evaluate and improve access to services and outcomes for patients. They agreed an electronic database for rectal cancer should be constructed to integrate demographic (including ethnicity data), diagnostic, treatment, outcome (including palliative care) and other clinical information to contribute to service and clinical performance monitoring and research to improve patient outcomes.

Information sent to the Cancer Registry needs to be improved particularly regarding distinguishing rectal cancer from colon cancers, which could be facilitated by the adoption of nationally agreed case definitions.

An effective national-level database that captures all patients with rectal cancer could improve equity of outcomes for patients. Such a database could be used as a quality tool to capture outcomes such as access to adjuvant or palliative systemic therapy, referral rates and timeliness of care, rates of margin positivity, stoma formation and reversal, as well as recurrence/mortality. Understanding differences in key quality measures could assist in the formulation and implementation of focused and efficient improvement measures.

In the context of the Ministry of Health’s Faster Cancer Treatment programme of work, there was discussion on the need to measure not only the timeliness of services but also the quality of services (faster is not necessarily better). The Summit’s presentation—Current policy initiatives in rectal cancer in New Zealand—highlighted that in order for information to be a powerful quality improvement tool, there needs to be quality improvement initiatives in place, not just indicators. An example of this is the National Referral Criteria for Direct Access Outpatient Colonoscopy.

Another key step towards achieving the required quality information is to standardise reporting, particularly mandating synoptic reporting in pathology. Synoptic reporting in pathology is considered best practice to assist clinicians in obtaining the required information to make treatment decisions and provide prognostic information.
Standardising reporting is considered a “low-hanging fruit” in terms of effort and speed of possible implementation. The Royal College of Pathologists of Australasia has developed a standardised reporting template for colorectal cancer, however, its utilisation is not mandated nor uniform.\textsuperscript{9}

Several tumour stream draft standards for service provision include a push for improved data collection. For example, Standard 8 requires that data relating to bowel cancer beyond the fields required by the Cancer Registry, including treatment data, are reported to existing and planned national repositories using nationally agreed dataset fields.

Standard 15 requires that multidisciplinary meetings identify patients at high risk of receiving inequitable care and auditable data on these patients is collected from along their cancer journey. (High risk is defined as Māori with either or both: stage III bowel cancer, comorbidities.) Standard 20 requires that auditable data on reasons for non-referral to adjuvant therapy are recorded for all patients who are not referred to adjuvant therapy.

**Engagement with the entire sector, including private providers**—Summit participants highlighted the importance of engaging across sector stakeholders including all specialties involved with the treatment of rectal cancer. The private sector should be engaged in any rectal cancer initiatives or discussions to ensure the entire patient journey is included. There is a sense that the private sector seems keen to contribute and participate in national rectal cancer initiatives.

Many clinicians work in both the public and private sectors, but engagement to date with private sector organisations has been limited in terms of national initiatives, including the draft standards for service provision. Consultation and engagement with surgical groups should include general and colorectal specialist surgeons, as well as ensuring input from providers involved in non-cancer centres.

**Focus on equity**—One of the important challenges facing clinicians in New Zealand is how to reduce inequities in cancer-related outcomes. The Summit presentation—*New Zealand’s place in the world of rectal cancer and inequity of outcomes in rectal cancer in New Zealand*—highlighted evidence relating to health service factors that contribute to poorer colorectal cancer survival among Māori.

Figure 2 illustrates the inequities that occur at multiple points along the care pathway that contribute to the differences in mortality for colon cancer between Māori and non-Māori. Data specific to rectal cancer are more limited.\textsuperscript{6}

In addition to ethnic inequities, regional inequities and particularly the challenge of ensuring that those living in rural New Zealand have equal access to quality colorectal cancer services are also important.

One way of improving outcomes for colorectal cancer patients at a national level is to ensure that they all have equal access to expert clinical and supportive care, regardless of ethnicity, geography, or socioeconomic status. Implementation of the National Tumour Standards and auditing outcome by rurality and ethnicity will also assist in ensuring improvements in equity.
Further data is expected on the impact of rurality and inequity and the relationship between these two when data from the National Colorectal PIPER project becomes available in Q1 2015.

**Figure 2. Oncology referral, review, offer and receipt of chemotherapy in Māori and non-Māori patients with stage III colon cancer, 1996–2003**

![Diagram showing oncology referral, review, offer and receipt of chemotherapy in Māori and non-Māori patients with stage III colon cancer, 1996–2003.](image)

*Note:* Percentages are standardised for age (25–64, 65–74 and 75 years and over) and sex.11

**Emerging technologies**—Genomic studies have revolutionised our understanding of the biology of colon and rectal cancer, and have contributed significantly to our understanding and management of heritable colon and rectal cancer. *BRAF* mutation testing can assist in distinguishing between germ-line and sporadic (hypermethylated) MSI-high colon and rectal cancer, and *Kras*, and *Nras* mutations are widely used in selecting patients for EGFR inhibitor therapy.11

Whilst genomics has helped us understand the biology of colon and rectal cancer, its full potential is yet to be realised. Also, a deeper understanding of the genomic basis of cancer may help us identify important therapeutic differences between left and right-sided tumours and rectal cancer.

Microarray analysis, and more recently next generation sequencing analysis of colon and rectal DNA and RNA, has enabled researchers to identify the combinations of genes that need to be turned on or off for colon and rectal cancers to grow and survive. In addition to enhanced biological understanding, genomics and related technologies are starting to have a clinical impact in CRC. While initially most
commonly used to assist CRC prognostication, genomics is now being used to predict treatment response in CRC.

A well-known example of genomic treatment stratification relevant to CRC is Ras mutation analysis to determine tumour molecular pathway disruption, in order to stratify epidermal growth factor receptor monoclonal antibody therapy. Large international projects integrating rectal cancer genomic, pathological and clinical data are now facilitating drug and diagnostic research for rectal cancer including the CBioPortal for Cancer Genomics,\textsuperscript{12} the International Cancer Genome Consortium (ICGC),\textsuperscript{14} and the Cancer Genome Atlas project (TCGA).\textsuperscript{14}

The presentation at the Summit—\textit{Gene sequencing studies of rectal tumours from the international TCGA consortium and New Zealand work}—provided an update on the genomic studies undertaken in relation to colon and rectal cancer, including tumours from NZ patients and international data. The presentation advocated more integrated NZ research teams involving laboratory scientists in partnership with clinicians to ensure clinical relevance of NZ CRC research.\textsuperscript{15}

An important research priority would be the continued development of molecular pathology in identifying predictive biomarkers to help pathologists enhance prognosis and enhance specificity of systemic therapy. Most crucial are those markers used to predict response to certain therapies, including toxicity, thereby directing clinicians to the most appropriate therapy and avoiding potentially harmful ones. This is likely to require improved infrastructure to deal with tissue collection in every hospital.

Presentations and discussions at the Summit highlighted the area of rectal cancer presenting with synchronous metastatic disease as being an area of particular complexity, with limited evidence to guide practice. This subject was seen a priority for further research, and this could be undertaken in the New Zealand context with scientific and clinical collaboration.

\textbf{Harmonisation of best practice}—The draft \textit{Standards for Service Provision for Patients with Bowel Cancer in New Zealand}\textsuperscript{7} provides a starting point for ensuring there is harmonisation of best practice in the care of patients with rectal cancer. The objective of the standards is to promote nationally coordinated and consistent standards of service provision across New Zealand. It was noted that no consensus exists on the optimal selection of patients for preoperative therapy and that further work is needed to achieve greater harmonisation of practice.

It is anticipated the standards will drive change in practice for better patient care. A prerequisite to tracking the success of standards, however, when they are implemented, is to have good quality data. Data will allow standards to be monitored and identify where there are gaps. Once gaps are identified, resources can be channelled to the areas of greatest need.

\textbf{Importance of multidisciplinary team meetings}—International evidence shows that multidisciplinary care is a key aspect to providing best-practice treatment and care for patients with cancer.\textsuperscript{16–18} Multidisciplinary care involves a team approach to treatment planning and care provision along the complete patient cancer pathway.

Cancer Multidisciplinary Meetings (MDMs) are part of the philosophy of multidisciplinary care. Effective MDMs can result in positive outcomes for patients
receiving the care, for health professionals involved in providing the care and for health services overall.

An audit conducted in the UK examined the rate of circumferential resection margin (CRM) involvement in resected rectal cancer, comparing rates in those discussed at MDM and those not.

The audit found that those discussed at MDM had a significantly lower rate of CRM involvement than those whom were not discussed at MDM. After a policy of compulsory discussion was instituted, the rate of CRM involvement dropped from 12.5% to 3%. In other cancer types, staging of gastro-oesophageal cancer was most accurate in those whom had discussion at MDM.

Several less measurable benefits are also reported. These benefits include improved treatment planning, improved equity of outcomes for patients with cancer, more patients being offered the opportunity to enter into relevant clinical trials, improved continuity of care and less service duplication, improved coordination of services, improved communication between care providers, optimisation of resources, with effective MDMs resulting in more efficient use of time and resources.

Discussion during the session described MDMs as a vehicle to:

- Drive quality of care—MDMs are a mechanism for collective decision-making. It allows for different potential patient pathways to be discussed. It enables the lead clinician, responsible for the patient’s care to make an informed decision, ensuring all possible options have been explored; and
- As an opportunity to collect valuable information—multidisciplinary teams through MDMs should be responsible for collecting and managing the information related to patients with colorectal cancer.

Some participants raised a concern that MDMs are still not recognised or resourced appropriately, and some regional centres describe difficulty linking with Cancer Centres due to lack of access to, or inadequate quality, video conferencing equipment. MDMs represent a large resource commitment. Given the importance of MDMs in driving quality of care and in collecting required information, it is essential these are appropriately resourced.

Conclusions

Colorectal cancer is a priority cancer in New Zealand. Rectal cancer is particularly complex and requires considerable multidisciplinary collaboration. Evidence demonstrates that Māori and Pacific peoples are at risk of receiving inequitable care.

The National Rectal Summit demonstrated a high level of provider commitment to improving quality of care and equity of access to treatment for all New Zealanders. To improve outcomes, a robust and integrated clinical information system is required to provide contemporaneous, accurate, and comprehensive data on patient characteristics, investigations, treatment, and outcomes. Engagement needs to be comprehensive and involve all providers including those in the private sector.

Rapid advances in science will need to be incorporated into existing treatment paradigms in the near future. The development of high quality patient-level data
coupled with comprehensive tissue collection would be a major research advantage for New Zealand, and could deliver significant short- and long-term improvements in patient outcomes. The infrastructure required to deliver high-quality outcomes for rectal cancer is likely to be of benefit across multiple tumour streams.

By collaboration between policymakers, providers, researchers, and patients, New Zealand is well placed to be a world leader in combating this complex and important disease.

**Competing interests:** Nil.

**Author information:**

- Christopher Jackson, Medical Oncologist, Southern Blood and Cancer Service (Southern DHB), Dunedin; Senior Lecturer in Medicine, Dunedin School of Medicine, University of Otago.
- Nieves Ehrenberg, Managing Consultant, Sapere Research Group, Wellington
- Frank Frizelle, Professor of Surgery, Christchurch School of Medicine, University of Otago, Christchurch
- Adrian Balasingam, Consultant Radiologist, Christchurch Radiology Group and Canterbury DHB, Christchurch
- Diana Sarfati, Associate Professor, Public Health, University of Otago, Wellington
- Maria Pearse, Consultant Radiation Oncologist, Auckland City Hospital, Auckland
- Susan Parry, Clinical Director of the NZ Ministry of Health Bowel Cancer Programme and of the New Zealand Familial Gastrointestinal Cancer Service based at Auckland Hospital, Auckland
- Cristin Print, Associate Professor, Clinical Molecular Medicine & Pathology, School of Medical Sciences, University of Auckland
- Michael Findlay, Professor of Oncology and Director of Cancer Trials New Zealand, University of Auckland, Auckland
- Ian Bissett, Associate Professor, University of Auckland and consultant surgeon at Auckland City Hospital, Auckland

**Acknowledgements and funding:** The Rectal Summit was hosted by the New Zealand Society for Oncology. The meeting was supported by an unrestricted educational grant from Roche Products (NZ). Additional Summit sponsors were CMS Alphatech, Elekta, Merck Serono and Bayer Pharmaceuticals (NZ). Sapere Research was commissioned to assist with drafting of the manuscript. All authors accept responsibility for content of this manuscript.

**Correspondence:** Christopher Jackson, Southern Blood and Cancer, Private Bag 1951, Dunedin 9054, New Zealand. Fax: +64 (0)3 4709689; email: christopher.jackson@southerndhb.govt.nz
References:


Anorectal melanoma: not a haemorrhoid

Greg Turner, Sarah Abbott, Tim Eglinton, Chris Wakeman, Frank Frizelle

Abstract

Aim Melanoma of the anorectum is a rare malignancy which is particularly aggressive compared to cutaneous melanoma. Due to its presenting symptoms, location and rarity there is often a delay in diagnosis. The purpose of this paper is to raise awareness of anorectal melanoma in New Zealand by presenting our institution’s experience of four cases.

Methods The presentation, management and outcomes of four cases are described. A review of the literature surrounding anorectal melanoma was also carried out.

Results The four cases (3 male, 1 female, aged 30–87 years) all presented with haemorrhoidal symptoms of anal discomfort and/or outlet rectal bleeding. Three patients had metastatic disease at presentation, and the remaining patient was found to have a concurrent lymphoma which was treated with chemotherapy before he underwent excision of the melanoma. Surgical excision is the mainstay of treatment and recent literature suggests transanal excision of the primary tumour to have equivalent overall survival to abdominoperineal resection.

Conclusion Anorectal melanoma is rare tumour with a poor prognosis. Patients are commonly misdiagnosed as having haemorrhoids; therefore a high index of suspicion is needed to enable early diagnosis. Metastatic disease is common at presentation, and the key prognostic indicator. Local control can be obtained with transanal excision, avoiding the morbidity of abdominoperineal resection. Adjuvant therapies available at present provide little survival advantage.

Melanoma is commonly thought of as a skin cancer however it may also affect the mucosal surface. Anorectal melanoma is a rare mucosal malignancy which displays particularly aggressive tumour biology compared to cutaneous melanoma.

Due to the location, rarity and variable appearance there is often a delay before the diagnosis is made. Many patients present with rectal bleeding and/or anorectal discomfort, and are often misdiagnosed with haemorrhoidal disease. Thirty percent of anorectal melanomas are unpigmented, contributing to misdiagnosis. Patients may also present with palpable inguinal lymphadenopathy.

The mainstay of treatment is surgery, with abdominoperineal resection historically being the procedure of choice. More recently, with the acknowledgment of the very poor prognosis, trans-anal excision (with or without local radiotherapy) has been shown to provide equivalent oncological outcomes with less morbidity and better quality of life. Survival rates are directly related to stage of disease; and regardless of the extent of resection, the prognosis remains dismal.
We present four cases that have been treated at our institution over 12 years. The aim of this paper is to raise awareness of this rare condition and describe new directions in therapy.

**Case reports**

The four cases to be described are summarised in Table 1 below.

**Table 1. Patient demographics and outcomes**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at diagnosis</th>
<th>Gender</th>
<th>Stage at diagnosis†</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>87</td>
<td>Male</td>
<td>II</td>
<td>Died of disease 13 months after diagnosis</td>
</tr>
<tr>
<td>B</td>
<td>65</td>
<td>Female</td>
<td>III</td>
<td>Alive with metastatic disease 7 months after diagnosis</td>
</tr>
<tr>
<td>C</td>
<td>81</td>
<td>Male</td>
<td>I</td>
<td>Died disease-free 5 years after diagnosis</td>
</tr>
<tr>
<td>D</td>
<td>30</td>
<td>Male</td>
<td>III</td>
<td>Alive with metastatic disease 1 month after diagnosis</td>
</tr>
</tbody>
</table>

† Staging as described by Iddings et al6:

I: Localised disease
II: Regional lymph node involvement
III: Distant metastases

**Patient A** is an 87-year-old male who presented with several months of anal discomfort with associated bleeding per rectum. On examination there was a small mass arising from the anal canal. He underwent examination under anaesthesia and excision biopsy of a presumed anal cancer. Histology confirmed malignant melanoma.

Staging computed tomography (CT) of the abdomen and pelvis and magnetic resonance imaging (MRI) of the pelvis identified left inguinal lymphadenopathy, but no lymphadenopathy in the mesorectal or pelvic nodes. Subsequent fine needle aspiration (FNA) confirmed metastatic melanoma to the left inguinal region. After discussion at the Colorectal Oncology Multidisciplinary Meeting (CMDM) he received radiotherapy to the anus and underwent leftinguinal lymph node dissection.

Restaging PET-CT performed 4 months after diagnosis revealed two new large metastatic left external iliac nodal masses. He received radiotherapy to this area.

Eleven months following diagnosis he developed visible melanoma deposits in the right buttock and perineum, as well as a lesion in the T7 vertebra causing spinal cord compression. He received further palliative radiotherapy to these regions.

Unfortunately his disease continued to progress and he died 13 months after diagnosis.

**Patient B** is a 65-year-old female who presented with rectal bleeding and a sensation of prolapse over approximately twelve months. She was initially diagnosed with haemorrhoids and colonoscopy revealed a 2 cm polyp 1–2 cm from the anal verge.

She underwent transanal excision. Histological examination revealed malignant melanoma. Staging CT revealed an enlarged right inguinal node and a mesorectal...
node, as well as multiple pulmonary and hepatic metastases. After discussion at the CMDM she was referred to Medical Oncology where she was considered for a clinical trial of ipilimumab.

Unfortunately her disease progressed rapidly prior to commencing the trial and at 7 months after diagnosis is not undergoing any further treatment.

**Patient C** is an 81-year-old man who presented with anal discomfort and itch to his GP, who was concerned and referred the patient to a plastic surgeon, who subsequently referred the patient on to a colorectal surgeon.

Colonoscopy revealed a pigmented butterfly-shaped lesion in the anal verge expanding into the anal canal (Figure 1). Biopsy confirmed invasive melanoma. Staging CT showed a large subcarinal mass and further lesions within the spleen and left kidney. FNA of the chest lesion revealed non-Hodgkin lymphoma.

After discussion at the CMDM he underwent R-CHOP\(^3\) chemotherapy to treat the lymphoma with a view to delayed surgical resection of the melanoma. He responded well to chemotherapy and underwent trans-anal excision 10 months after diagnosis. Histology showed melanoma *in situ* but no residual invasive melanoma, consistent with regressed malignant melanoma.

He remained under close clinical follow-up and restaging investigations at 1 year showed remission of the lymphoma and no evidence of metastatic melanoma. He died of other causes 5 years after diagnosis.

**Figure 1. Photograph of Patient C demonstrating a pigmented lesion arising from the anal verge extending into the anal canal (biopsy confirmed invasive melanoma)**
Patient D is a 30-year-old male who presented with a 9-month history of fresh per rectal (PR) bleeding and rectal pain. He was diagnosed with haemorrhoids and referred for a surgical opinion at which point it was noted he had a pedunculated rectal polyp. He underwent colonoscopy which showed no further bowel pathology. Biopsy of the polyp revealed malignant melanoma. He underwent transanal excision for diagnostic and therapeutic purposes. At surgery it was noted to be approximately 3 cm in size, pedunculated and arising from the anorectal junction. The histology is demonstrated in Figure 2.

**Figure 2. Low magnification micrograph of polyp demonstrating extensive infiltration of anorectal mucosa and the submucosal stalk (the malignant cells are positive for Melan-A and SOX-10 immunohistochemical stains in keeping with malignant melanoma)**

Postoperatively he underwent a staging CT which showed extension of the primary tumour into the right mesorectal fat with surrounding local lymph nodes, extensive hepatic metastatic disease (Figure 3) as well as possible small bowel and pulmonary metastases. The patient was referred to Medical Oncology and intends to participate in a clinical trial of ipilimumab.
Discussion

Anorectal melanoma is a rare tumour, accounting for less than 1% of all colorectal malignancies. It was first described in 1857 by Moore and accounts for only 2% of all melanomas, yet is the third most common primary location for such tumours, surpassed only by skin and eyes. Between 22–30% of anorectal melanomas are amelanotic and this is associated with a worse prognosis.

The overall prognosis for anorectal melanoma is poor. Cagir et al. reported 177 cases of anorectal melanoma from the SEER database diagnosed between 1973–1992. They found anorectal melanoma accounted for 0.05% of all colorectal tumours diagnosed in that period, and demonstrated overall survival rates of 56% and 15% at one and five years respectively, with a mean overall survival of 15 months.

This condition occurs most often in the 6th and 7th decades of life, and despite our patient series, there is a reported higher rate in females (2.2:1).

Patients most commonly present with rectal bleeding and/or anal discomfort, and are commonly misdiagnosed as having haemorrhoids.

Staging—Melanoma is excluded from the AJCC staging system for anal cancers. Some series stage disease as localised (stage I), regional lymph node involvement (stage II) or distant metastatic disease (stage III).

Between 15 and 24% of patients have distant metastases at the time of diagnosis, similarly there is an even higher rate of regional lymph node involvement.

Iddings et al. described the prognostic significance of lymphatic metastases. They reported 142 cases of anorectal melanoma, of which 60% had localized disease at
presentation, 19% with regional lymph node involvement, and a further 21% with distant metastases.

Outcome was directly related to disease stage, with median survival of 24 months, 17 months and 8 months respectively (Table 2). Furthermore they reported mesorectal lymph node involvement to be uncommon, with most lymphatic disease found in the inguinal regions.

### Table 2. Survival outcomes of anorectal melanoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Median survival (months)</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Localised disease</td>
<td>24</td>
<td>26.7%</td>
</tr>
<tr>
<td>II Regional lymph node involvement</td>
<td>17</td>
<td>9.8%</td>
</tr>
<tr>
<td>III Distant metastatic involvement</td>
<td>8</td>
<td>0%</td>
</tr>
</tbody>
</table>

Survival outcomes for Anorectal Melanoma by stage for 143 patients, Iddings et al.

**Anatomic considerations**—Bello et al.\(^\text{10}\) report little effect on prognosis whether the melanoma arises from the rectum, anorectal transitional zone or the anus. Tumours arising from the rectum and anorectum had a median Breslow thickness of 12mm and 8mm respectively, compared to a median Breslow thickness of 6.5mm in those arising from the anus.

Nearly two-thirds of tumours in the rectum or anorectum recurred systemically, whereas anal melanomas more often recurred in the regional lymph nodes. Overall median survival was 27 months for rectal tumours, 28 months for anorectal tumours, and 22 months for those arising from the anus. There was no statistically significant difference between survival or recurrence with anatomic location.

**Surgical treatment**—The primary treatment modality for anorectal melanoma is surgery. There has been some debate in the literature regarding the procedure of choice. Abdominoperineal resection (APR) is commonly performed, but more recent evidence has shown trans-anal excision (TAE) to offer equivalent survival with significantly less morbidity.\(^\text{2,6,9,11}\)

In view of the higher prevalence of inguinal rather than mesorectal lymph node metastases, some advocate sentinel lymph node biopsy alongside TAE.\(^\text{12}\) This approach is well established in the management of cutaneous melanoma but its role in anorectal melanoma is less clear;\(^\text{13-15}\) however PET-CT may be more helpful and less invasive.

Series reporting TAE have not observed high rates of isolated local recurrence.\(^\text{16-18}\) Yeh et al.\(^\text{19}\) report the rate of isolated local recurrence is comparable regardless of whether undergoing TAE or APR. They hypothesise systemic dissemination is an early event in tumorigenesis so by the time the primary lesion is clinically apparent, micrometastases are well established. Pessaux et al.\(^\text{2}\) advocate APR for salvage surgery in the rare instance of isolated local recurrence.

**Adjuvant therapy**—Radiotherapy and chemotherapy are generally reported to be of limited value in anorectal melanoma.\(^\text{2,9}\) Radiotherapy may have a role in local control as shown in patient A.
Kelly et al\textsuperscript{20} report radiotherapy having a role in maintaining local control following sphincter preserving surgery, however found little benefit for overall survival. Hay et al\textsuperscript{21} describe one case of an elderly patient deemed unfit for surgery who underwent external beam radiotherapy with an excellent response, with no signs of recurrence or distant spread at 12-month follow-up.

**Targeted therapies**—A better understanding of the molecular pathogenesis of mucosal melanoma (including anorectal melanoma) is leading to development of potential targeted therapies, particularly to slow progression of advanced disease. A proportion of mucosal melanomas will have an identifiable mutation in BRAF or KIT genes (both recognised proto-oncogenes), however the rate is significantly lower than cutaneous melanoma.\textsuperscript{22}

Small trials have shown a potential role for imatinib (a tyrosine kinase inhibitor) in those with an identified KIT gene mutation, with 23–54\% of patients with metastatic melanoma showing partial response.\textsuperscript{23,24}

Vemurafenib (a BRAF inhibitor) has shown improved survival in metastatic cutaneous melanoma, however there is no evidence for its use in mucosal melanoma at present.\textsuperscript{25}

Ipilimumab (a monoclonal antibody directed at CTLA-4—thought to be a tumour-associated antigen) has been investigated for treatment of metastatic mucosal melanoma,\textsuperscript{26} however the response to treatment has not been dramatic in studies conducted to date.

**Conclusion:**

Anorectal melanoma is a rare tumour with a poor prognosis. Patients are commonly misdiagnosed as having haemorrhoidal disease and a significant number of lesions are amelanotic, therefore a high index of suspicion is needed to enable early diagnosis and treatment while the lesion is still potentially curable.

Metastatic disease is common and is the key determinant of overall survival. Local control can be effectively achieved with transanal excision, sparing patients the morbidity of abdominoperineal resection. Adjuvant systemic therapy options available at present provide little survival advantage.

**Competing interests:** Nil.

**Author information:** Greg Turner, Surgical Registrar, Department of General Surgery, Christchurch Hospital, Christchurch; Sarah Abbott, Surgical Registrar, Department of General Surgery, Christchurch Hospital, Christchurch; Tim Eglinton, Colorectal Surgeon and Associate Professor, Department of General Surgery, Christchurch Hospital and University of Otago, Christchurch; Chris Wakeman, Colorectal Surgeon and Clinical Senior Lecturer, Department of General Surgery, Christchurch Hospital and University of Otago, Christchurch; Frank Frizelle, Colorectal Surgeon and Professor of Surgery, Department of General Surgery, Christchurch Hospital and University of Otago, Christchurch

**Acknowledgements:** The authors thank Dr Wendy McBurnie for contributing the histology image and description included in this paper.
**Correspondence:** Professor Frank Frizelle, Department of General Surgery, Christchurch Hospital, Private Bag 4710, Christchurch 8140, New Zealand. Fax: +64 (03) 364035; email: Frank.Frizelle@cdhb.health.nz

**References:**

5. Moore WD. Recurrent melanosis of the rectum, after previous removal from the verge of the anus, in a man aged sixty-five. Lancet. 1857;1:290


Pseudotumours and IgG4-related disease: a case report

Paul Tan, Graeme Taylor, Rennae Thiessen, Lutz Beckert

Abstract

We report a case of a patient presenting with abdominal pain, weight loss and CT imaging showing mass lesions in the chest and abdomen associated with lymphadenopathy. He was diagnosed as having IgG4-related disease and responded well to steroid treatment.

Case report

A 77-year-old man with known idiopathic non-specific interstitial pneumonia presented with a 3-week history of epigastric discomfort, anorexia and weight loss of 7 kg.

Clinical examination revealed mild epigastric tenderness without evidence of organomegaly or palpable lymphadenopathy. His full blood count and biochemistry tests were within normal limits except for elevated serum lipase of 324 U/L (normal range 8–78 U/L) and marginally elevated amylase of 58 U/L (normal range 8–53 U/L).

A chest X-ray revealed a right hilar lesion. His CT chest abdomen and pelvis showed chest and abdominal lymphadenopathy and mass lesions in the right lung and both kidneys. These findings were thought to be consistent with disseminated malignancy or lymphoma.

The patient underwent an EBUS guided fine needle aspiration of his subcarinal and right hilar lymph nodes followed by a core biopsy of the abdominal paraaortic lymph node/lesion. No malignant cells were seen in any samples.

Core biopsy histology showed a fibroinflammatory process associated with obliterative phlebitis and >30 IgG4 positive plasma cells per high power field in keeping with IgG4 related disease.

Subsequently his serum IgG4 levels were found to be elevated at 3.03g/L (range 0.03–2.01) and he was started on prednisone therapy, 0.5 mg/kg with a tapering regimen.

He made good symptomatic recovery with radiological improvements on serial CT scanning and reductions in his IgG4 levels to 1.52 g/L.
Figure 1. Serial CT scans showing resolution of abdominal paraaortic lymphadenopathy following prednisone therapy (see arrow)

Figure 2. Histology, left to right: Core biopsies showed fibrosis and lymphoplasmacytic infiltrates (H&E stain, magnification ×40); focally there was obliterative phlebitis (Elastic van Geison stain, magnification ×100) and there were >30 IgG4 positive plasma cells per high-power field (IgG4 immunostain, magnification ×200)

Discussion

IgG4-related disease is a fibroinflammatory entity that was only recognised to have systemic manifestations in the last decade.\textsuperscript{1,2} Conditions such as Riedel’s thyroiditis and Type 1 autoimmune pancreatitis are now considered to be part of the spectrum of IgG4-related disease.\textsuperscript{1}

Clinical presentations are dependent on the organ involved and patients can present with mass lesions that may be mistaken for malignancy, such as was the case in this instance. Tumefactive lesions have been described in many organs systems including...
the kidneys, pancreas, lungs, salivary glands, lymph nodes, thyroid and periorbital regions.\textsuperscript{3,4,5}

IgG4 has also been described to cause a NSIP pattern on CT scanning.\textsuperscript{3,6} In our case the NSIP pattern on radiology was thought to be independent as it remained stable for a period of 4 years and was uninfluenced by the prednisone course.

The diagnosis of IgG4-related disease is made on tissue biopsies showing lymphoplasmacytic infiltrates, a storiform pattern of fibrosis, obliterative phlebitis and increased numbers of IgG4 plasma cells.\textsuperscript{7}

There is a paucity of data regarding the use of serum IgG4 levels in extrapancreatic manifestations of IgG4 related disease for diagnosis or disease activity monitoring. However in IgG4 related autoimmune pancreatitis, elevated IgG4 levels have been reported to have a diagnostic sensitivity of 76% and specificity of 93%.\textsuperscript{8}

The role of serum IgG4 levels in monitoring for disease activity is unclear. Kamisawa et al\textsuperscript{9} identified that 30% of patients with elevated serum IgG4 in spite of treatment relapsed versus 10% in patients with normal serum IgG4 levels.

The optimal treatment for this condition has not been established but patients typically respond well to oral glucocorticoid therapy with symptomatic and radiological improvements. Other immunosuppressive drugs such as azathioprine and mycophenolate are used, but have not been well studied, and for the most part the natural history of patients with this condition is not well defined.

\textbf{Competing interests:} Nil.

\textbf{Author information:} Paul Tan, Respiratory Physician, Department of Respiratory Medicine, Christchurch Hospital, Christchurch; Rennae Thiessen, Radiologist, Department of Radiology, Christchurch Hospital, Christchurch; Graeme Taylor, Pathologist, Department of Pathology, Nelson Hospital, Nelson; Lutz Beckert, Respiratory Physician, Department of Respiratory Medicine, Christchurch Hospital, Christchurch

\textbf{Correspondence:} Lutz Beckert, Department of Respiratory Medicine, Christchurch Hospital, Christchurch 8011, New Zealand. Fax: +64 (0)3 3640914; email: lutz.beckert@cdhb.health.nz

\textbf{References:}


Missed melanomas

On 6 May 2013 my eldest son aged 52 died following a Grade IV metastatic brain melanoma. Marc will always be deeply loved and missed by his children, family and many friends. He was also a very caring and popular Christchurch dentist, a keen sportsman and a musician. As his still grieving father, it is only now that I am able to write this, in the hope that others will not suffer a similar, avoidable and terrible premature death.

Four years ago Marc visited his Christchurch GP, concerned about a lump on his scalp. It was dismissed as being of no importance. Several months later he returned as it had increased in size and was interfering with his surgical loupes. He was again told it was unimportant, so he decided to consult a surgeon, where a biopsy showed the lesion was a melanoma. Major neck and sentinel node dissection found no lymphatic involvement, but symptoms earlier this year showed widespread melanoma (Stage IV) in his brain, which had presumably spread earlier via the cerebral circulation.

Sneyd and Cox\(^1\) noted that in 2007 one person died of melanoma every hour in the USA, but that early diagnosis and treatment could lead to a 5-year survival rate of 99%.

New Zealand has a much higher rate than the US, and early detection here is very poor. Since my son’s death, a former classmate at Otago was recently found to have a lesion in the same location. This too was not taken seriously by his GP, who made a small incision and then announced it was nothing to worry about. Again, no biopsy was undertaken. Fortunately he visited a surgeon friend who diagnosed melanoma. This was removed and also followed by sentinel biopsy, which also showed no metastases. Hopefully, the diagnosis was earlier than in my son’s case, but not thanks to his primary caregiver.

The same week as my son’s funeral, front-page publicity in the *The Dominion Post* documented yet another fatal melanoma case, this time in a recent immigrant South African ultra-marathon runner with a young family.\(^2\) When he visited his local GP he noticed a black lump in his axilla, who again failed to treat it seriously. Six months later he was dead. The Health and Disability Commissioner ruled his death from melanoma was due to a lack of proper follow-up care by his New Zealand GP. But despite this, and the opinion of melanoma expert Richard Martin, an ACC medical “expert” ruled that it could not be proven that a proper follow-up would have prolonged his life. His wife and young family received no compensation.

Having lived and worked in both Canada and the United States on two occasions, I have now reached the conclusion there may be more merit in their adversarial system than in the lumbering, expensive and heartless monstrosity ACC has become. At least the North American, Australian and other medical systems expect incompetent health providers to be accountable. Surely, this is better rather than running for cover under ACC and walking away with no responsibility, possibly to repeat their errors.
Ironically, in New Zealand, it is now the lawyers who are now suing ACC, where our no-fault system was originally supposed to help and care for those who suffered from medical “misadventure”. I have personally been requested for opinions in such cases. Let us call a spade a spade. This is not always misadventure, it is often negligence, and it appears to be on an increasing scale.

New Zealand has a very high incidence of melanoma. It has been clearly proven that early detection means increased survival rates for many who contract this dreadful condition. It is of the utmost importance that all physicians and other health professionals have (or learn) the diagnostic skills necessary to identify early melanomas, and if necessary refer patients for further appropriate evaluation and treatment. Ignorance is no excuse.

I trust this message will be taken on board, and my son can rest in peace.

Peter A Foreman BDS (Otago), FACD, FAGD, FADSA, Dip AAPM (USA)
Pain Management Consultant (part time)
Formerly ADHB (Auckland Regional Pain Service)
Auckland, New Zealand

References:
Update from the New Zealand Familial GI Cancer Service

Dear Colleagues

In view of some of the changes at the NZ Familial GI Cancer Service and in the world of familial GI cancer over the past few years, we thought a letter outlining these may be helpful.

Firstly we changed our name from Registry to Service. The rationale for this change was to reflect the fact that now, in addition to assessing and “registering” families (for whom we co-ordinate surveillance) we are increasingly being asked to provide management advice for individuals and families, registered or otherwise.

In addition we now have branches in Auckland, Wellington and Christchurch. A/Prof Susan Parry, Gastroenterologist, continues as our National Clinical Director/ Medical Advisor in Auckland with Mr John Keating, Colorectal Surgeon our Medical Advisor in Wellington and Dr Teresa Chalmers-Watson, Gastroenterologist and Mr Chris Wakeman, Colorectal Surgeon, our Medical Advisors in Christchurch.

Lynch Syndrome

Aspirin as a chemopreventative agent—We are now recommending aspirin, if appropriate, to all those who carry a Lynch Syndrome mismatch repair gene mutation. This follows the Lancet 2011 publication (Vol. 378:2081-87) of the first randomised trial of aspirin as a chemoprevention agent with cancer as the primary end point (CAPP2 study). The long-term data showed no significant difference in time to first colorectal cancer in the intention to treat analysis. However, the per-protocol analysis revealed a significant difference with a hazard ratio of 0.41 (p=0.02) providing clear evidence of the effectiveness of aspirin as a chemo-preventative agent in this group via a delayed effect on CRC. We have opted to recommend low dose Aspirin (100-300mg) rather than the high dose aspirin used in the trial because of the potential side effects. The CAPP 3 trial which will help to answer this question is due to start shortly.

Interval cancers—Despite frequent colonoscopic surveillance, interval colorectal cancers are documented in Lynch Syndrome patients. Unfortunately in NZ over the last year we have had three such CRC’s in Lynch Syndrome patients undergoing annual colonoscopy – these procedures have been performed in both large and small centres and by highly regarded endoscopists.

A paper by Vasen H et al in Gastroenterology 2010;138:2300 -2306 documented a cumulative CRC risk of 6% after 10 year follow-up of 205 families with Lynch Syndrome undergoing 1-2 yearly colonoscopy. Parry S et al in Gut. 2011 Jul;60(7):950-7 reported the cumulative metachronous CRC risk for 332 MMR gene mutation carriers undergoing regular colonoscopy, following a segmental resection for CRC, to be 16% at 10 years, and 41% at 20 years. This compared with no metachronous CRC in those who had extensive colectomy as the initial cancer operation.
This highlights the need for great care when undertaking surveillance colonoscopy in patients with proven or presumed Lynch Syndrome but it also highlights the need to discuss the role of more extensive surgical resection when an MMR carrier is diagnosed with their first CRC.

**Extra-colonic cancers**—For all new patients diagnosed with Lynch Syndrome we are now writing to their General Practitioners and specialists involved in their care including Gynae-Oncologists and Urologists to make them aware of this diagnosis and the need for awareness of the increased risk of extra-colonic cancers/surveillance as per the National Guidelines for Gynaecological and Urological malignancy.

**Familial Adenomatous Polyposis (FAP)/MutYH Associated Polyposis (MAP)/Serrated Polyposis Syndrome (SPS)**—There is now more of an emphasis on cumulative polyp count for both adenomatous and serrated/hyperplastic polyps. An increasing adenomatous polyp count over years may lead to genetic testing for Attenuated FAP and MYH associated polyposis.

New guidelines and criteria are being developed in conjunction with the Genetics Service. For hyperplastic/serrated polyps an increasing cumulative count may also lead to a diagnosis of the Serrated Polyposis Syndrome (SPS) and a change in the recommended surveillance intervals for the patient and their first degree relatives. We are happy to provide advice on surveillance intervals or engage in discussion re the appropriateness, timing and optimal extent of resection for patients with polyposis.

We are also recommending that all FAP and MAP patients have annual thyroid examinations. There is a slightly increased risk of thyroid cancer in these patients but there is no worldwide consensus on thyroid screening. The Cleveland Clinic recommend annual ultrasound but the British favour annual manual examination. Screening ultrasound potentially picks up non-significant lesions leading to a cascade of investigations and treatment which may not be needed and may cause complications.

**Patient/family education**—Our Christchurch branch is planning patient & family information sessions this year. Our Auckland branch ran sessions for both Lynch Syndrome and FAP/MAP patients/families at the end of last year and these were well attended and well received. We hope to have a separate Doctors education session in the next year.

The National Guidelines relating to colorectal cancer risk and recommended surveillance are on the Ministry of Health website [www.health.govt.nz](http://www.health.govt.nz) and our Service website [www.nzfgcs.govt.nz](http://www.nzfgcs.govt.nz) contains patient information on Lynch Syndrome, FAP/MAP and SPS along with our contact details.

Please feel free to contact us at anytime.

**Chris Wakeman, John Keating**
Colorectal Surgeons

**Susan Parry, Teresa Chalmers-Watson**
Gastroenterologists

New Zealand Familial GI Cancer Service
Auckland Office
Phone: +64 (0)9 3078991
Measurement of cigarette butt litter accumulation within city bus shelters

Background—Transportation settings such as bus stops are increasingly the target for new smokefree area policies, including in New Zealand (e.g. plans by Auckland City Council). Relevant issues for considering smokefree settings include secondhand smoke (SHS) exposure, nuisance, litter, fire risks and the normalisation of smoking. National survey data in New Zealand indicates that SHS exposure at a bus stop or train station is regularly reported. Other data indicates that public transport users report nuisance and health concerns around being exposed to SHS in these settings. Previous work has found markedly elevated levels of fine particulates from tobacco smoke in New Zealand bus shelters that were enclosed and partially enclosed. In two studies we found that a majority of smokers litter their cigarette butts, including at bus stops. In the survey presented here we attempted to new approach to studying the smoking at bus stops problem—by measuring cigarette butt litter and its accumulation rate.

Methods—The study area was a convenience sample of three major bus routes in Wellington City (largely around the researchers routine travel to work). “Bus shelters” were defined as discrete structures at bus stops with at least three walls and a roof (i.e. excluding partially sheltered bus stops that have some protection from surrounding buildings or overhanging shop roofing).

The three distinct areas of interest in terms of butt litter were the:

(i) Shelter floor (as defined by the shelter walls);
(ii) Rectangular area of footpath extending directly from the shelter to the street curb; and
(iii) Street gutter directly in front of the shelter (as defined by the concrete surfacing vs asphalt surfacing of the road).

At bus stops without a shelter, the bus stop area was defined as that extending 6 metres from the bus stop signpost (in the direction of the bus arrival). In these cases there were two distinct areas surveyed: (i) the rectangular area of footpath extending 6 metres from the sign post to the street curb; (ii) the street gutter extending 6 metres behind the signpost. This area ran parallel to the footpath section surveyed.

On day 1 of the sampling we counted all the cigarette butts in the above areas for all the bus stops on the selected routes (on either side of the road). Then all these identified butts were removed. Day 2 of the sampling followed exactly the same route as on day 1, with sampling of the bus stops being as close to 24-hours later as possible.

The sampling days were all on weekdays and we selected periods where the weather forecast was for no rain and with wind velocities all being <35 km per hour.
(according to the MetService forecast for the city). Sampling took place at non-peak commuting times when shelters were largely unoccupied.

**Results**—There was no evidence of cleaning or any other kind of bus stop maintenance between observer visits to the bus stops. During the second data gathering period, certain litter items were very frequently recalled and recognised from the first observation period. On average, 0.5 new items of litter (excluding butts) appeared per stop (range: -2 to 3 items), with only 12.9% of the stops (4/31) showing a reduction in litter counts.

A total of 314 cigarette butts were identified and removed in the baseline survey, and 123 new butts were identified in the repeat survey at 24-hours (Table 1). More new butts accumulated in the gutters compared to bus shelter floors (p=0.005), or on the adjacent pavement (p<0.0001, Student’s two-tailed t-test). Somewhat unexpectedly, bus shelters with gaps between the walls and the floor had a significantly greater accumulation of new butts, compared to shelters where the walls and floor were connected (2.2 vs 0.7 new butts p=0.014).

On average, 2.5 new butts accumulated at bus stops with a rubbish bin less than 5 metres from the bus shelter or sign post (tabulated data available on request). In contrast, bus stops with no bin in sight accumulated an average of 1.3 new butts, though this difference was not statistically significant (p=0.062).

**Table 1. Cigarette butts at bus stops at the baseline survey and accumulating after 24-hours**

<table>
<thead>
<tr>
<th>Area at the bus stops</th>
<th>Baseline (with all the butts subsequently removed)</th>
<th>New butts at the point of 24-hours after the baseline survey</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of areas* with any butts (%)</td>
<td>No. of butts</td>
</tr>
<tr>
<td>Bus shelter floor (n=34 shelters)</td>
<td>13 (38)</td>
<td>61</td>
</tr>
<tr>
<td>The pavement directly in front of the shelter, or for open bus stops, 6 metres from the bus stop signpost (in the direction of the bus arrival) (n=67)</td>
<td>21 (31)</td>
<td>57</td>
</tr>
<tr>
<td>The gutter directly in front of the shelter, or for open bus stops, 6 metres from the bus stop signpost (n=67)</td>
<td>52 (78)</td>
<td>196</td>
</tr>
<tr>
<td><strong>Total – all of the above areas (n=168)</strong></td>
<td><strong>86 (51)</strong></td>
<td><strong>314</strong></td>
</tr>
</tbody>
</table>

**Discussion**—This study suggests that it is feasible to assess cigarette butt accumulation at bus shelters in a systematic way. Therefore this type of method (in terms of before and after studies) could be used to study the impact of interventions such as the introduction of no-smoking signage at bus stops and policies requiring smokefree bus stops.

This study also provides additional evidence that smoking regularly occurs at bus stops and that smokers frequently litter their butts (including within bus shelters).

These findings are consistent with two previous New Zealand studies of smokers discarding their butts.5,6 This level of littering appears to be unrelated to the
availability of, and proximity to, rubbish bins. Nevertheless, the results we obtained will probably underestimate smoking at these bus stops, since we will have missed butts from smokers: (i) who did dispose of butts appropriately (in rubbish bins); or (ii) who disposed of butts in places outside of our study areas (e.g., to the sides or behind the shelter, onto the road and not in the gutter, or down drains).

Acknowledgement: The authors acknowledge Dr Nevil Pierce for his assistance with the statistical analyses.

Jane Oliver, George Thomson, Nick Wilson
Department of Public Health
University of Otago Wellington
Wellington, New Zealand
olija865@student.otago.ac.nz

References:


Does one size fit all? National elective operation hospital discharge rates may not be a good fit for all New Zealand district health boards

Background—In New Zealand, the Ministry of Health frequently uses national elective rates to calculate the number of operations that will be needed each year. Furthermore it uses this to advocate for an increase or decrease in the number of operations per district health board (DHB) accordingly.

The idea behind this calculation is that New Zealanders have similar needs whereby the only differences are due to age, gender, ethnicity and New Zealand deprivation (NZDep) distribution among the DHBs.

Health survey data in the year 2011/2012 clearly showed that there were huge differences between DHBs for most of the parameters investigated including smoking rates, obesity and overweight rates, physical activity rates, healthy nutrition, cholesterol and hypertensive medication use.\(^1\,^2\,^6\) These factors all work as risks explaining most, if not all, elective operation volumes across each DHB.\(^1\,^2\,^6\)

Hip and knee replacement are strongly linked in literature to obesity.\(^1\,^2\) In addition, these can be linked to almost all other risk factors that are explored in the health survey.\(^1\)

Angiograph, angioplasty, coronary bypass, cholecystitis and cataracts are linked to almost all the above risk factors.\(^5\) In addition, even ones which seem far away from these risk factors, such as prostate and hernias, have shown, through studies, to have a close relationship with the above risk factors.\(^2\,^3\,^5\,^6\)

If these risk factors have indirect, if not direct effect on the need for operations, and hence the number, and the risk factors vary extensively between DHBs, then why do all DHBs have the same national rate?

Standardising the rate by age, gender, ethnicity and NZDep will not address the issue of the discrepancy due to these risk factors.

Conclusion—Having a different elective operation rate for each DHB will be more reliable and efficient than having one national rate for all.

Mazin Ghafel Almurrani
Planning and Funding
Auckland / Waitemata District Health Board
Mazing@adhb.govt.nz
Auckland, New Zealand

References:
Hospital fees

Excerpt from "Dominion Notes” published in NZMJ September 1913;12(47):555–556.

To a deputation which waited upon him recently, the Inspector-General of the Health Department (Dr. T. H. A. Valintine) expressed the opinion that more should be done in the way of collecting hospital fees from persons well able to pay them. His views in regard to this matter, with a suggested remedy, were embodied in a circular read at a meeting of the Wellington Hospital and Charitable Aid Board.

In the circular Dr. Valintine drew attention to the following matters:—

(1) The growing tendency on the part of persons who are well able to pay ordinary medical and nursing fees to seek admission to the public hospitals of the Dominion;

(2) that this tendency has necessitated hospital boards largely increasing the accommodation for all classes or sickness;

(3) that; not without reason, many local authorities are protesting at the gradually increasing expenditure, especially on the part of persons who can pay the whole or part of the cost of their maintenance;

(4) that it is necessary for boards to look to an increase in the revenue to be derived from maintenance fees to meet the growing cost of our institutions rather than to an increase in the levies on local authorities;

(5) that many hospital boards have not made a serious effort to augment the income to be derived from the first-named source;

(6) that there is no uniformity with regard to the maintenance fees charged by the various boards.

"In view of the above," the Inspector-General continued, "I would suggest that the boards of the Dominion adopt a uniform maintenance fee of £3 3s. per week. This need not entail hardship on those who cannot afford to pay the full or even part of the fee, as it is quite within the powers or a board (vide section 70) to charge persons according to their means for treatment received, and to make a rebate in the case or any person unable to pay the full maintenance fee. Each case should be dealt with on its merits as the officers appointed by the boards to enquire the ability or patients to pay fees may advise. I submit with all confidence that much can be done to increase the income to be derived from maintenance fees without in any way inflicting hardships. More rigorous enquiries should also be made as to the means of those applying for admission to our institutions, as the beds should undoubtedly be reserved for those who are not in a position to pay the ordinary fees for medical and nursing attendance.”
Validation of DNA methylation biomarkers for pre-eclampsia. I Knarston¹, E Macaulay¹,², H Roberts¹,², T Slatter¹,², N Hung¹,², C Devenish³, I Morison¹,².
¹Department of Pathology, Dunedin School of Medicine, University of Otago, Dunedin, ²Gravida: National Centre for Growth and Development, Auckland, ³Women’s and Children’s Health, Obstetrics and Gynaecology, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand.

Preeclampsia (PE) is a dangerous condition of pregnancy associated with abnormal placental development. Studies indicate that epigenetic modifications to the placenta may increase women’s susceptibility to PE. DNA methylation is an important epigenetic modification that alters gene expression by the addition of a methyl group to cytosine residues adjacent to guanines (CpG sites). Reduced Representation Bisulfite Sequencing (RRBS) was performed prior to this study to identify CpG sites that are differentially methylated in PE versus control placenta. This study aimed to validate the differential methylation of a selection of CpG sites that were identified by RRBS in order to determine their suitability as epigenetic biomarkers of PE.

Differentially methylated CpG sites across 20 genes were interrogated by Sequenom MassARRAY to validate the RRBS results. Sequenom is a highly quantitative assay that measures individual CpG-site methylation. Amplicons were designed to cover candidate CpG sites and 30 placental samples were analysed (15 PE and 15 control). Sequenom and RRBS data was compared to determine successful validation.

Data analysis revealed that accurate prediction of methylation depends on RRBS sequencing coverage. Using stringent filtering criteria (e.g. RRBS reads ≥ 20), differential methylation can be validated for these candidate genes. For example, a CpG site in CPLX1 displayed a validated difference in mean methylation for PE versus control placenta (12.1% by Sequenom, \( P = 0.054 \) and 9.9% by RRBS, \( P = 0.059 \), unpaired Student’s \( t \)-test). Furthermore, Sequenom was able to identify 9 additional CpG sites, among 5 genes, showing differential methylation between PE and control, ranging from 6-35%, \( P < 0.05 \).

This study confirmed differential methylation in pre-eclampsia at numerous CpG sites across the genome, and may discover epigenetic biomarkers for this placental disease. Current work examining the changes in gene expression will reveal if these methylation changes are likely to be functional.
COMMD10 is important for zymogen granule formation in AR42J pancreatic acinar cells. I Malahay, T Cheung, L Bright, F McDonald. Department of Physiology, Otago School of Medical Sciences, University of Otago, Dunedin.

Pancreatitis is caused by defects in protein trafficking or premature activation of pancreatic digestive enzymes leading to self-destruction and inflammation of the pancreas. COMMD10 is a novel protein which may assist formation or delivery of premature digestive enzymes to zymogen granules (ZGs) in pancreatic acinar cells. This process is defective in pancreatitis. This study aimed to develop a pancreatic acinar cell model to image ZGs, and identify whether COMMD10 influences ZG formation.

AR42J pancreatic acinar precursor cells were treated with vehicle or 10 nM or 100 nM dexamethasone to promote formation of ZGs. For immunocytochemistry AR42J cells were reverse-transfected with COMMD10-siRNA or control siRNA. Cells were then treated with 10n M dexamethasone for 72 hours, fixed, immunostained for the ZG enzyme carboxypeptidase A (CPA) and visualised using conjugated Alexa Fluor-488™. AR42J cells expressing CPA-positive ZGs were counted and expressed as a percentage of total cells.

AR42J cells treated for 72 hours with both 10 and 100 nM dexamethasone successfully formed zymogen granules. In COMMD10 knockdown AR42J cells there was a significant decrease in the proportion of cells producing CPA-positive ZGs (22 % ± 4.1) compared to both wild-type (38 % ± 1.7, P < 0.01 unpaired Student’s t-Test) and mock transfected cells 36 % ± 2.9, P < 0.005, unpaired Student’s t-Test), n=268-1774. Moreover, the proportion of cells forming CPA ZGs was not significantly different between wild-type and mock transfected cultures (P > 0.05, unpaired Student’s t-Test).

Therefore COMMD10 is a protein influential in zymogen granule formation in pancreatic acinar cells, and further study will aid in understanding the process of digestive enzyme secretion by the pancreas. Building a model for pancreatic secretion will contribute to deciphering the mechanistic basis of pancreatitis.

Increased CD163 expression defines a subgroup of glioblastoma multiforme. K Ward-Hartstone1, A Taha2, N Hung3, R Kemp1, T Slatter3. 1Department of Microbiology and Immunology, Otago School of Medical Sciences, 2Department of Surgical Sciences, 3Department of Pathology, Dunedin School of Medicine, University of Otago, Dunedin.

Glioblastoma multiforme (GBM) is a high-grade brain tumour, with a poor median patient survival of 15 months. Glioblastoma multiforme can be separated into three subgroups based upon the mechanism used to maintain the tumour telomere length. Approximately 40% of tumours are positive for telomerase (TEL), 20% of tumours are negative for telomerase and instead use an alternative telomere lengthening mechanism (ALT), and in 40% of tumours the telomere maintenance mechanism is unknown (non-determined telomere maintenance mechanism, NDTMM). These three subgroups are associated with different patient prognoses and therapeutic responses. Data from a transcriptome analysis of eight GBMs collected in Dunedin suggested that ALT positive tumours had a more pro-inflammatory phenotype compared to TEL.
positive tumours. In particular the monocyte/macrophage marker CD163 was increased in ALT GBMs. The aim of this study was to confirm that ALT positive GBMs had increased CD163, compared to other subtypes of GBM.

Paraffin embedded brain tumours from 31 patients (7 ALT, 15 NDTMM and 9 TEL) were sectioned and CD163 was detected using immunohistochemistry and light microscopy. The percentage of tumours positive for CD163 was determined for each GBM subgroup.

Not only was there increased CD163 protein expression in ALT positive brain tumours compared to the other subgroups, but in 80% of the patients the cells that were positive for CD163 were those surrounding tumour cells. This pattern was not seen in the TEL positive tumours and was only present in 9% of NTDMM tumours.

This study has confirmed the transcriptome finding that CD163 is more highly expressed in the ATL tumours compared to other subgroups. It now needs to be determined if these CD163 expressing cells surrounding the tumour cells can be used as a prognostic indicator or as a diagnostic target to treat ATL positive tumours.

Measuring pulsatile luteinizing hormone secretion in a prenatal androgen treated model of polycystic ovarian syndrome. C Marshall, M Prescott, R Campbell. Centre for Neuroendocrinology and Department of Physiology, Otago School of Medical Sciences, University of Otago, Dunedin.

Polycystic ovarian syndrome (PCOS) is the most common cause of infertility, affecting up to 10% of adult women, and is associated with an increased pulsatile luteinising hormone (LH) secretion. Prenatal androgen (PNA) treatment is known to induce a PCOS-like phenotype in female mice. However, to date, it has been impossible to demonstrate whether PNA treated mice have abnormal pulsatile LH secretion patterns, due to the large volume of blood required for LH detection. The present study aimed to determine whether PNA treated mice have abnormal LH pulsatility using a recently developed assay that uses small volumes of serial blood samples.

Pregnant dams were injected with dihydrotestosterone (PNA treated group) or a sesame oil vehicle (vehicle treated group) at embryonic days 16, 17 and 18. Female offspring of treated dams were studied in adulthood where serial blood samples (5 µL) were collected every 10 minutes over a three-hour period. The LH in each sample was detected by the enzyme-linked immunosorbent assay (ELISA) to measure LH concentration over time, in order to compare the pattern of LH secretion.

PNA treated mice in diestrus were found to have significantly higher LH pulse frequency (2.40 ± 0.24 pulses, mean ± SEM, n = 5) than vehicle treated mice in diestrus (1.50 ± 0.29 pulses, n = 4, P < 0.05, unpaired Student’s t-test) over a 120 minute sampling period.

This work provides the first evidence for increased pulsatile LH secretion in a mouse model of PCOS, further validating the use to this model to better understand aspects of PCOS that cannot be studied in humans, such as changes in brain structure that may underpin the endocrine abnormalities of the disorder.
Aortic Diameter shows a bimodal risk association for atherosclerotic arterial disease. B Drinkwater¹, A van-Rij¹, M Williams², N Curtis¹, G Hill¹, G Jones¹. Department of Surgical Sciences¹, Department of Medicine², Dunedin School of Medicine, University of Otago

Previous data from our research group suggested that there may be a correlation between abdominal aortic diameter (AAD) and the incidence of atherosclerotic cardiovascular diseases (CVD). The data suggested that an individual with larger or smaller than average AAD may be at greater risk of having CVD than those with a “normal” sized aorta. This project set out to accurately define this possible relationship and validate it in an independent cohort.

An initial cohort of 1859 elderly, consecutive participants of the Otago Vascular Genetics Study was used as a hypothesis-generating cohort. A replication analysis was then conducted in a second independent cohort of 1046 patients undergoing coronary angiography at Dunedin Hospital.

AAD measures were used to identify gender specific size strata associated with various forms of CVD. In the discovery cohort, AAD had a bimodal (smallest and largest 12.5% strata) pattern of relative risks for all of the vascular diseases assessed (presence of carotid, coronary and peripheral arterial disease), independent of traditional cardiovascular risk factors. These results were partially replicated in the second independent cohort, in which, by univariate analysis, the same bimodal associations were observed. However, after adjusting for traditional cardiovascular risk factors, only small AAD in women and large AAD in men remained significantly associated with concurrent arterial disease.

Aortic diameter may represent a useful independent indicator of global arterial disease risk. Both smaller and larger than normal aortic diameters appear to have increased risk associations with a range of CVD phenotypes. We believe that our findings have the potential to inform future abdominal aortic aneurysm screening programmes, with knowledge of aortic diameter being used to alter management of modifiable risk factors if individuals fall within the at-risk strata of aortic diameter.

The effect of riboceine on glutathione, glutathione peroxidase and plasma lipid levels in Lp(a) mice. T Kader¹, C Porteous¹, S Gieseg², S. McCormick¹. ¹Department of Biochemistry, Otago School of Medical Sciences, University of Otago, Dunedin, ²School of Biological Sciences, University of Canterbury, Christchurch.

Riboceine is a cysteine analogue designed to increase synthesis of the anti-oxidant glutathione (GSH). GSH is the cofactor for glutathione peroxidase (GPx) that reduces oxidised lipids. Low GPx activity and increased oxidised lipids are associated with the development of cardiovascular disease (CVD). We hypothesised that riboceine will increase GSH and GPx and in turn, lower oxidised lipids. As lipid metabolism pathways are regulated by oxidised lipids, we hypothesised riboceine may alter total plasma lipid levels.
Nine Lp(a) mice were supplemented with riboceine (4 mg/day/mouse) in drinking water for 8 weeks and nine were controls. Plasma and liver GSH was measured by HPLC. GPx activity in both liver and erythrocytes were measured spectrophotometrically. Various lipoprotein components (total cholesterol, HDL, LDL, TG) were measured by enzymatic or immunoassays. Oxidised lipids were measured by fluorometric thiobarbituric acid reactive substances (TBARS) assay.

Plasma and liver GSH levels were significantly increased in riboceine treated mice compared to controls (4.21 ± 1.01 versus 1.67 ± 0.15 nmol/mL, respectively; P = 0.0243 (plasma), 0.84 ± 0.05 versus 0.67 ± 0.04 µmol/g, respectively; P = 0.0252 (liver) (mean ± SEM), n = 9, unpaired Student’s t-test). Erythrocytes and liver GPx of treated mice significantly increased (7.52 ± 1.85 versus 1.95 ± 0.15 U/mg protein; P = 0.0196 (erythrocytes), 1.01 ± 0.08 versus 0.61 ± 0.08 U/mg protein; P = 0.0021 (liver). Oxidised lipids were significantly decreased in both plasma and liver. Total cholesterol levels were reduced, particularly LDL (27.22 ± 6.40 and 43.59 ± 4.196 mg/dL in riboceine treated and control, respectively, P = 0.0482). Total apoB levels showed a significant decrease in treated mice.

These results suggest that riboceine may be a promising intervention to increase protection against CVD.

**Optimising quantification of cardiac sympathetic nerve activity. T Hall, N Joe, D Schwenke. Department of Physiology, Otago School of Medical Sciences, University of Otago, Dunedin.**

It is well recognised that following myocardial infarction (MI), there is a significant and sustained increase in cardiac sympathetic nerve activity (cSNA), which enhances the risk of secondary heart failure and potentially fatal ventricular arrhythmias. Accurately quantifying changes in cSNA, particularly following acute MI, is critical for discerning the relative role of various signalling pathways implicated in triggering the increase in cSNA, as well as assessing the efficacy of possible therapeutic strategies. Intriguingly, there is no current uniform method of cSNA quantification. Accordingly, this study evaluated the precision of a non-invasive predictor of cSNA, specifically heart rate variability (HRV), compared to the gold standard technique of cSNA measurement, electrophysiological nerve recordings in an acute MI model.

Twenty male Sprague-Dawley rats were anaesthetised and the femoral artery catheterised for measurement of arterial blood pressure and heart rate. A left thoracotomy exposed the heart, enabling cardiac sympathetic nerve isolation and placement onto platinum electrodes. MI induction was achieved through ligation of the left anterior descending coronary artery. Both the integrated nerve signal, which encompasses total nerve activity, and HRV, a non-invasive predictor of autonomic cardiac control, which assesses variations in the beat-to-beat interval of heart rate, were recorded before, and for four hours following MI.

Acute MI stimulated a dramatic five-fold elevation in the cSNA signal within 120 minutes of the infarct event (P < 0.03, ANOVA test), facilitated primarily by an augmented firing rate (pre-MI = 12.2 ± 2.5 Hz, 120 minutes post-MI = 47.7 ± 10.4 Hz, mean ± SEM, P < 0.007). In comparison, HRV did not significantly change within 4-hours post-MI (LF/HF ratio pre-MI = 0.12 ± 0.04, post-MI = 0.08 ± 0.03).
These findings indicate that HRV analysis alone may not provide an entirely accurate approximation of cSNA, particularly following acute MI in an anaesthetised rodent model.

**Effects of quitting cannabis smoking on respiratory health. H Shin, R Hancox. Department of Preventive and Social Medicine, School of Medicine, University of Otago, Dunedin.**

Cannabis is the most widely-used illicit drug worldwide and its use in New Zealand is almost as widespread as tobacco. Smoking cannabis is known to cause airway inflammation and symptoms of bronchitis, such as cough and sputum production. Little is known about what happens to these symptoms if people quit cannabis smoking. This is important because bronchitis symptoms such as chronic cough often present a challenging clinical problem. The aim of this study was to investigate if quitting is associated with an improvement in cough and sputum production.

We explored the impact of quitting cannabis on respiratory symptoms in the Dunedin Multidisciplinary Health and Development Study, a population-based birth cohort. Participants have been followed throughout childhood and into adulthood with very high follow-up rates. Cannabis and tobacco smoking histories and information on respiratory symptoms were obtained at ages 21 and 38 years.

917 subjects provided data on cannabis use and respiratory symptoms at both ages 21 and 38 years. Among those who regularly (weekly) used cannabis at both ages (n = 61), the prevalence of cough increased from 33% to 48% whereas it decreased from 30% to 23% in quitters (n = 87). The prevalence of sputum production was 38% at age 21 and 33% at 38 in continued users compared to 30% and 12% respectively in quitters. Adjusting for sex, tobacco use and asthma, quitters were no more likely to have cough (OR = 1.70, P = 0.115) or sputum production (OR = 1.11, P = 0.801) at age 38 than who did not use cannabis at either ages.

This study has shown that respiratory symptoms of cough and sputum production improve after quitting cannabis use. This may provide an incentive for cannabis users with chronic cough and sputum production to consider stopping cannabis use. Cannabis smoking cessation should be considered as a potentially treatable cause of chronic bronchitis.

**Behavioural effects of phencyclidine treatment in rats. P Cinco, P Liu. Department of Anatomy, Brain Health Research Centre, University of Otago, Dunedin.**

Phencyclidine (PCP) is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist. It induces schizophrenia-like symptoms in humans, hence suggesting a role of the NMDA glutamate receptor hypofunction in the pathogenesis of schizophrenia. The evidence linking PCP exposure to schizophrenia has led to the development of the PCP model of the disease. This study aimed to investigate how repeated PCP treatment affected behavioural performance in rats.
Sixteen male adult Sprague-Dawley rats received either saline (2 mL/kg, n = 8) or PCP (5 mg/kg, n = 8) subcutaneously once daily for 12 consecutive days followed by a 4-day washout period and behavioural testing in the Y-maze, open field and object recognition memory task.

In the Y-maze test, there were no significant differences between groups in the number of arm entries and percentage of spontaneous alternation. In the open field, the PCP group generated significantly shorter path length (PCP 16.61± 0.91 m, Saline 19.88 ± 0.98 m) and moved less (PCP 54.59% ± 2.54, Saline 63.46% ± 2.25) (all P < 0.05, unpaired t-tests), with no significant difference between groups in the duration of rearings or the time spent in the outer zone of the apparatus. In the object recognition memory test, the PCP group had markedly reduced time in exploring objects (Phase 1: PCP 13.88 ± 1.82 s, Saline: 27.13 ± 4.58 s; Phase 2: PCP 10.01 ± 1.41 s, Saline 18.13 ± 3.36 s; P < 0.005, ANOVA), however spent similar time in exploring the novel object when compared to the saline group.

The present study demonstrated that repeated treatment of PCP led to reduced locomotion and motivation, but did not affect exploration, spatial working memory and object recognition memory. These findings suggest that the behavioural changes induced by PCP under the current treatment regime only partially represent schizophrenia-like symptoms in humans.
Use of macrolides in mother and child and risk of infantile hypertrophic pyloric stenosis (IHPS)

Macrolide use in infants during the first 2 weeks after birth has been associated with an increased risk of IHPS, but it is unclear if the risk is also increased with later use and with maternal use during late pregnancy and lactation.

This matter is reviewed in this study from Denmark. Data from a nationwide cohort of almost 1 million mothers and babies born between 1996 and 2011 has been collated with the prescription of macrolides.

880 infants developed IHPS. Compared with infants with no use of macrolides, the adjusted rate ratio for IHPS in infants with use of macrolides during days 1–13 after birth was 29.8 and during days 14–120 the rate ratio was 3.24. The rate ratio for maternal use of macrolides for days 0–13 after birth was 3.49. Maternal use of macrolides during pregnancy resulted in rate ratios for IHPS of 1.02 during 0–27 weeks and 1.77 during 28 weeks to birth. The researchers conclude—macrolide treatment of young infants and their mothers within the first 2 weeks of birth, and possibly during late pregnancy, was associated with IHPS.

BMJ 2014;348:g1908.

Antibiotic restriction in USA

The emergence of bacteria resistant to antibiotics is a very serious problem. Inappropriate prescription may be the main cause. Patients failing to take the whole prescribed course may be another. Possibly, the use of antibiotics in livestock for promotion of growth may be the most important cause.

Consequently, it is rewarding to note that the US Food and Drug Administration (FDA) has recently announced that 25 of 26 pharmaceutical companies have agreed to relabel their products to stop the use of antimicrobial drugs in livestock for promotion of growth. The FDA hopes the restriction will prevent acquisition of resistance to some antibiotics used in human treatment.

Lancet 2014;383:i.
Erratum


http://journal.nzma.org.nz/journal/127-1392/6080 and

The authors advise updated correspondence details and Dr Ross Scott-Weekly (not an author) is thanked in the acknowledgement section for his statistical work on this paper.

Please refer to the links above for the corrected copy.

NZMJ