PROCEEDINGS

St Vincent's Clinic

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PROCEEDINGS

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EDITORIAL

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Editor, *Proceedings*

This is perhaps the largest issue of *Proceedings* to date. It has been produced in record time as Mr Chris Thomas, our publisher, is away from his desk from October 2014 due to exceptional circumstances (see below). My thanks to all contributors for their co-operation in meeting this early deadline.

This Issue begins with an article on the novel oral anticoagulants which have become available in Australia over the past three years. These effective drugs serve as an alternative to Warfarin and are much easier for patients in that blood monitoring is not required. However, there are strict guidelines, limitations of usage and risks all of which are clearly explained by Drs Roy (cardiologist), Omari (vascular physician) and Joseph (haematologist).

The Urology Department of St Vincent's Clinic has produced two articles. Dr Philip Stricker and Dr Jackson have provided a state-of-the-art 2014 update on prostate cancer care. Drs Yuen and Ende describe their introduction in NSW (via St Vincent's Private Hospital), of the new surgical technique of robotic radical cystectomy.

This year's Sandra David Oration is by Bishop Anthony Fisher whose interesting article explores the ethics of the inevitable current and future rationing of healthcare. For those of us in our last quartile of life expectancy, it is reassuring to read Bishop Fisher's balanced views perhaps arguing more for the consideration of severity of need of treatment and the expectation of effectiveness of treatment rather than the provision of care or lack of it based purely on age. Bishop Fisher has recently been appointed Archbishop of Sydney.

Asthma is prevalent in our society and Dr Janet Rimmer, respiratory physician, describes and comments on the seventh and latest (2014) *Australian Asthma Handbook* which is, for the first time, a web-based resource. The Handbook outlines the current best practice guidelines for the management of asthma.

Colorectal cancer is likely to occur in 1:20 Australians. Screening for early detection and treatment is of paramount importance. Current recommendations for colorectal cancer screening are described by Dr Alissa Walsh, gastroenterologist.

Dr Cecelia Gzell, radiation oncologist, has been a recent welcome appointment to the staff of St Vincent's Campus. Her article describes current controversies in the management of malignant brain tumours, gliomas. She describes new therapies which involve a multidisciplinary approach and how these have resulted in improvements in survival and functional outcomes for patients with gliomas.

Technology continues to advance the adequacy and safety of diagnostic investigations. Dr James Otton, cardiologist, describes the latest developments in cardiac imaging for the assessment of patients presenting with different types of heart disease. James was recently a recipient of a Foundation Travelling Fellowship.

Dr Michael McGrath, vascular physician, has suggested a new type of article for *Proceedings* i.e. one which provides a pictorial synopsis of the various clinical presentations of different diseases. He and sonographer, Miss Lee Brown, have got the ball rolling with some pictures and descriptions of some of the clinical presentations of vasculitis. I hope this will prove to be a popular new concept for future editions.

The St Vincent's Clinic Foundation has this year provided more than $740,000 in research grants and awards. The recipients of these grants and their topics of research are shown on pages 38 and 39.

Mr Chris Thomas has been the publisher of *Proceedings* since its inception in 1993. For the last seven years, he has been Chief Executive Officer of Transplant Australia. This year, commencing in October, he is fulfilling a lifelong dream of cycling from Perth to Sydney. He is raising money to help the transplant programs at Children's Hospital Westmead and Royal Children's Hospital, Melbourne. I urge you to contribute to this worthy cause by visiting http://transplanttrek.everydayhero.com/au/chris

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Overview of Novel Oral Anticoagulant Agents (NOACs)

Introduction

Vitamin K antagonists (VKAs), particularly Warfarin, have been the treatment of choice for preventing arterial and venous thromboembolism (VTE) in *appropriately selected high-risk patients* for the last 60 years. Deciphering which patients are at high-risk and will benefit from anticoagulation and those who are at higher risk of bleeding remains a challenge for clinicians, as often these factors overlap.

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Why not VKAs?

Warfarin was first discovered in the 1920s as a compound which caused haemorrhage in cows after eating mouldy sweet clover hay, and had its first use as a pesticide against rodents. The stigma of "rat poison", particularly for patients asked to take the drug, has never left.

Warfarin has a number of characteristics which limit its clinical use. Firstly, the delayed onset and offset of action often requires bridging therapy with heparin or unfractionated heparin until the desired anticoagulant effect is achieved. Secondly, warfarin requires routine coagulation monitoring and dose adjustments to compensate for the many food-drug interactions and drug-drug interactions that alter the levels of its therapeutic effect. These variations in therapeutic effect can also give rise to complications – namely spontaneous bleeding in overtreatment or thromboembolism in under treatment.

Novel Anticoagulant Agents (NOACs)

After the first novel anticoagulant Ximelagatran was withdrawn due to liver toxicity in 2005, there has been growing anticipation regarding these new agents. Approval from the Therapeutic Goods Administration (TGA) for transition from warfarin to agents targeting either thrombin (Dabigatran) or factor Xa (Rivaroxaban and Apixaban) has been relatively swift in Australia and these agents have been approved by the TGA since 2011. Unlike warfarin, which has a narrow therapeutic window and requires individualised dosing based on the international normalized ratio (INR), the NOACs have a broad therapeutic window, with major pharmacologic advantages over VKAs which include rapid onset/offset of action, few drug interactions, and predictable pharmacokinetics. This enables fixed dosing in adults without the need for laboratory monitoring or dose adjustments for body weight.

In Australia and worldwide, regulatory agencies have approved these agents for specific indications based on results from clinical trials demonstrating efficacy and safety compared to warfarin (for thromboprophylaxis in patients with non-valvular atrial fibrillation and for the treatment/secondary prevention of VTE) and low molecular weight heparin (for venous thromboprophylaxis following knee arthroplasty). Despite good evidence the universal adoption of these agents into clinical practice has been slower than expected due to a number of factors including higher drug cost, uncertainty about dosing in some patient populations (e.g. extremes of body weight, renal dysfunction) and the lack of specific antidotes to these agents. In addition, the inability of some laboratories to provide rapid measurement of drug levels concerns some clinicians.

THE NOACs

Dabigatran (Pradaxa)

Dabigatran is a thrombin inhibitor. After oral administration, Dabigatran etexilate is converted in the gut and liver to Dabigatran, its active form. It is a potent, competitive, direct, reversible non-peptide antagonist of the activation site of thrombin, the final effector in blood coagulation. The inhibition of thrombin prevents the conversion of fibrinogen to fibrin, cross linking of fibrin monomers, platelet activation and the inhibition of fibrinolysis.

Unlike heparin and low molecular weight heparin, which inhibit free (unbound) thrombin, Dabigatran has the ability to inhibit free *and* bound thrombin, thus preventing thrombus expansion.

In patients with normal renal function, the half-life of Dabigatran is approximately 13 hours, increasing to > 24 hours in patients with a creatinine clearance (CrCl) < 30mL/min., as renal excretion is the dominant elimination pathway.

Rivaroxaban (Xarelto)

Rivaroxaban was the first oral direct factor Xa inhibitor to be developed and is an oxazolidinone derivative that is a potent reversible and selective direct inhibitor of factor Xa. Inhibition of factor Xa increases clotting times and decreases the formation of thrombin, the pivotal enzyme required for the generation of fibrin, platelet activation and thrombus formation. Rivaroxaban has a half-life of approximately 5-9 hours in young people and 11-13 hours in the elderly, with primarily (66 per cent) renal excretion. It has an excellent oral bioavailability (60-80 per cent) with good absorption from the GI tract and no significant effects by different foods on absorption.

Apixaban (Eliquis)

Apixaban is a reversible, direct and highly selective inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, Apixaban prevents thrombin generation and thrombus development. The half life of Apixaban is 8-15 hours and only 27 per cent of the drug is renally excreted.

CLINICAL INDICATIONS FOR USE OF NOACs

Atrial Fibrillation (Non-valvular)

Atrial fibrillation (AF) is a common condition estimated to affect 1-2 per cent of the population in Australia (0.5 per cent 40-50yrs, 5-15 per cent 70-80 years). It has an increasing prevalence and is responsible for a significant and growing societal financial burden. Each of the three NOACS available in Australia have been evaluated in large clinical trials for non-valvular AF. The key findings of the randomized trials comparing Dabigatran (RELY), Rivaroxaban (ROCKET-AF) and Apixaban (ARISTOTLE) are summarized in **Table 1**.

All of these trials were designed to show non-inferiority of the new agents when compared to warfarin. In addition to the desired effect of preventing ischaemic stroke these agents have uniformly demonstrated a robust reduction in intracranial bleeding with rates of other major bleeding similar to, or lower than, warfarin. This reduction in intracranial bleeding relative to warfarin is observed regardless of the time in therapeutic range. Indeed, even in centres with the best INR management, the risk of intracranial bleeding was lower with the novel agents than with warfarin. Also of note was the approximate 10% reduction in mortality demonstrated in trials of all 3 agents for non-valvular AF.

Choosing between a NOAC and Vitamin K Antagonist (Warfarin)

For new patients with non-valvular AF and at least one risk factor for stroke or for patients on warfarin with difficulty maintaining the therapeutic range, a NOAC should be considered if no contra-indications exist. For patients already on warfarin with stable INRs, the clinical benefit of switching therapies may be limited and the main reason for choosing a NOAC under this circumstance is patient preference. For this patient population the issue of drug cost is important.

Relative contra-indications to NOAC therapy include severe renal impairment or labile renal function and for these patients warfarin may be preferred. A suggested approach to personalizing anticoagulation therapy is outlined in **Table 2**.

Table 1. *Trials of NOAC agents in non-valvular atrial fibrillation*

	Dabigatran	Rivaroxaban	Apixaban
Trial name	RE-LY	ROCKET-AF	ARISTOTLE
Dose	150,110	20 (15)*	5 (2.5)*
Frequency	Twice daily	Once daily	Twice daily
N	18113	14266	18206
Design	PROBE** Non-inferiority	Double blind Non-inferiority	Double blind Non-inferiority
AF criteria	AF x 1	AF X1 <6 months	AF or PAF x 2 in 12 months

*Dose adjusted in patients with perceived reduced drug clearance
**Prospective, open-label, blinded end-point evaluation

Where warfarin remains the optimal treatment

In all of the studies of AF, patients with haemodynamically significant valvular disease were excluded. As there is no evidence for NOACS in patients with valvular disease and AF these patients should receive warfarin.

The *RE-ALIGN* study examined the potential for using Dabigatran instead of warfarin to prevent thromboembolism in patients with mechanical valves. The trial was stopped early due to increased events in the Dabigatran group. These increased events may be due to the fact that warfarin also inhibits the synthesis of factors VII, IX , X and thrombin, potentially making it more effective for preventing thrombus formation on a mechanical prosthesis. From this evidence warfarin is still clearly the drug of choice for thromboprophylaxis in patients with mechanical heart valves.

Choosing between NOACS

Compliance is an important issue in the use of NOACs, particularly as these agents have such short half-lives. A single daily dose (Rivaroxaban) might be preferable to a twice-daily dosing regimen (Dabigatran or Apixaban) if compliance is likely to be an issue. In both the RELY and ROCKET-AF studies, gastro-intestinal bleeding was more frequent with a NOAC (Dabigatran and Rivaroxaban) than warfarin. Thus in patients who have a history of reflux or peptic ulcer disease or have suggestive symptoms then Apixaban may be the preferred agent. Due to their metabolism by CYP3A4 enzymes in the liver, patients on HIV protease inhibitors, anti-fungal agents, Rifampicin and Clarithromycin should avoid Apixaban and Rivaroxaban.

VENOUS THROMBOEMBOLIC DISEASE

VTE, comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common condition. Often underestimated, VTE may occur in up to 1 in 1000 Australians per annum, with mortality occurring from PE in the short-term and among hospitalised patients, PE remains the commonest cause of preventable death. In the longer term, the sequelae of VTE includes pulmonary hypertension and chronic venous insufficiency resulting in lower limb ulceration, oedema and cellulitis; all of which pose a significant burden of disease to the patient and the Australian health care system. Therefore, appropriate measures of thromboprophylaxis to prevent VTE and effective therapies for the treatment and secondary prevention of VTE are vital.

Table 2. *Choice of anticoagulant based on patient characteristics.*

Characteristic	Anticoagulant Drug Choice
Mechanical valve or valvular AF	Warfarin
Liver dysfunction with increased INR	Warfarin
Stable on warfarin	Warfarin
CrCI <30ml/min	Warfarin
CrCI 30-50ml/min	Rivaroxaban or Apixaban
Dyspepsia/Upper GI symptoms	Rivaroxaban or Apixaan
Recent gastrointestinal bleed	Apixaban
Recent ischaemic stroke on warfarin	Dabigatran
Recent acute coronary syndrome	Rivaroxaban or Apixaban
Poor compliance with BD dosing	Rivaroxaban

Table 3. *Total Hip or Knee Arthroplasty (VTE prophylaxis) NOAC dosing*

	Dabigatran	Rivaroxaban	Apixaban
CrCI>50mL/min	220mg2.5 (2 x 110mg) once daily	10mg once daily	2.5mg twice daily
CrCI 31 – 50mL/min	150mg (2 x 75mg) once daily		
CrCI 15 – 30mL/min	Avoid	Avoid	Avoid

Currently, in other patient groups such as non-arthroplasty orthopaedic procedures, non-orthopaedic surgery or medical inpatients at risk of VTE, NOACs are not approved in Australia for VTE prophylaxis use.

A: Thromboprophylaxis

Currently in Australia, all NOACs are approved for the prevention of venous thromboembolism among patients undergoing hip or knee arthroplasty surgery (**Table 3**). Extended prophylaxis is recommended for patients undergoing hip surgery with the recommended duration of therapy being 10 days after knee arthroplasty and 28–35 days after hip arthroplasty surgery.

Among arthroplasty patients, both Rivaroxaban 10 mg daily and Apixaban 2.5 mg twice daily were each found to be superior to Enoxaparin 40 mg daily with no difference in major bleeding rates. Dabigatran (150 mg and 220 mg once daily) was as effective as Enoxaparin 40 mg daily at preventing VTE and any cause mortality with no significant difference in major bleeding events.

B: Treatment of VTE and prevention of recurrent VTE

Rivaroxaban is currently the only NOAC approved in Australia for the treatment of patients presenting with acute DVT and/or PE. In the EINSTEIN trials, Rivaroxaban alone was compared with Enoxaparin followed by a VKA for three, six, or 12 months. The Rivaroxaban dose was 15 mg twice daily for three weeks followed by 20 mg daily thereafter. Of note, this dosing regimen is different to that utilised in AF patients discussed earlier in this paper. Among VTE patients, an acute 3 week phase of a higher total daily Rivaroxaban dosage (in two divided doses) is utilised, followed by a subsequent once daily regimen. In the VTE patient cohort, Rivaroxaban was found to be non-inferior with respect to the primary efficacy outcome of symptomatic recurrent VTE versus Enoxaparin/VKA therapy. The principal safety outcomes of major and clinically relevant non-major bleeding were not significantly different between the two groups.

In relation to the prevention of recurrent VTE, Rivaroxaban is currently the only NOAC approved in Australia (**Table 4**). In the continued-treatment study (EINSTEIN-EXTEND), patients with confirmed DVT or PE who had already completed 6 to 14 months of anticoagulation therapy were randomized to Rivaroxaban therapy or placebo. Rivaroxaban reduced the primary efficacy

outcome of symptomatic VTE recurrence by 82 per cent (1.3 per cent vs 7.1 per cent) compared with patients on placebo, yet with a similar safety outcome of major bleeding (0.7 per cent vs 0 per cent).

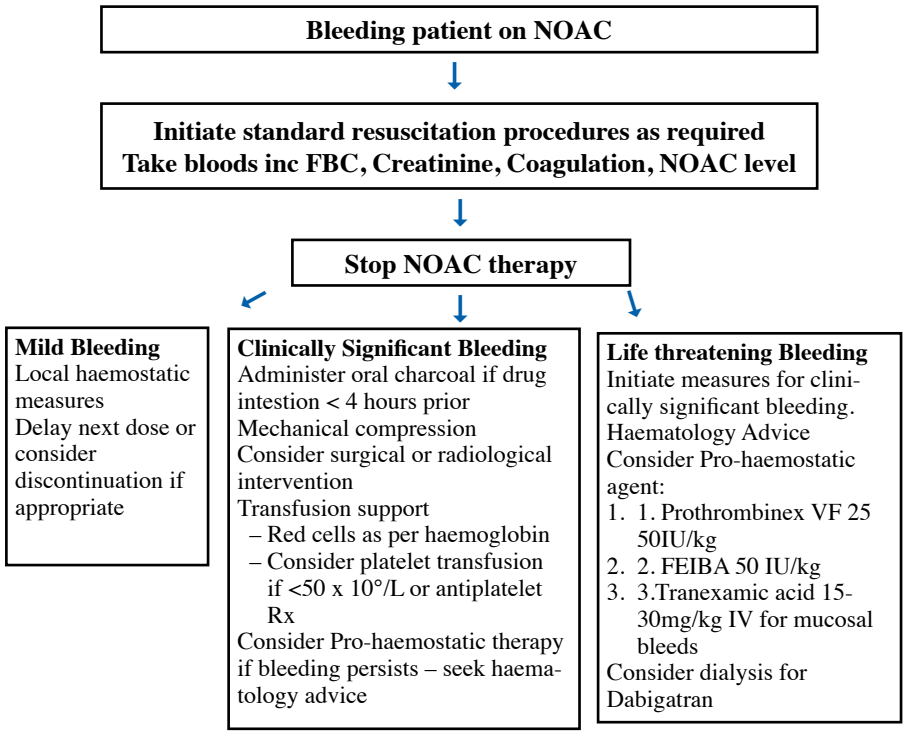
Finally, for some subgroups of acute VTE, NOACs may not be the ideal first choice anticoagulant therapy. In particular, certain areas of VTE pose clinical challenges regarding NOAC use for the clinician due to limited or no data regarding the use of NOACs in these clinical scenarios. Such conditions include malignancy-related VTE; pregnancy-associated VTE; thrombophlebitis; anti-phospholipid syndrome and Heparin Induced Thrombocytopenia. Therefore NOAC utilisation is not recommended in these groups and standard anticoagulation therapies should be implemented according to current accepted guidelines.

SPECIAL CONSIDERATIONS IN THE USE OF NOACs

Laboratory Testing

Although NOACS do not require monitoring, laboratory testing can be useful in certain clinical scenarios, particularly in cases of bleeding, urgent surgery or recurrent thromboembolism. Standard coagulation tests (i.e APTT, PT and TT) are variably affected by these agents and may provide qualitative information about the presence of some NOAC. Specific assays for drug quantification are available in tertiary coagulation laboratories (**Table 5**).

Figure 1. *Management of NOAC associated bleeding*



Management of Bleeding

Given the absence of specific NOAC antidotes or reversal agents at the present time, strategies for the reversal of these agents are not robust. As the use of these agents becomes more prevalent, the number of bleeding related events is likely to increase. Currently, recommendations on bleeding management are based on expert opinions and case based experience rather than extensive trials or broad clinical experience.

Minor bleeding can be managed with local measures and consideration given to temporary drug cessation. Major bleeding should involve immediate discussion with a haematologist as there are some differences between thrombin inhibitors and Factor Xa inhibitors. Dabigatran, specifically can be removed with dialysis in contrast to Apixaban and Rivaroxaban which are highly protein bound. If the severely bleeding patient presents within 4 hours of ingestion of the drug then activated charcoal could be given to minimize further absorption.

Pro-haemostatic agents have limited evidence but have been used in isolated cases of severe bleeding anecdotally. The activated prothrombin complex concentrate, FEIBA (which is available in Australia and the 4-factor prothrombin complex concentrates (which is not available in Australia) have been shown to reduce bleeding in animal models and reduce anticoagulant effects in healthy volunteers. **Figure 1** outlines the management of NOAC associated bleeding.

Pre-operative management of patients on NOACs

Approximately 25 per cent of patients commenced on anticoagulation will require temporary cessation within two years. The NOAC agent and patient characteristics (kidney function, age, history of bleeding complications, concomitant medication) as well as surgical factors should be taken into account when deciding optimal timing for discontinuation and recommencement

Table 4. *Treatment or Prevention of Recurrent VTE Dosing Regimen*

Rivaroxaban	
CrCl ⩾ 30 mL/min	15mg twice daily for 3 weeks followed by 20mg once daily

Table 5. Coagulation assay changes with NOAC agents

	Dabigatran	Rivaroxaban	Apixaban
Significant Anticoagulant effect unlikely	APTT* and TT† normal	PT‡ normal	Therapeutic Apixaban not excluded by normal PT
Anticoagulant effect present	TT prolonged APTT prolonged	PT prolonged	PT prolonged or normal
Specific assays to quantify drug presence	Dilute thrombin clotting time (Hemoclot assay)	Modified anti-Xa assay (Rivaroxaban specific)	Modified anti-Xa assay (Apixaban specific)

• activated partial thromboplastin time, † thrombin time, ‡ Prothrombin time

of the drug. **Table 6** outlines a suggested management approach for preoperative interruption of NOACs.

Restarting NOAC agents after surgery

For procedures with immediate and complete haemostasis, the NOAC can be resumed anywhere from eight to 24hours h after the intervention, depending on the nature of the surgical procedure. For certain surgical procedures resuming full dose anticoagulation within the first 48-72 hours may carry a bleeding risk that outweighs the risk of thromboembolism/cardio-embolism. When using NOACs this is especially important given that there is still no specific antidote for these agents. For patients at high risk for VTE, consideration should be given to starting a reduced dose of the agent e.g. Rivaroxaban 10mg once daily or Dabigatran 110-150mg *once* daily, starting the evening after surgery and continuing until it is deemed safe to resume full anticoagulation. For patients at risk of bleeding but low risk for VTE or AF related stroke, therapeutic anticoagulation can be delayed for greater than 72 hours until there is no further risk of bleeding or potential need for re-intervention. A guideline for postoperative resumption of NOACs post operatively is outlined in **Table 7**.

Conclusions

NOACS represent a huge leap forward in the quest to replace warfarin, not only because of the convenience for the patient but also due to improved safety, particularly with respect to intracranial bleeding. These agents are also likely to continue to expand their indications as evidence from ongoing studies becomes available.

While the ease of use of NOACSs facilitates more widespread conversion from warfarin as the standard anticoagulant agent, care needs to be taken to ensure patient safety is not compromised by lack of education and experience with these agents.

Table 6. *Preoperative discontinuation of novel anticoagulants prior to elective surgery*

Drug	Renal Function	Low bleeding risk surgery*	High bleeding risk surgery†
Dabigatran 150mg BD			
Half Life 12-17 h	Normal or mild impairment (CrCI>50mL/min)	Last dose: 2 days before surgery (skip 2 doses)	Last dose:3 days before surgery (skip 4 doses)
	Moderate Impairment (CrCI 30-50 mL/min)	Last dose: 3 days before surgery surgery (skip 4	Last dose 4-5 days before surgery surgery doses)
Rivaroxaban 20mg OD			
Half Life 5-9 h (healthy) 11-13 h	Normal or mild impairment CrCI>50mL/min	Last dose: 1 day before surgery (skip 1 dose)	Last dose: 3 days before surgery (skip 3 doses
	Moderate Impairment CrCI 30-50mL/min)	Last dose: 1 day before surgery (skip 1 dose)	Last dose: 3 days before surgery (skip 3 doses)
Apixaban 5mg BD			
Half life 8-15 h	Normal or mild Impairment CrCI>50mL/min	Last dose: 1 day before surgery (skip 2 doses)	Last dose: 3 days before surgery (skip 4 doses)
	Moderate Impairment (CrCI 30-50mL/min)	Last dose: 3 days before surgery (skip 4 doses)	Last dose: 4 days before surgery (skip 6 doses)

***aiming for mild to moderate residual anticoagulant effect at surgery.**
†aiming for no or minimal residual anticoagulant effect at surgery.

Table 7. *Postoperative resumption of novel anticoagulants.*

Drug	Low Bleeding Risk Surgery	High Bleeding Risk Surgery*
Dabigatran	Resume 24 hours after surgery, 150mgBD daily.	Resume 48-72 hours after surgery, 150mg twice
Rivaroxaban	Resume 24 hours after surgery, 20mg once daily.	Resume 48-72 hours after surgery, 20mg once daily.
Apixaban	Resume 24 hours after surgery, 5mg twice daily.	Resume 48-72 hours after surgery, 5mg twice daily.

***For patients at high risk of thromboembolism, consider using a reduced dose regime eg Dabigatran 110-150mg once daily, Rivaroxaban 10mg once daily or Apixaban 2.5mg twice daily**

Key point summary

- Unlike warfarin, NOACS do not require laboratory monitoring to guide ongoing therapy.
- NOACs are indicated for thromboprophylaxis post hip/knee arthroplasty and only Rivaroxaban is approved for the treatment and secondary prevention of VTE events.
- NOACs are indicated for thromboprophylaxis in patients with non-valvular atrial fibrillation, and should be considered when commencing anticoagulation for the first time or in patients who are poorly controlled with warfarin.
- Standard laboratory coagulation assays provide only a qualitative estimate of some NOACs however specific assays for quantitative measurements are available in tertiary laboratories
- Currently there are no clinically available specific antidotes or reversal agents for NOACs.

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An Update in Prostate Cancer Care in 2014

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Introduction

Prostate cancer continues to be a serious healthcare issue in Australia being diagnosed in almost 20,000 Australians and resulting in 3,000 deaths per annum.[1] The controversy of prostate cancer screening continues with further debate over when to test and when to treat. Some cancers are clearly indolent and others are clearly highly aggressive and an individual approach is therefore mandated. This makes it exceedingly difficult to have a universal policy regarding early detection. Furthermore, although the trials of prostate cancer screening have shown some benefit, they have also shown considerable over detection of insignificant cancers.[2] Trials comparing watchful waiting to surgery, whilst showing a significant benefit to surgery, have also shown considerable overtreatment.[3]

What has changed recently is that there is now increased use of active surveillance for patients with low-risk prostate cancer and this is therefore reducing overtreatment. Furthermore, improved imaging with multiparametric MRI has been shown to improve early detection and screening for prostate cancer. Improved surgical and radiotherapeutic options plus some of the less tested focal therapies are also changing the way prostate cancer is managed. Finally, many more options are now available for patients with advanced castrate-resistant prostate cancer. This article summarises the progress made in these areas and our research at St Vincent's.

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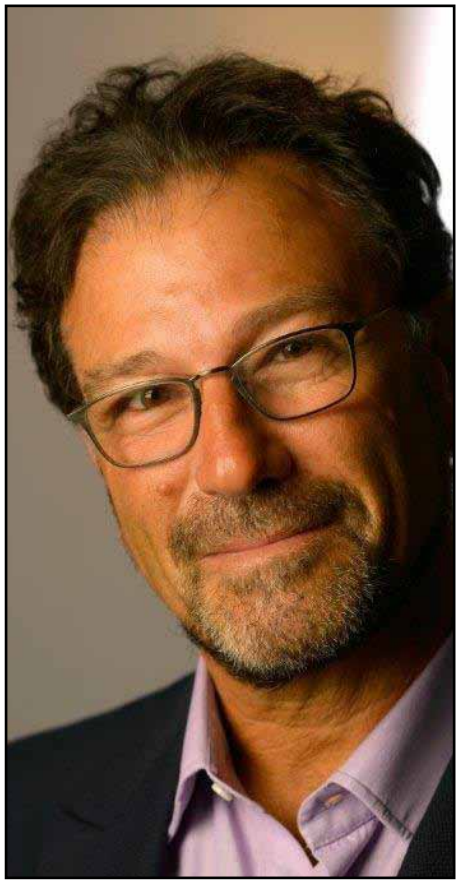

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Prevention

There is no recommended prevention policy for prostate cancer. Although the 5-alpha-reductase inhibitors have been shown to be effective in reducing the incidence of low-risk cancers, there has been a slight concern about a possible increased risk of high-grade cancers.[4] While this concern continues, they will not be widely used. Dietary and lifestyle modification have also been proposed to prevent prostate cancer based on population studies. General advice currently is to:

a. eat a healthy heart diet minimising saturated fats and refined sugars;
b. avoid obesity;
c. maintain normal levels of cholesterol, blood pressure and blood glucose through diet and exercise or prescription medication;
d. ensure adequate vitamin D levels.

Early Detection And Screening

Four randomised screening trials on prostate cancer have now been completed.[2, 5-7] Two from Europe have shown a survival benefit of screening men with prostate cancer. The Göteborg trial showed a 50 per cent reduction in prostate cancer mortality over 14 years in the screened group.[6] In this trial, the number needed to treat to save one life was 12, a comparable figure to breast cancer screening.

The overall tendency has been to direct early detection at a younger age group, particularly those at higher risk due to family history or racial origin, after informed consent. A single PSA at the age of 40 as advocated by the Urological Society of Australia and New Zealand has been shown to be predictive of the lifelong risk of developing life-threatening prostate cancer.[8] This could help stratify patients into high- and low-risk

categories. Early detection of prostate cancer still requires a combination of PSA testing and digital rectal examination. Newer tests including the urinary PCA3 test (a urinary biomarker derived from prostate-derived messenger RNA) and the Prostate Health Index (PHI which incorporates the pro-PSA isoform more commonly expressed in patients with prostate cancer) have been rather disappointing in improving the accuracy of detection. The most accurate predictor of prostate cancer has continued to b16e the PSA relative to age and PSA velocity.[9] A much more targeted patient testing policy with informed consent has been recommended by multiple authorities. Our group have developed a recommended algorithm **(Table 1)** recently published in the *British Journal of Urology*.[10]

Four recent publications, including one by our group, have added weight to the use of multiparametric MRI **(Figure 1)** for improved detection of prostate cancer at initial biopsy.[11-14] Although MRI is emerging as a new standard, its optimal use in prostate cancer detection is not clear at this stage. A possible future algorithm for early detection of prostate cancer could well appear as in **Table 2**.[15] The role of MRI in this algorithm would be to better select the patients requiring biopsy and to more accurately biopsy the lesions. MRI would also minimise the need for repeat biopsies in patients without missing significant cancers. Finally, MRI could also help avoid the over detection of low-risk cancers.

3. Better Biopsy Techniques

Transrectal ultrasound-guided biopsies have been the standard approach for prostate biopsy for over 30 years. Transperineal biopsy is a newer approach and has the benefit of increased sampling of the anterior part of the prostate[16, 17] ,where many cancers are missed, as well as having a much lower infection risk.[18]

The use of MRI to more accurately target prostate biopsy has also been confirmed to be more accurate than random biopsies. This can either be done with biopsy within the MRI machine or alternatively using MRI-ultrasound fusion technology. These emerging techniques will lead to fewer biopsy cores being taken and a more selective choice of patients to be biopsied. Several publications have shown improved accuracy with this technique.[19-21]

4. Improved Imaging

a) Multiparametric MRI

Multiparametric MRI is a new technique that incorporates T2-weighted imaging, diffusion-weighted imaging, dynamic contrast imaging and proton MRI spectroscopy to assess the likelihood of significant prostate cancer **(Figure 2)**. We recently published our experience of the technique, showing a negative predictive value of more than 90 per cent and a positive predictive value of more than 80 per cent.[14] It is most accurate in smaller prostates and in the peripheral zone. The use of multiparametric MRI, however, is extremely user-dependent and requires a high level of experience and high-quality, well-tuned MRI machines. It is not yet standard of care, nor currently rebated through Medicare. Its current uses include:

a. selecting patients to have biopsies;
b. enabling more accurate biopsy;
c. staging cancers before surgery and radiotherapy;
d. less invasively monitoring patients with low-risk cancers[22]

b) PET/CT scan

Positron emission tomography (PET/CT scan) can give both metabolic information from the PET scan and anatomical information from the CT scan. Prostate cancers generally do not metabolise glucose, hence PET/CT scans using either choline, acetate or PSMA-based radiotracer are proving to be more accurate than scans using a glucose analogue-based radiotracer in the detection of metastatic prostate cancer, particularly to lymph glands.

Sodium fluoride F-18 is another new radiotracer used in PET/CT scans and more accurately identifies bony metastatic disease than conventional bone scans.

5. Update On Treatment

a) Making a choice for localised prostate cancer

Generally the final decision of treatment for prostate cancer should occur after the patient has been counselled by a specialist with expertise in multiple options or multiple specialists with expertise in different modalities. For more difficult cases, multidisciplinary meetings should take place. The factors that influence the treatment include the grade and extent of cancer, the age and well-being of the patient, patient priorities and local factors such as prostate size and urinary symptoms. Recently, our group submitted our results on the quality of life outcomes for different treatment options to European Urology.[23] This showed considerable differences in functional outcomes such as sexual function between the different treatments. **Figure 3** shows, for example,

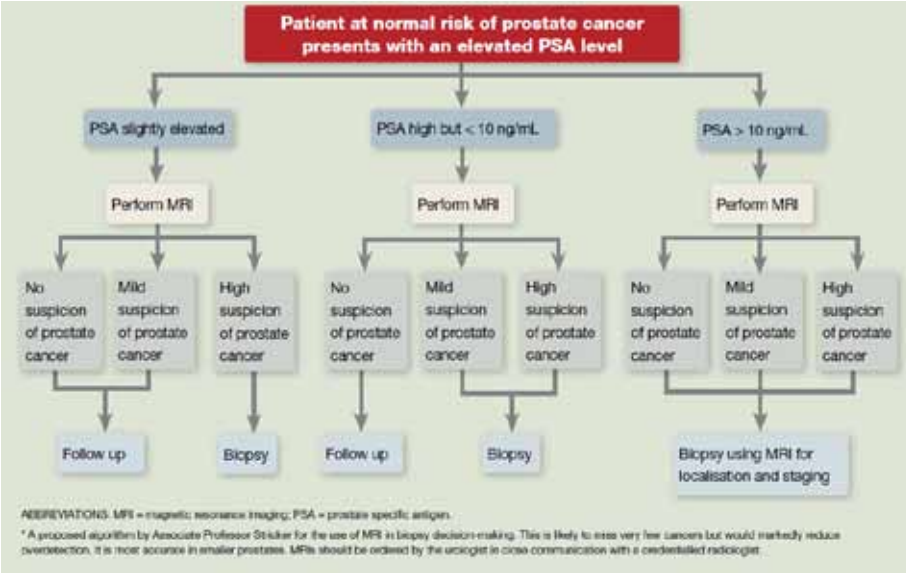

Table 1: *Risk-adjusted testing for prostate cancer: a proposed regimen for PSA-based screening a patient of normal risk derived from our group's article in BJU*

the sexual function over time after different treatments comparing them to baseline.

b) Robot-assisted laparoscopic radical prostatectomy

Evidence is increasing that an experienced robot-assisted laparoscopic radical prostatectomy gives equal oncological results with quicker recovery and return to normal activities and lower blood loss than the original gold standard of a well-performed open radical prostatectomy often in association with an extended lymph gland dissection. Our group recently published as part of a worldwide meta-analysis that robot-assisted radical prostatectomy may deliver improved functional outcomes.[24] Our group also recently published[25] a very large prospective single surgeon study showing the long length of the learning curve in performing robotic prostate cancer surgery cases relative to open surgery in terms of cancer cure and sexual and urinary outcomes. The study also confirmed that after the long learning curve for robotic surgery, results were significantly better in terms of sexual recovery and cancer outcomes for less aggressive cancers.[25] Whilst there has

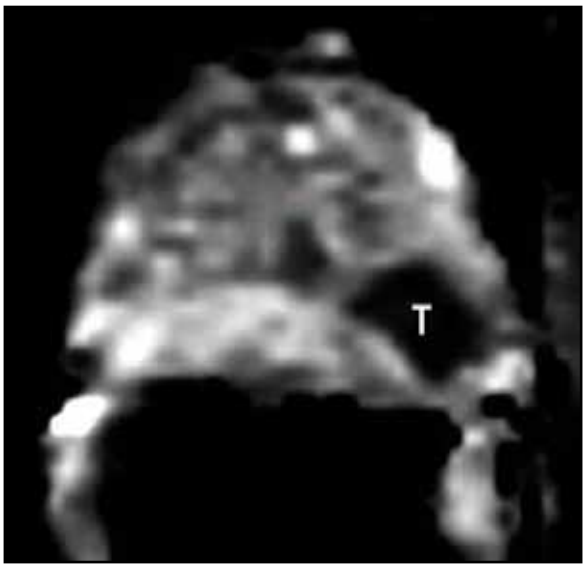

Figure 1: *A diffusion-weighted MRI image showing an area of restricted diffusion suggestive of prostate cancer T=Tumour*

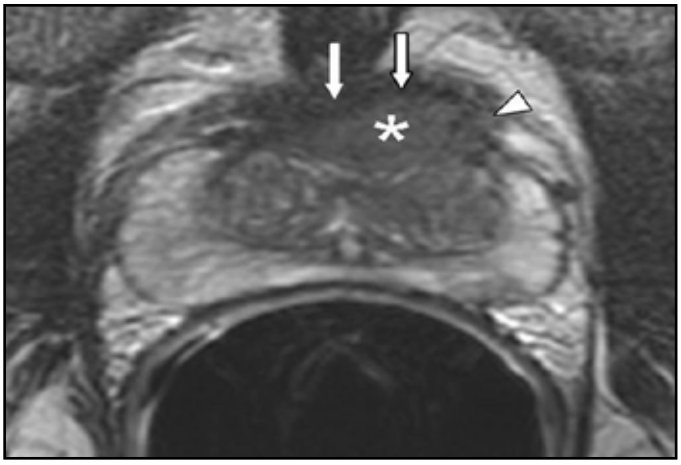

Figure 2: *MRI image showing an anterior prostate tumour. Transperineal prostate biopsy samples this area of the prostate more effectively than transrectal biopsy. *centre of tumour, pointers show tumour margin on the MRI*

TABLE 2. RISK-ADJUSTED TESTING FOR PROSTATE CANCER: A PROPOSED REGIMEN IN A PATIENT WITH 'NORMAL' RISK (NO HIGH RISK FACTORS)[*6]

	Age (years)			
	40 to 59[†]	60 to 69[†]	70 to 74[†]	75 and older[†]
PSA level (ng/mL)				
Below 0.6	Return in seven years or age 60, whichever comes first	No further screening	No further screening	No further screening
0.6 to 1.0	Return in five years	No further screening	No further screening	No further screening
Above 1.0 to 1.5	Return in two years	Return in two years	No further screening	No further screening
Above 1.5 to 2.0	Annual PSA	Return in two years	No further screening	No further screening
Above 2.0 to 3.0	Annual PSA	Annual PSA	No further screening	No further screening
Above 3.0	Refer to urologist	Refer to urologist	Consider annual PSA if below PSA 6.5 ng/mL Refer to urologist if PSA 6.5 ng/mL or above	Refer if PSA greater than age-specific reference range
Digital rectal examination				
Abnormal result	Refer to urologist	Refer to urologist	Refer to urologist	Refer to urologist

ABBREVIATIONS: DRE = digital rectal examination; PSA = prostate specific antigen.
* This is not a validated algorithm; however, it is evidence based. For further information see reference 6.
† Screening should not be undertaken if life expectancy due to age or comorbid illness is less than 10 years.

Table 2: *A proposed algorithm, incorporating MRI, for investigation of a patient with a raised PSA in a patient of normal risk (derived from our article in Medicine Today)*

also been evidence of improved oncological outcomes for earlier cancers, the overall the data from the literature suggests that surgeon experience is more critical than the technique used. It must also be noted that robot-assisted Radical Prostatectomy is significantly more expensive than it's open counterpart but this is partly offset by the saving related to less time in hospital and a quicker recovery.

c) Dose-escalation radiotherapy

Improved techniques allowing an increased dose of radiation to be delivered to the prostate and regional pelvic lymph glands have improved cure rates. This has been realised with the development of intensity-modulated radiotherapy (IMRT) and high-dose-rate brachytherapy (HDR), both of which can deliver higher doses of radiation to the target whilst minimising damage to surrounding structures.

IMRT and HDR are often combined with hormone therapy, particularly in patients with high-risk prostate cancer, and represent an accepted standard of care. Radiation oncologists are increasingly appreciating the need to irradiate the lymph node chain draining the prostate in these high-risk cases.

d) Low-dose-rate brachytherapy (LDR)

LDR is now a well-established treatment for high-volume Gleason 6 tumours and some Gleason 3+4=7 tumours. The long-term results appear to be equal to those of surgery. We recently published our long-term results showing that very high-volume tumours may not be ideal for this therapy.[26]

e) Active surveillance

Patients with low-volume, low-risk tumours are generally now recommended to commence active surveillance as the current standard of care. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) showed that there was no difference in overall survival at 12 years between observation and intervention for low-risk prostate cancer.[27] It is however critical that an adequate initial assessment is performed with either a saturation biopsy and/or a multiparametric MRI to ensure that no high-grade tumour has been missed. A 15-year follow-up for the largest series of active surveillance suggests this is a safe option and avoids unnecessary treatment in many patients.[28] Our group recently published a long follow-up of approximately 800 patients also confirming it's safety.[29] The current focus of research in active surveillance is to minimise invasive monitoring. We are increasingly using multiparametric MRI to monitor these patients, thereby minimising the need for periodic biopsies.[15]

f) Locally advanced prostate cancer

Multimodal therapy with a combination of surgery and radiotherapy or hormone therapy and radiotherapy is now a standard of care in this group. We have recently published our own data comparing surgery and high-dose-rate brachytherapy for this group of patients.[30]

g) Focal therapy

In highly selected individuals where there is an identified index lesion (the largest or most significant tumour focus within the gland) that is higher-grade than appropriate for simple active surveillance, there is an emerging trend worldwide to consider ablating the lesion and continuing the patient on active surveillance **(Figure 4)**. As yet, such focal therapy has no long-term track record and is generally confined to those patients where an index lesion is less than one-quarter of the prostate in size, has a significant Gleason 4 component and the patient refuses or is unsuitable for standard surgery and radiotherapy options but wants more than active surveillance alone. Focal therapy is an emerging treatment but by no means standard of care at this time.

We are currently trialling irreversible electroporation (also referred to as focal NanoKnife therapy - **Figures 5a,b,c**) in the management of highly selected patients. This treatment involves a day surgery minimally invasive procedure where several fine electrodes are placed into the prostate and high power pulsed electric current is passed across the tumour leading to irreversible damage to the cancer cells. Our group recently had accepted for publication the first case series on the safety of NanoKnife therapy.[31] This therapy is not currently standard of care and should only be undertaken in specialised units as either part of a clinical trial or after careful informed consent.

h) Advanced metastatic prostate cancer

Hormone therapy remains the first-line treatment for metastatic prostate cancer, with LHRH agonists or the newer LHRH antagonists which rapidly reduce testosterone to castrate levels being the standard of care. Patients are always counselled to adopt an appropriate diet and exercise program whilst on this therapy and to carefully monitor the onset of osteoporosis, a common side effect of this therapy. Bisphosphonates were the mainstay of treatment previously for osteoporosis but have now been superseded by the human monoclonal antibody denosumab.[32]

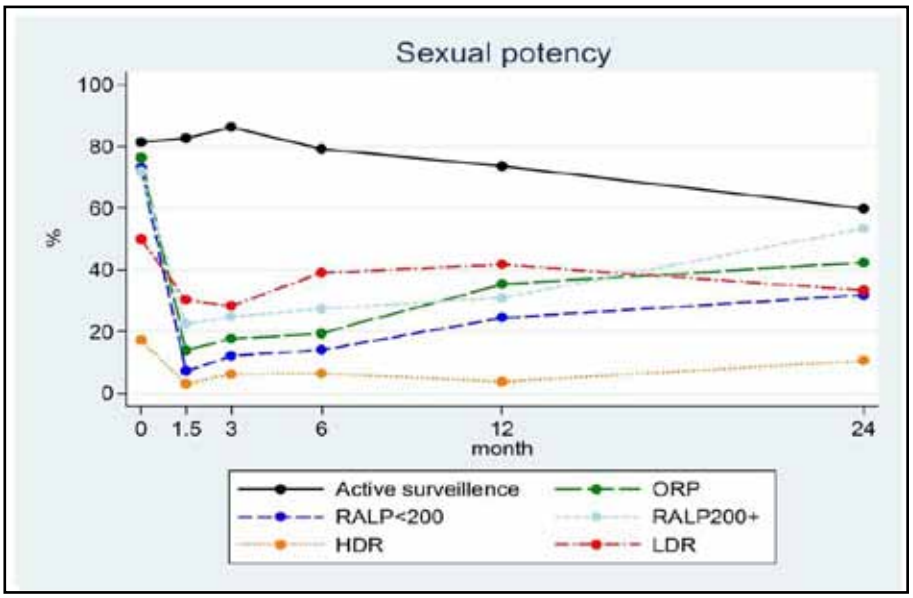

Figure 3: *Change in sexual potency over 2 years following various modalities of prostate cancer treatment including surgery (open and robotic), brachytherapy and active surveillence. After all forms of surgery , there is a decrease in potency which gradually recovers over 2 years.*

There have been some major developments in the management of patients who no longer respond to hormone therapy. These include the supra-antiandrogens, abiraterone[33] and enzalutamide[34] and now some active chemotherapy agents including Taxotere and cabazitaxel.[35] Finally, there are emerging drugs using immune therapy with a high level of promise in this difficult patient group.[36]

The other areas that are being intensely investigated are the management of patients with less than five secondaries (oligometastatic disease) and the use of neoadjuvant treatments prior to surgery and radiotherapy. We are currently conducting clinical trials in both of these areas.

Conclusion

The diagnosis and management of patients with localised and advanced prostate cancer is currently undergoing a major shift. Progress in imaging, new energy sources, immune therapies, improved quality of surgery, improved radiotherapeutic techniques and better understanding using biomarkers of the disease's natural history are having a profound impact on this disease. The next five to 10 years will usher in major changes in management.

Our current major areas of research interest at St Vincent's Prostate Cancer Centre, the Garvan and Kinghorn Cancer Centre (now coordinated by the nationally appointed Australian Prostate

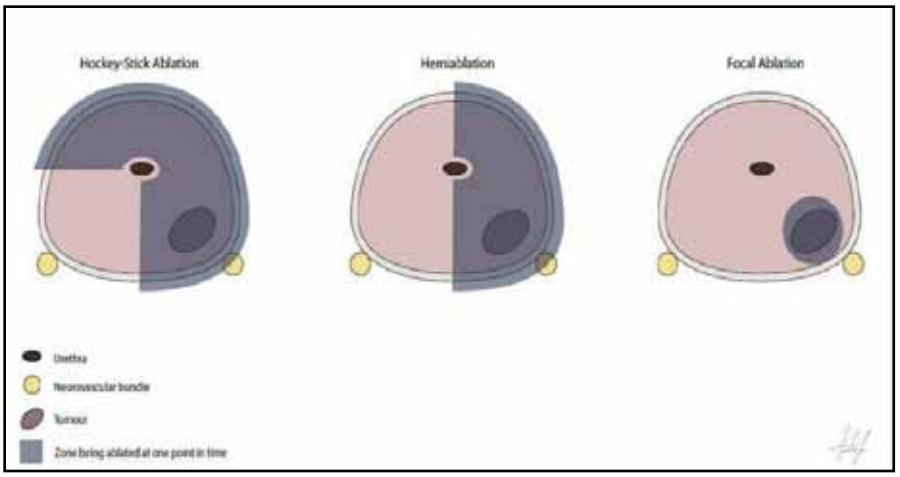

Figure 4: *Potential ablation templates for focal therapy*

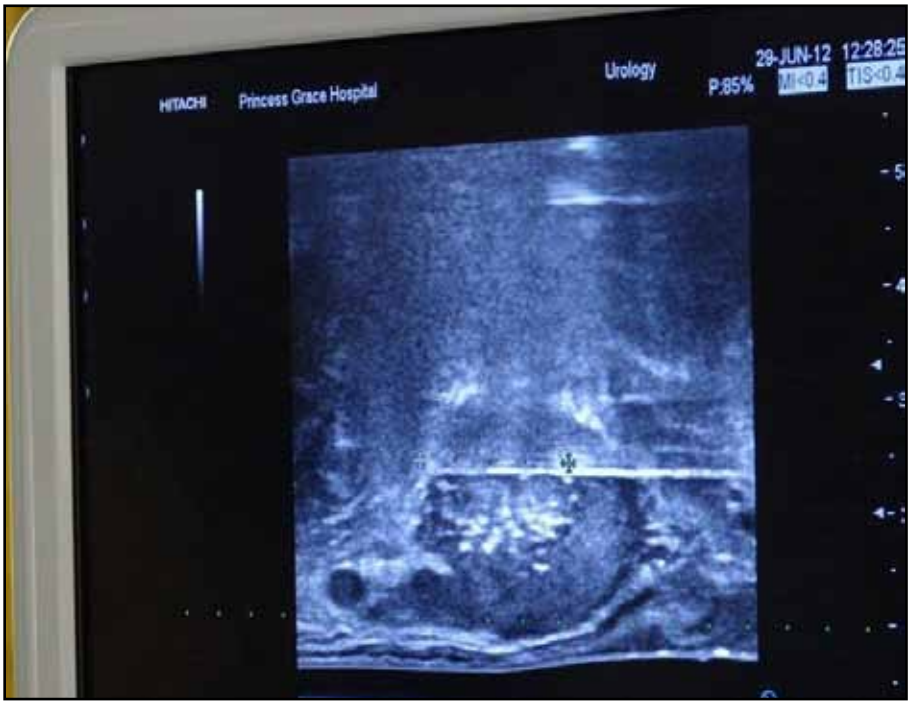

Figure 5a: *Irreversible electroporation (NanoKnife) therapy. Placement of electrodes under ultrasound guidance*

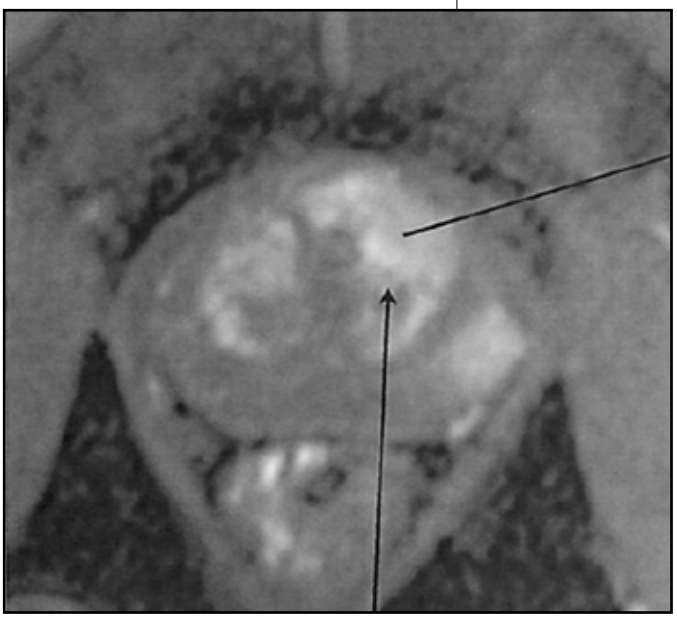

Figure 5b: *MRI image of prostate tumour prior to NanoKnife therapy. The cancer is an anterior tumour seen on MRI Diffusion weighted imaging. Arrow points to tumour*

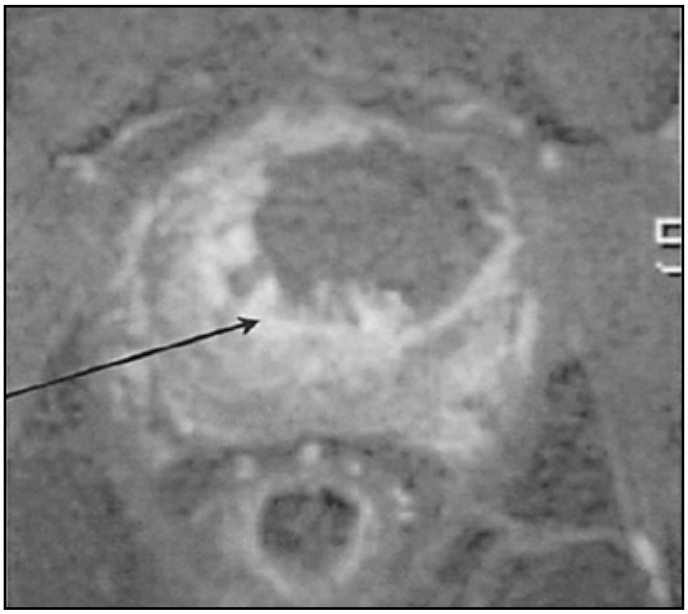

Figure 5c: *MRI image following NanoKnife therapy showing complete ablation of the tumorous area. Arrow point to the ablated tumour*

Cancer Research Centre – NSW) include the use of imaging, improving potency after robotic surgery, focal therapy, improved quality-of-life outcomes after different treatment options and finally imaging and immunotherapy for advanced disease.

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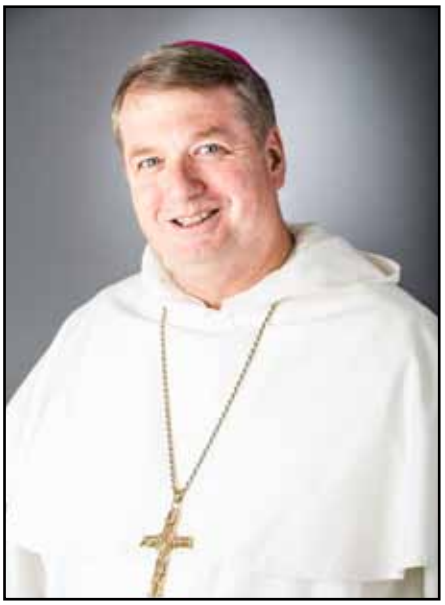
The Sandra David Oration

Healthcare rationing in Australia: should the young be favoured over the elderly?



Bishop Anthony Fisher OP

1. Introduction[1]

One of the most memorable lines in rock history is "I hope I die before I get old" from The Who's 1965 hit My *Generation*. When sneered in Pete Townshend's distinctively frustrated stutter, these words were symbolic of an attitude that marked many in his generation and from which Western culture is yet to recover. But how old is 'old'? Sandra David, for some years a Sister of Charity, educator and missionary, in whose memory this annual lecture is given, was only 57 when she died. This does not seem old to me, yet Janet Roebuck, in her classic study of the evolution of the idea of old age, puts it around 50.[2] Many countries have adopted 65 as the statutory retirement age, a point first chosen by Bismarck for the cynical reason that most working class men were dead by then and so would not draw the pension. Catholic clergy and religious seem to go much longer: you are only old enough to retire at 75 in the clergy, and nuns and popes can go forever...

A more objective definition starts with the natural or 'species-typical' life-span, "the life-span of most of us in the absence of specific mortal diseases and fatal accidents".[3] There comes a stage beyond which most people would think they had had *a fair innings* and would not feel cheated were they to die sooner rather than later; nor would others judge their death premature. (This is not to say that they are *ready* to die or that others will not *grieve* their passing.) Just when that is will be a part-biological, part-environmental, part-cultural matter: *Psalm 90* suggests 'threescore years and ten or four for those who are strong'. The last quarter or so of life up to (and beyond) the typical life-span is 'old age'. Once people have entered that phase of life they may engage in different projects, be honoured as 'elders' or warrant assistance of various sorts (pensions and superannuation, transport concessions, appropriate housing, spiritual care...). Healthcare obviously comes in here, and the specialty of geriatric medicine focuses on this phase of life and its particular challenges.

But should we spend so much on healthcare for the elderly, or would it be better, as some now suggest, to move some or all those resources to younger persons?

2. Australian Context

First, the context in which this question is asked: in 2011-12 Australia spent $140.2 billion on healthcare, amounting to 9.5 per cent of GDP, up from 8.4 per cent only a decade before. Recurrent expenditure on health is now around $6,000 per person, of which governments cover 70 per cent.[4] The Australian Government will continue to increase expenditure on healthcare as our population grows and ages and as advances in healthcare technology and expectations also accelerate.[5]

In 2002 13 per cent of the Australian population were aged over 65; by 2051 this is expected to have more than doubled to 27%. The proportion aged 85 and over will have jumped from 1.4 per cent to nine per cent over the same period.[6] Older people utilise healthcare resources to a much greater extent than younger people; though they account for about a sixth of the general population they utilize more than a third of hospital admissions and around half the hospital bed days.[7]

Calling it 'the intergenerational fairness agenda', some commentators now openly ask whether younger people should be expected to fund this.[8] *In The Pinch: How the Baby Boomers Took Their Children's Future - and Why They Should Give It Back* David Willetts argues that the over-65s are a burden on the young and that their expectations of endless pensions, health and aged care must be curtailed.[9] Daniel Knowles declared in the *Spectator* that "the baby-boomer generation is the most cosseted, untouchable, powerful generation in our history", that they "are living far longer than was envisaged" and costing too much, and that younger people cannot be expected to keep them in the style to which they have become accustomed. The elderly should pay their 'fair share' themselves and draw less upon the public purse.[10]

Allocating healthcare on the basis of age – what I call hereafter *age rationing* – is the policy of excluding persons over a certain age from certain treatments, scaling back care as they get older or preferring the young when there is competition for some intervention. In many countries older people already have less medical contact than their condition warrants and 'ageism' in healthcare has been well documented.[11] South Australian researchers, Julie Luker and Karen Sommers, found that though functional recovery after treatment is similar for older and younger stroke patients, older ones were much less likely to receive appropriate provision in the Australian hospital studied. They concluded that age is

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Bishop of Parramatta

probably a barrier to receiving optimal care after stroke in Australia.[12]

The Australian General Practice Network says there is "substantial anecdotal evidence" that many patients in aged care facilities do not receive timely and appropriate GP and PHC services, and that this suboptimal care leads to avoidable hospitalisations. They cite Catholic Health Australia research that found most aged care providers faced an "ongoing struggle" to secure GP services, with many resorting to inappropriate transfers to emergency departments and patient care being compromised at times.[13] The Australian and New Zealand Society for Geriatric Medicine has made similar findings and noted that where GPs services *are* available to those in residential care it is often only from older gentlemen practitioners.[14] Other studies have at least tentatively suggested that there is systemic or occasional, direct or indirect, conscious or unconscious, age rationing in various areas of healthcare in Australia, as overseas.[15]

3. The clinical case for and against age rationing

The clinical rationale for age rationing is that older people receive little or no benefit or are less likely than younger people to benefit from particular treatments; age is thought to be a useful rule of thumb both for appropriateness of an intervention (even were resources unlimited) and for sorting according to capacity to benefit (where resources are finite).

The problem with this is that age is at best a very rough guide to prognosis: it is the multiple diseases and physiological impairments that commonly accompany old age which affect average outcomes from some medical interventions, not age itself. Because individuals vary enormously in their rate of biological ageing it would therefore seem more logical to use the relevant physiological impairments as the clinical basis for rationing rather than the surrogate of age.

Though counterintuitive, the elderly often respond better than the young to certain treatments and a medical 'stitch in time' for the elderly can save 'nine' down the track, thereby saving resources overall. Dialysis patients over 65 have a better survival rate than those between 55 and 64; renal transplants are as successful in the elderly as in younger people. There is likewise little difference between younger and older recipients of many cardiac interventions. Geriatrician John Grimley-Evans says denying the elderly treatments on the grounds of supposedly 'poor prognosis' is often a case of 'aggravated ageing'.[16] Surveying the evidence John Young concludes that age rationing is "unsustainable" on clinical grounds.[17]

4. The fair innings case for age rationing

Nonetheless, many people think that *ceteris paribus* the younger person should get the ICU bed or heart-for-transplant, for ethical rather than clinical reasons.[18] Australian philosopher Peter Singer argues that since healthcare rationing is inevitable we should use a rational basis for doing it: "life-years saved" would be one such rational basis; even better would be quality of life years saved; either way, putting scarce healthcare resources into the young will yield longer and greater benefits.[19] Yet the Australian population is wary of such utilitarian reasoning. Nord et al suggest "that Quality of Life Years (QALY) maximization receives very limited support when the consequence of the maximizing strategy is a perceived loss of equity".[20] In other places I and others have argued that QALYs do not withstand clinical and philosophical scrutiny as a basis of healthcare allocation. [21]

The classic ethical cases for age rationing were elaborated by Daniel Callahan and Norman Daniels.[22] Both began with the notion of the fair innings or "a life long enough to experience those opportunities that life typically affords people".[23] For individuals to seek more than a natural life-span, especially at the expense of other important goods, might represent a lack of *prudence* or *fortitude* with respect to sickness and death, and a kind of *intemperance* with respect to healthcare. St Basil the Great counselled Christians to avoid treatment that "requires such undue thought or effort or expenditure as to make our whole life revolve around solicitude for the flesh."[24] Different temperaments, commitments and life-plans mean people prioritise life and health differently, but there comes a point where seeking more may be both vain and in vain.

What's more, expecting others to foot the bill for one's aspiration to endless earthly life and health might represent an unreasonable preference for self and disregard for others and the common good.[25] Healthcare systems may aspire to give everyone a good chance of a reasonable length of life in reasonable health. But faced with competing demands they must taper off provision to those who've already had this in favour of those who have not. Last year Callahan claimed the voracious appetite of the elderly for healthcare was making them a *hazard* to the young.[26] "A good society ought to help young people become old people, but is under no obligation to help the old become indefinitely older."[27]

There are, however, a number of problems with the fair innings rationale for age rationing. What length of life might one *reasonably* expect and what health opportunities up till then?[28] Is it unreasonable for someone in Swaziland to aspire to more than the 31.9 years 'typically afforded' in that region? As technology and economy improve so does life expectancy, and we rightly rejoice that more people enjoy a longer period of old age, in better average health, than was common in the past.

Nor is it clear that prudence would counsel skewing healthcare entitlements towards one's early years, as the fair innings theorists assert. Many older people do in fact want healthcare such as resuscitation despite their children and health professionals thinking otherwise; what older people judge as adequate 'quality of life' is also different.[29] A 2007 study in *Nursing Ethics* found people over 60 feared younger people categorizing them as 'old' because this means 'low priority' for healthcare.[30] Even if people behind a 'veil of ignorance' would prefer age rationing, those who actually suffer the burden of such a policy are better placed to assess its reasonableness.[31]

5. A FAIRNESS CASE AGAINST AGE RATIONING

5.1 What justice requires

Fair innings accounts commonly assume that justice requires that people get the same amount of resources such as healthcare.[32] But every parent understands that larger and older children need more food; every doctor understands that sicker people need more healthcare. If healthcare is intended for the sick as such, then *prima facie* the just way to allocate it will be *to the sick*, and first *to the sickest*; no wonder that the elderly receive much of this attention. No-one complains that children chew up a 'disproportionate' share of education resources: that is precisely whom they are for!

Healthcare has traditionally expressed and been governed by Hippocratic and Judeo-Christian ideals of valuing people equally; it has therefore been allocated on the basis of need – as far as possible, addressing equal needs equally and different needs differently.[33] To adopt different principles that deprive the elderly of healthcare could reflect and would generate further bias against an already vulnerable group.[34] Those who live 'too long' would be seen and treated as burdens; sensitivity to their needs would be dulled.[35] Justice demands better.

5.2 What medicine requires

Furthermore, healthcare is not just a 'resource' like a mineral to be distributed by the free market or government. The doctor-patient relationship concerns a profound human service not well captured by consumer language or resource allocation concepts. Age rationing tends to homogenize 'the elderly' in the eyes of carers as a demographic rather than several individuals, indeed as a swarm of voracious but unworthy consumers of a resource which must be guarded from them.[36] Healthcare would be radically affected were professionals expected to assess who has had their 'fair share' of life-span or opportunities before 'wasting' any more attention on them.[37]

It should also be recognized that the rescue imperative of traditional medicine – which can be criticized for encouraging healthcare profligacy – has also been very fruitful both in assisting particular patients and in advancing medicine itself. Geriatric medicine and healthcare more generally would not advance were the elderly or very sick abandoned.[38]

5.3 What the elderly deserve

Furthermore, the elderly are the ones who, on average, have made the greatest contribution to the health system as taxpayers, as well many other areas of society, in the reasonable expectation that their needs would be accommodated in due course. To deny them healthcare could amount to unjust enrichment, even theft, by the young.

One way societies that treat the elderly less well than they might in other spheres still demonstrate that they value older people is by providing dignified health and aged care. Such care expresses fundamental values such as equal respect for persons, the sanctity of life and the rescue imperative, concern for the weak and suffering, and reverence for elders. As the costs of health and other care of the elderly continue to rise, there will be a pressure to scapegoat, abandon, even kill, the elderly as a cost-cutting measure.[39] There are good reasons to resist that pressure now by a strong insistence that age not be a criterion of healthcare distribution.[40]

5.4 What healthcare need implies

A satisfactory resolution of healthcare allocation dilemmas begins by offering some account of the place of life and health in a human story and what is needed to promote those goods; of personal responsibility for health and healthcare; of the traditions, norms and virtues of healthcare practice; of the responsibilities of all societies to provide for the needs of their members in healthcare; of the capacities and proper goals of our particular society; and of the scope and limits of the right to healthcare.[41] This will suggest that patients, health professionals and health services should give priority to people's most important needs over less important ones, and to those with more important needs over those with less important ones.

On this needs-based account of healthcare allocation, priority should be given *ceteris paribus* to the patient:

- whose need is more urgent
- who is more likely to benefit from the treatment or likely to gain the greater or longer benefit from it
- who is likely to gain the same benefit from less of the treatment or need the treatment for a shorter time or less frequently
- who is likely to suffer the lesser burden from the treatment or likely to suffer the greater harm without it or has fewer or no real alternatives to the treatment.

5.5 What Christian faith inspires

Justice, on this account, supports healthcare allocation according to need but not age.[42] But the distribution of healthcare is not only about justice, narrowly construed. Healthcare systems also tell a story of the kind of people we are and wish to be. Care for the elderly reveals the quality of intergenerational relationships, attitudes to ageing and the elderly themselves, filial affection, gratitude and duty. Their inclusion suggests we value life and health, above all persons, even if they are frail, vulnerable, sick or suffering.[43] Age rationing suggests a very different narrative.

Christians tell the story of the Good Samaritan by themselves engaging in healing with neighbourly compassion and generosity. We cannot imagine the Good Samaritan assessing whether the man beaten and left for dead had already had a typical life-span or sufficient life opportunities, or doing a QALY and cost-benefit analysis before deciding whether he was worth investing care in. That we don't know whether the victim in the original story was young or old highlights that age is irrelevant to such a corporal work of mercy.[44]

In *Evangelium Vitæ* St John Paul II wrote of the 'intolerable' neglect that some of the elderly, handicapped and dying experience. He exhorted us "to preserve, or to re-establish where it has been lost, a sort of covenant between generations", a relationship of acceptance,

solidarity, closeness and service.[45] This would suggest a preferential option for the elderly in healthcare rather than rationing against them.

Conclusion

The elderly are not a problem, market or budget: they are real individuals, our own people, ancestors, eventually ourselves. Healthcare is largely *for them*, not something we have to keep *from them*. Of course we need principles of fairness here and virtues like medical temperance. But to wish we were dead before we are old, or that the old were dead before they burden us, is no anthem for a good society.

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New Australian Asthma Handbook 2014

This article provides an overview of the process for the development of the new Australian Asthma Handbook and a summary of the main changes from the previous version.

Australia was one of the first countries to publish asthma guidelines with an article in the *Medical Journal of Australia* in 1989 titled *Asthma Management Plan*, 1989 by Anne Woolcock et al **(Figure 1)**. This was followed by the *Asthma Management Handbook* in 1990 produced by the National Asthma Council (NAC) a body that was established in the late 1980s in response to the then epidemic of asthma deaths in Australia. The mission of the NAC is to "bring together all forms of endeavour in the field of asthma and associated conditions in order to improve the quality of life and health outcomes of people with asthma and their carers".

There have been 6 previous versions of the *Asthma Management Handbook*, the last produced in 2006 **(Figure 2)**. These have all been hard copy booklets with identical web site content. The challenge that the NAC has now addressed largely in response to a user survey is to progress to an interactive digital format. So the latest version launched in 2014 is primarily a web- based resource at ästhmahandbook.org.au" **(Figure 3)** and renamed the *Australian Asthma Handbook* accompanied by the *Quick Reference Guide* **(Figure 4)**. There is also a "digital patient version of the Handbook called My Asthma Handbook **(Figure 5)**.

Australian Asthma Handbook process: this was commenced in 2010 with a survey of over 1000 primary care health professionals to determine preferences for the format and content of the next version, evidence of gaps in quality of care or quality use of medicine and identification of topics needing updating.

This resulted in the prime on- line source (*Australian Asthma Handbook*) accompanied by a 38 page hard copy booklet, *Quick Reference Guide*.

The *Australian Asthma Handbook* Version 1.0 was launched in Canberra on

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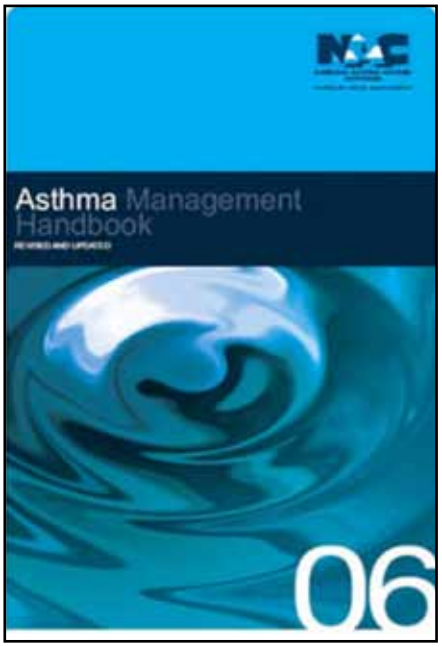

Figure 2: *Asthma Management Handbook 2006*

A/Prof Janet Rimmer

THORACIC SOCIETY OF AUSTRALIA AND NEW ZEALAND

Asthma management plan, 1989

Ann Woolcock, Abraham R. Rubinfeld, J. Paul Seale, Louis L. Landau, Ral Antic, Charles Mitchell, Harold H. Rea and Paul Zimmerman

The aim of publishing this plan is to provide guide-lines that can be used by all doctors who treat patients with asthma. It is hoped that, in the long term, improved treatment will reduce the morbidity and mortality that is caused by this disease in Australia and New Zealand. Until methods to prevent the disease are found, a rigorous approach to treatment is needed. This requires an agreed management plan that provides a logical approach to the treatment of the disease, and which can be used and adapted by individuals and groups who are interested in improving both the treatment and the education of patients with asthma.

This plan is for the long-term management of patients with asthma and does not deal with the treatment of acute attacks. It applies to all patients of more than three years of age who have symptoms that suggest asthma. These symptoms include wheezing, chest tightness and chronic or recurrent cough. The diagnosis of asthma should be confirmed objectively as outlined in the plan.

The current concept of asthma

In this article, the term "asthma" refers to the underlying abnormality in the airways and not to the episodes of airway narrowing, which are referred to as "attacks".

Asthma is thought to be a form of airway inflammation that is characterized by oedema, infiltration with inflammatory cells (especially eosinophils), hypertrophy of glands and smooth muscle and damaged epithelium. This inflammation results from the abnormal release of mediator substances but its causes and pathogenesis are not understood completely. The inflammation allows the airways to narrow too easily and too much in response to a wide range of provoking stimuli (triggers), resulting in attacks. In general, the more severe the asthma, the more frequent and severe are the attacks.[1]

Figure 1: *Asthma Management Plan 1989*

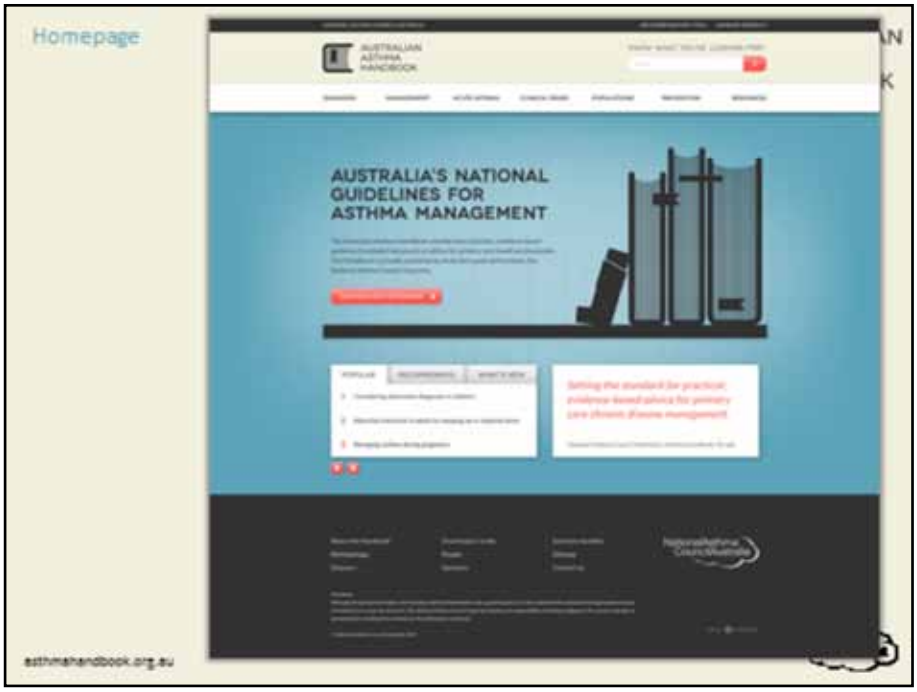

Figure 3: *Web based Australian Asthma Handbook*

4th March by the Honourable Peter Dutton, Australian Government Minister for Health and Minister for Sport. In the first 6 weeks there were 19,361 visits to the *Australian Asthma Handbook* site with most visitors viewing up to 10 pages of content and with an average visit time of 6.45 minutes. Interestingly, 3954 visits were via mobile devices.

Methodology:

Guidelines development was based on AGREE 11 (Appraisal of Guidelines for Research and Evaluation) with NHMRC grading of evidence- based research.

There was an overarching Guidelines Committee which oversaw the whole project. A multidisciplinary approach was utilised with 17 interdisciplinary working groups composed of a range of health professionals assigned to each section. In the process 350 clinical questions were asked and there were 5 systematic reviews undertaken **(see Table 1)**. A range of methodology was used including a limited number of systematic reviews, informal structured literature searches, adaptation of guidance or evidence syntheses from reliable sources and working group consensus. A medical writer was used to provide a cohesive style with a focus on clear practical advice, with a patient-centred approach.

Review was undertaken by independent expert reviewers and stakeholders, and endorsement obtained so far from the key bodies - The Royal Australian College of General Practitioners, Australian Primary Health Care Nurses Association and The Thoracic Society of Australia and New Zealand. The *Australian Asthma Handbook* has also been accepted for inclusion on the NHMRC's Clinical Practice Guidelines Portal which has rigorous selection criteria.

Structure of the website:

The topics are presented as recommendations, written as action statements with separate supporting commentary and more information topics.

There have been a number of key changes from the last version in 2006 to the current version in 2014. These are as follows:

1. Accessibility
2. Terminology
3. Definition of asthma
4. Approach to diagnosis of asthma
5. Classification of asthma control and severity
6. Indications for preventer treatment
7. Considerations before stepping up preventer treatment
8. Emphasis on personalised treatment
9. Exercise
10. Pregnancy

Table 1: *Systematic reviews*

Allergen avoidance	Is it effective in improving asthma control? Which avoidance strategies are most effective in controlling symptoms?
Exercise	Does planned physical activity improve asthma outcomes compared with no planned physical activity in children and adults with asthma?
Weight loss	Does a weight loss intervention or program improve asthma outcomes in obese/overweight adults/children with asthma, compared with usual care? Does surgically induced weight loss improve asthma outcomes in obese patients with asthma, compared with usual care?
GORD	Does GORD treatment/therapy improve asthma control in people with asthma who have a clinical diagnosis of GORD?
Pregnancy	What are the effects of (i) asthma and (ii) asthma treatment on pregnancy outcomes?

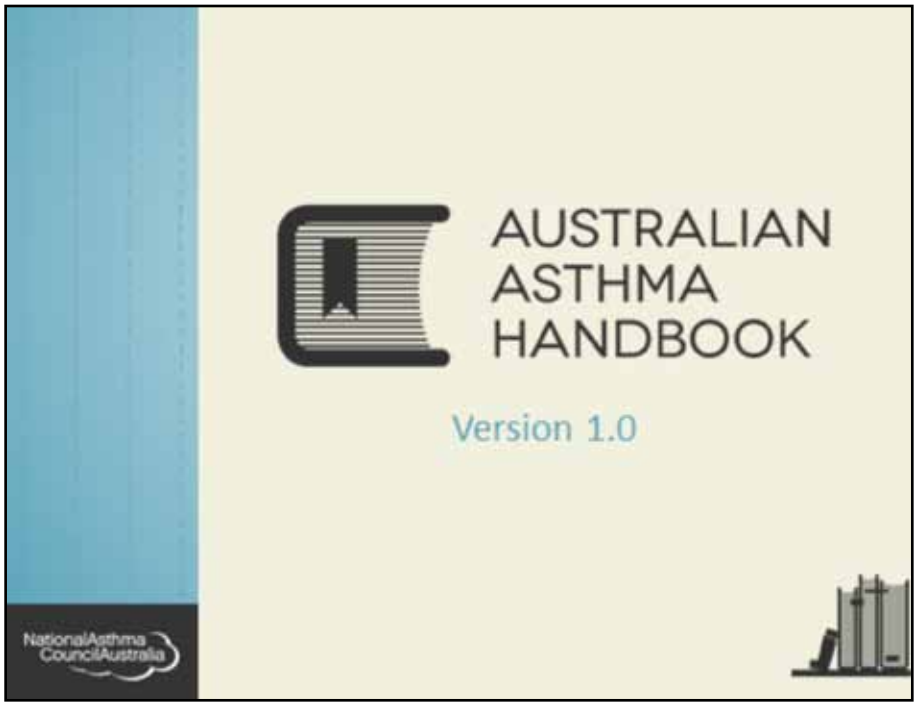

Figure 4: *Hard copy Australian Asthma Handbook*

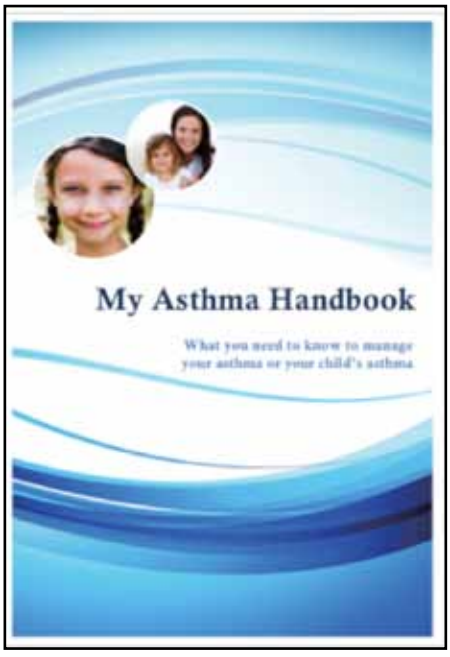

Figure 5: *Digital patient version of the Asthma Management Handbook called My Asthma Handbook*

1. **Accessibility** this is described above.

2. **Terminology Changes**
   - Medications ➠ medicines
   - Categories of asthma medicines have been reduced to try and avoid confusion and to reduce the likelihood of using LABAs (long-acting beta agonists) as sole medications.
     – 2006: relievers, preventers, symptom controllers, combination inhalers
     – 2014: relievers, preventers, combination inhalers
   - Worsening asthma: the term "exacerbation" has been replaced with the word "flare-up".
   - Asthma control: the term "asthma control" has been replaced with "symptom control and future risk"

3. **Definition of asthma**

In 2006, asthma was defined as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular mast cells, eosinophils, T lymphocytes, macrophages, neutrophils and epithelial cells. In susceptible individuals, this **inflammation** causes **recurrent episodes of wheezing**, breathlessness, chest tightness and coughing particularly at night or in the early morning. These episodes are usually associated with widespread but **variable airflow obstruction** that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing **bronchial hyperresponsiveness** to a variety of stimuli.

The 2014 definition is a more practical definition and does not mention inflammation or bronchial hyperresponsiveness but is defined as:

- **Asthma is a chronic lung disease, which can be controlled but not cured**
- In clinical practice, asthma is defined by the presence of **both**:

1. **Excessive variation in lung** function ('variable airflow limitation', i.e. variation in expiratory airflow that is greater than that seen in healthy people) and
2. **Respiratory symptoms** (e.g. wheeze, shortness of breath, cough, chest tightness) that vary over time and may be present or absent at any point in time.

There is additional recognition of the presence of airway inflammation, airway hyperresponsiveness and variable lung function. In addition, it is recognised that asthma is probably a heterogenous disease and in older patients the overlap syndrome with COPD is important.

4. **Diagnosis of asthma**

The current approach to diagnosis is outlined in **Figure 6** and summarises the approach using history, physical examination, the consideration of other diagnoses and documentation of variable airflow limitation. The latter is defined as an increase in FEV1 ≥ 200ml or ≥12% post 100mcg (4 puffs) of salbutamol. If this is not demonstrable, then change may be documented in response to treatment or a bronchial challenge may be required.

5. **Asthma control and severity** was widely used terminology but is now replaced with
   - Asthma control: symptom control and future risk

'Symptom control'

Frequency of symptoms, waking due to asthma, activity limitation, reliever use (excluding use before exercise). A number of questionnaire tools are suggested including the Asthma Score, Asthma Control Questionnaire and Asthma Control Test which enables the use of a standardised set of questions at each visit.

Lung function no longer included in this domain as overall there is a weak correlation between symptoms and FEV1 in asthma.

'Risk factors'

Or 'future risk' for adverse outcomes, i.e. risk factors for exacerbations, life-threatening asthma, accelerated decline in lung function, side-effects. Low lung function is an important predictor of risk.

Asthma severity is defined as a retrospective label after the patient has been on treatment for at least 3-6 months, and common problems have been identified and treated. This has led to two additional categories of asthma

'Difficult-to-treat severe asthma': due to adherence issues, inappropriate or incorrect use of medicines, environmental triggers or co-morbidity.

'Treatment-resistant severe asthma': control not achieved despite the highest level of recommended treatment, or control can be maintained only with the highest level of recommended treatment

Lung function is now included with future risk rather than with 'current control'. Low lung function is an important predictor of poor outcomes (exacerbations and development of fixed airflow limitation), independent of symptoms. In some patients the discordance between symptoms and lung function is important

High FEV_1 despite frequent respiratory symptoms ‡ think of alternative or additional cause, e.g. cough due to post-nasal drip; vocal cord dysfunction; $beta_2$-agonist over-use; cardiac disease

Low FEV_1 despite few symptoms ‡ think of limitation of lifestyle; poor perception

6. **Indications for preventer treatment**

This means that regular treatment with an ICS-based preventer is now recommended for ***most*** adults with asthma with an emphasis on low dose ICS **(Table 2)**. The rationale for the extension of therapy to a wider asthma population is, that even so-called mild or intermittent asthmatics can have severe exacerbations, and that low-dose ICS is strongly protective for asthma-related death at **low cost and risk of side effects. It should be noted that combination therapy is very widely used in Australia so that about three quarters of patients are prescribed combination (ICS/LABA)** therapy which is much more expensive than an ICS alone.

The differences between initiation of prevention therapy from 2006 and 2014 are shown in **Table 3**.

7. **Stepping up and stepping down therapy:**

This concept should be discussed early in the treatment of adults. It is relevant to

Table 2: *Total daily dose equivalents of inhaled corticosteroids for adults*

Total daily dose (mcg)	HFA-beclomethasone	budesonide	ciclesonide	fluticasone propionate	fluticasone furoate
low	100-200	200-400	80-160	100-200	NA
medium	250-400	500-800	240-320	250-500	100
high	>400	>800	>320	>500	>200

the initial stabilisation of symptoms and also to the management of flare- ups which should be facilitated with the use of a personalised Asthma Management Plan (www.asthmahandbook.org.au/management/adults)

8. Emphasis on personalised treatment

Asthma management is not just about medications but also the provision of information, continuing education, skills and tools for self-management, including:

- training in correct inhaler technique
- information and support to maximise adherence
- information on smoking, healthy eating, physical activity, healthy weight and immunization.
- a written asthma action plan which enables management of flare-ups.
- information about avoiding triggers, where appropriate.
- identification and management of comorbid conditions that affect asthma or contribute to symptoms. These could include upper airway disease such as rhinitis and rhinosinusitis, upper airway dysfunction, reflux disease, obesity, obstructive sleep apnoea, chronic airflow limitation, aspirin exacerbated airway disease, allergic bronchopulmonary aspergillosis.

9. Exercise and asthma

There is excellent evidence that physical training should be recommended to adults and children with asthma, as part of overall asthma management, for its beneficial effect on quality of life. This may include focusing on and managing exercise induced bronchoconstriction. It is important to advise patients that having asthma should not prevent them doing physical activity, including exercise training.

10. Pregnancy

Recent studies have emphasised the importance of avoiding untreated or poor asthma control as well as avoiding exacerbations during pregnancy which may lead to adverse outcomes for both the mother and baby. The risks associated with poor asthma control outweigh the risks associated with the use of asthma medicines. Similarly most asthma medicines can be safely used by breastfeeding women. Switching asthma medicines to Category A listed medicines is preferably done prior to conception. During pregnancy, asthma should be regularly monitored with the aim of maintaining asthma control. Down titration of medicines is not a priority.

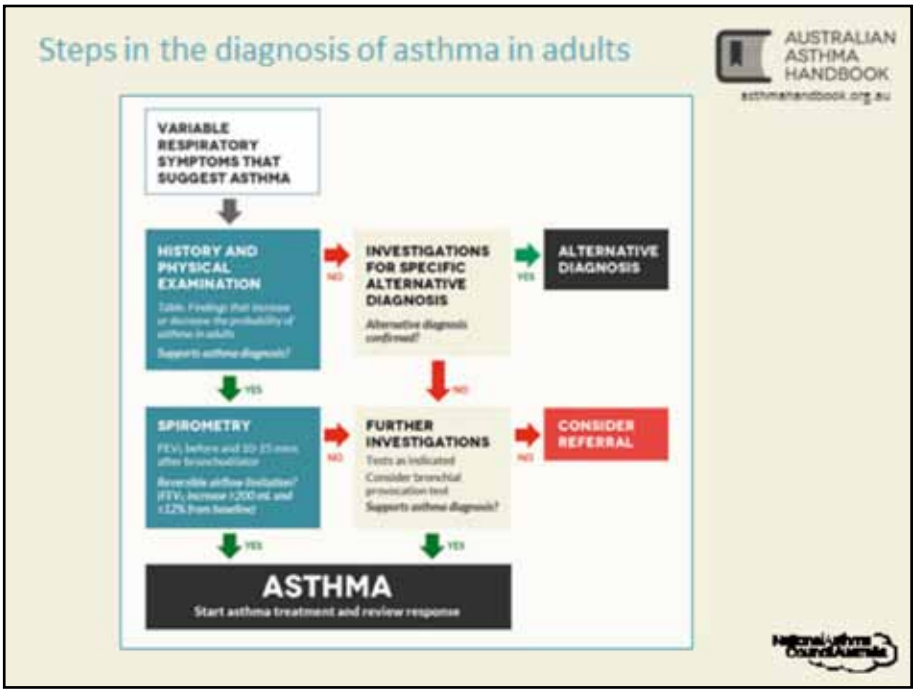

Figure 6: *Algorithm for the steps in the diagnosis of asthma*

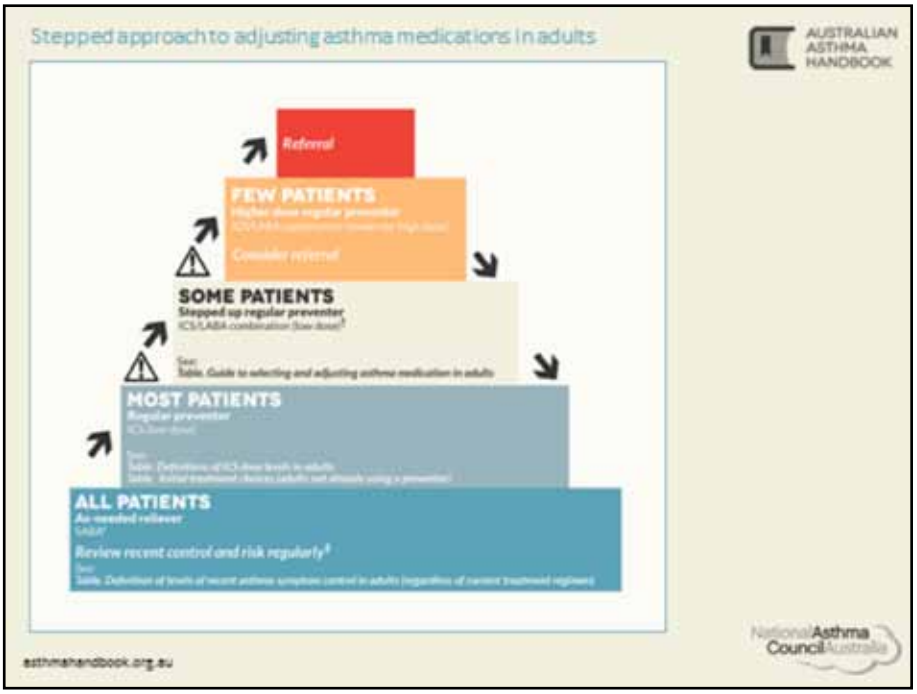

Figure 7

The overall risk of women with asthma having a baby with a minor congenital abnormality is slightly greater than non-asthmatic women, but there is no increase risk in major congenital abnormalities.

The 2014 **Australian Asthma Handbook** continues a long tradition of excellence in asthma education with a major step forward in the utilization of digital technology.

Table 3: *Initiation of preventer (inhaled corticosteroid therapy, ICS) therapy in asthma:*

	2006	2014
SABA*	≥3 times per week	NA
exacerbation	Last 2 years	Last 12 months
symptoms	≥3 times a week	> 1 every 2 weeks
nocturnal asthma	≥1 a week	NA
reduced lung function	yes	NA

*SABA: short acting beta 2 agonists

Colorectal Screening – it does make a difference

Dr Alissa Walsh

Introduction

Colorectal cancer (CRC) continues to be a major health problem for Australians, being one of the commonest cancers in Australia. One in 20 Australians are likely to develop the disease. From age 40 there is increased risk for individuals, which rises sharply at age 50. The latest national figures available in 2001, reveal colorectal cancer as being responsible for 13 per cent of cancer deaths. Each year there are about 12,600 new cases of CRC and 4,700 deaths.[1]

CRC is a malignant tumour that starts in the bowel wall and is generally confined locally for a relatively long period before spreading through the bowel wall and metastasising to lymph nodes and other parts of the body. Survival rates are significantly improved when the disease is detected and treated early. The aetiology of CRC is complex and appears to involve interactions between inherited susceptibility and environmental factors.[2,3] CRC usually requires intensive treatment, which imposes a considerable burden to the patient, a high risk of complications and high costs. Despite advances in treatment, 40-50 per cent of patients presenting with symptomatic CRC eventually die of metastatic disease.[4]

Risks for Colorectal cancer

Risk factors for CRC are: age over 40 years, a personal history of adenomas or CRC, a family history of adenoma, CRC or gynaecological cancer, or a personal history of Inflammatory Bowel Disease (ulcerative colitis and Crohn's disease).

CRC risk in relatives of patients with adenoma or CRC is approximately doubled compared to the average risk.[5] The risk is substantially (three- to six-fold) greater for those who have a first-degree relative with CRC diagnosed at an early age (<45 or 55 years) or when two close relatives have had CRC irrespective of age at diagnosis.[6] The observed increases in risk may be due in part to shared dietary and lifestyle factors, either alone or in combination with predisposing genetic factors.

Interest in hereditary predisposition to colorectal cancer has increased greatly over the past 15 years, largely because of identification of genes associated with familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch syndrome. Both disorders have an autosomal dominant mode of transmission within families and carry a very high risk for cancer. In untreated FAP, mutation carriers have a lifetime risk for colorectal close to 100 per cent.[7] In HNPCC, their risk for colorectal and or other syndrome cancers is 70-90 per cent.[8] We encourage that all patients be guided to a family cancer registry as this has been shown to reduce cancer incidence in family members.[9]

Polyps

The majority of CRCs are thought to arise from benign precursor lesions called adenomas and the "adenoma to carcinoma" pathway has been acknowledged for decades and is well documented. Adenomas are usually elevated and may be sessile or pedunculated. A minority are relatively

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flat and these may be slightly raised, flat or slightly depressed. Adenomas are typed according to histological architecture as tubular, tubulovillous and villous. They are also classified according to grade of epithelial dysplasia as mild, moderate and severe, or alternatively, as showing low- and high-grade dysplasia. The progression of early adenoma to invasive cancer generally takes years and this is one of the main characteristics that makes CRC suitable for population screening as this time allows such a good window of opportunity.

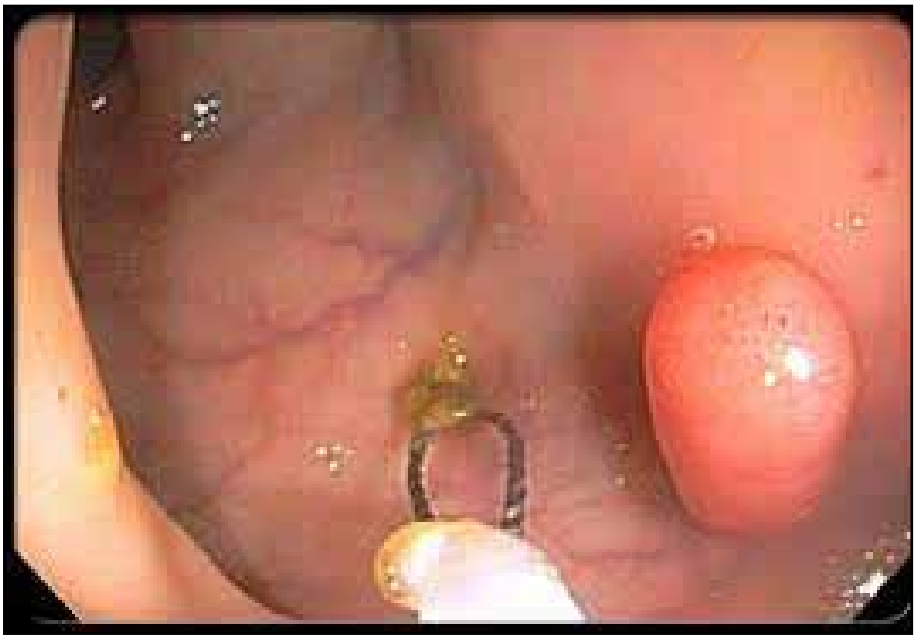
More recently, another precursor lesion has been recognised: the serrated polyp. Serrated polyps are characterised by a saw tooth appearance of the crypt epithelium. Although initially felt to be innocent, it is now known that they are prone to develop into CRC and are likely to be the cause of "missed" or interval cancers after colonoscopic screening. This has prompted considerable interest in removal of these polyps to prevent the development of colorectal cancer.[10]

Alarm symptoms

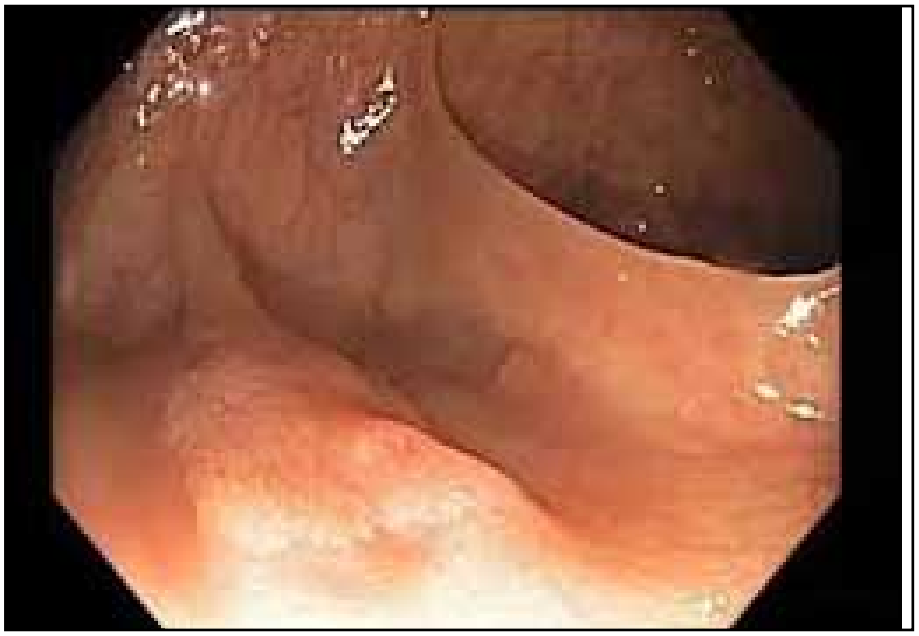
Rectal bleeding is the most important symptom. It is not always possible to be certain from the patient's description of the bleeding that is necessarily originates from a simple lesion such as haemorrhoids, rather than an adenoma or cancer. Indeed, haemorrhoids may coexist with colorectal neoplasia. Therefore rectal bleeding requires investigation with a colonoscopy. Gastrointestinal bleeding is a common cause for iron deficiency anaemia. It is usually occult and CRC is a common pathology. Other symptoms include change in bowel habit or abdominal pain.[11]

Screening by Faecal Occult Blood testing

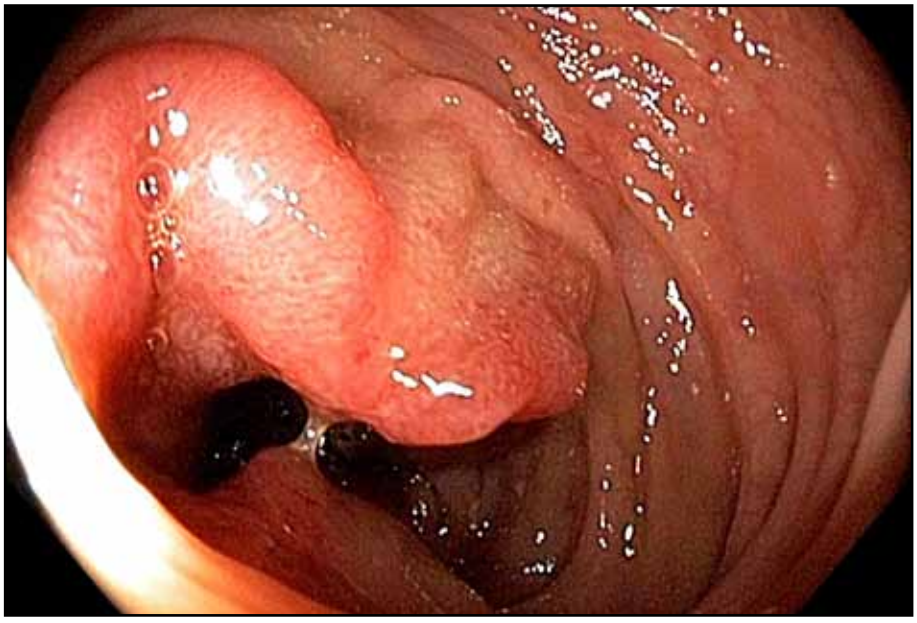
Faecal occult blood tests (FOBTs) are a non-invasive and cheap assay to detect microscopic amounts of blood that a considerable proportion of advanced adenomas and the majority of cancers give rise to. Screening for CRC based on FOBT has been demonstrated to reduce mortality in population studies. Randomised controlled trials at the



An adenoma



A serrated adenoma



A colorectal cancer

population level indicate that screening with FOBT reduce colorectal cancer in populations selected on the basis of age. These have shown benefit for 45-50 years and upward. FOBT screening reduces overall mortality from colorectal cancer by 15-33 per cent and reduces incidence of colorectal by 20 per cent.

Two main types of FOBT are available – guaiac tests and immunochemical tests. Guaiac tests are based on the pseudoperoxidase activity of haem. Immunochemical tests utilise antibodies against human haemoglobin and are not affected by diet or medications, making dietary restriction unnecessary and therefore participation rates within the community are higher. They are highly sensitive for colonic bleeding. In population screening programs, a person with a positive FOBT has a 30-45 per cent chance of having an adenoma and a 3-10 per cent chance of CRC. FOBT serve to refine the likelihood of CRC being present. A person with a positive FOBT is 12-40 times more likely to have CRC than somebody with a negative test.[12]

It is mandatory that a positive FOBT (even if only one of the samples is positive) be appropriately investigated by diagnostic evaluation of the colon.

Colonoscopy

Colonoscopy is currently the most accurate investigation for assessing the colon and rectum. The sensitivity of colonoscopy for CRC is 95 per cent.[13] Colonoscopy allows biopsy and histological confirmation of the diagnosis. It also allows identification and removal of synchronous polyps. Screening intervals depend on family history and number and type of polyps removed. Screening colonoscopy studies tend to identify up to seven times more patients with cancer annually than are diagnosed with symptomatic cancers in the absence of screening.[14]

Colonoscopy is performed as a day case procedure and usually needs sedation. It is associated with a complication rate of 0.14 per cent, compared with a rate of two per cent for therapeutic colonoscopy. In a review of six prospective studies of colonoscopy, about one in 1000 patients suffer perforation, three in 1000 suffer major haemorrhage, and between one and three in 10,000 die as a result of the procedure. There are occasional, serious complications associated with bowel preparation of the use of sedation.[15]

CT colonography

CT colonography (virtual colonoscopy) is probably the best test for patients with an incomplete colonoscopy or for those patients who cannot undergo colonoscopy. It is inaccurate for lesions less than 1cm in size. A good preparation is important for an adequate test. The sensitivity and specificity per patient of CT colonography for lesions of 5mm or greater is 67 per cent and 75 per cent respectively, and for lesions greater than 1cm, is 90 per cent and 82 per cent respectively. MR colonography is an experimental procedure that is currently being investigated and evaluated.[16,17]

Conclusion

CRC is an ongoing important health issue. There is vast evidence that population screening reduces colorectal cancer incidence and mortality. Through adequate history taking with emphasis on symptoms and family history, FOBT and colonoscopy, colorectal cancer can be prevented or detected early at which stage there is a high cure rate.

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Controversies in Glioma Management

Dr Cecelia Gzell

Introduction

Gliomas arise from glial cells and include astrocytic tumours, oligodendrogliomas, ependymomas, and mixed gliomas. They are the most common primary intracranial tumour and represent approximately 80 per cent of malignant brain tumours.[1,2] More than 1,400 new cases of malignant brain tumour are diagnosed each year in Australia[3] and whilst gliomas remain relatively rare compared to breast, prostate, and lung cancers, they cause considerable morbidity and mortality. Glioblastoma multiforme (GBM, WHO grade IV) remains the most common histological subtype in adults and the incidence in Australia within patients aged >65 years is increasing.[4] Currently the median age of diagnosis of GBM in Australia is 61 years[5] and the median survival is in the order of 15 months.[6] Despite the introduction of concurrent and adjuvant temozolomide chemotherapy to standard adjuvant radiotherapy, only approximately 30 per cent of patients aged <45 years, and two per cent of patients aged over 65 years survive longer than 2 years.[2] Conversely, low grade gliomas (WHO grade II) which are typically diagnosed in younger patients (~20-45 years) have significantly longer survival with an expected 5 year survival of >75 per cent.[7,8]

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Adult Low Grade Glioma Management

The optimal treatment algorithm in adult low grade glioma (LGG, WHO grade II) remains unclear. At present the two ongoing controversies remain the extent of surgical excision and the timing of radiotherapy.

With respect to the extent of surgery, there appears to be an international trend toward upfront aggressive surgery rather than biopsy and watchful waiting approach.[7–11] Smith et.al.[7] demonstrated significantly improved five and eight year survival with ≥90 per cent extent of resection (EOR) compared with <90% EOR (5yr survival of 97% v 76%, and 8 year survival of 91% v 60 per cent respectively). Another study conducted in Norway at two distinct hospitals which opted for separate approaches to management (one used the biopsy and watchful waiting approach for all patients and the other used an upfront surgical management approach) demonstrated similar findings.[8] Both hospitals had a median follow-up of seven years and similar baseline characteristics of the patients. The median overall survival in the biopsy group was 5.9 years and the median survival in the surgical group was not reached. The estimated five year survival was 60 per cent versus 74 per cent respectively. They demonstrated an absolute survival difference of 14 per cent at five years between the two approaches and 24 per cent at seven years **(Figure 1)**. There is now more convincing evidence that early aggressive surgery improves overall survival but it remains unclear whether it reduces malignant transformation.

The timing of radiotherapy (RT) also remains controversial. The landmark European Organisation for Research and Treatment of Cancer (EORTC) trial of immediate versus delayed RT showed no difference in median survival between the two groups but prolonged progression-free survival in the upfront RT group.[12] Is the lack of difference in median survival purely the result of inadequate follow-up as almost all patients received RT at some

point? To address this ongoing question the EORTC and Radiation Therapy Oncology Group (RTOG) are both conducting prospective trials seeking to evaluate the efficacy of radiotherapy and either temozolomide or a combination of procarbazine, vincristine, and lomustine (PCV) in high-risk LGG patients.

One of the concerns over early or "upfront" radiotherapy has been the risk of neurocognitive impairment in a group of patients that is likely to live a reasonable length of time and therefore likely to be burdened with potential late effects of treatment. Despite studies attempting to evaluate neurocognitive outcomes after radiotherapy, the jury is still out with respect to how much damage is caused by radiotherapy, as any neurological deterioration is likely to be a cumulative effect from the tumour itself, surgery, and radiotherapy.[13,14] Certainly in my practice I routinely spare the hippocampus (at least contralaterally, if the ipsilateral hippocampus is within the RT field) in all patients in an attempt to reduce any late neurocognitive neurotoxicity **(Figure 2)**.

In addition, there is emerging evidence for the use of chemotherapy to avoid or delay RT (particularly in patients with oligodendrogliomas who have large volume of disease). There is evidence that both PCV and temozolomide are efficacious in LGG (more so in oligodendroglioma than astrocytoma, particularly if there is 1p chromosomal loss) but the time to response is long and may take many months and therefore patients may need to be treated for up to 24 months.[15]

Thus LGG patients remain a heterogeneous group with no clear optimal treatment paradigm and in whom multidisciplinary discussion is vital.

Anaplastic Gliomas

There have been recent significant changes in the role of chemotherapy in WHO grade III (or anaplastic) oligodendrogliomas or oligoastrocytomas. Traditionally these tumours were treated with maximal safe surgical resection followed by radiotherapy with the addition of temozolomide considered optional. However, the long-term follow-up data of the EORTC 26951 and RTOG 9402 trials were published in 2013[16,17] and revealed that the addition of sequential PCV chemotherapy to adjuvant RT resulted in improved median survival (MS) in patients in the chemotherapy arm (42 v 31 months) with patients who were 1p 19q co-deleted having longest survival (MS not reached v 112 months in RT only arm) **(Figure 3)**.[17] With these results came the difficult question for clinicians- can these results be transferable to likely expected results using temozolomide instead of PCV? Certainly some centres overseas have returned to using PCV in light of these results. Temozolomide is better tolerated than PCV chemotherapy and in the EORTC and RTOG trials the median number of cycles delivered was only three of the prescribed 6. In Australia, the preference remains to continue using temzolomide however, PBS funding of temozolomide in grade III tumours is lacking and this results in considerable out of pocket expense for patients. But with this evidence, my practice would be for all 1p 19q co-deleted patients to have RT followed by six cycles of temzolomide.

With respect to anaplastic astrocytomas, or non co-deleted oligodendrogliomas/oligoastrocytomas there is a large international trial currently running to investigate the role and optimal timing of temozolomide in addition to adjuvant radiotherapy, the EORTC 26053, "CATNON" (concurrent and adjuvant temozolomide chemotherapy in non-1p/19q deleted anaplastic glioma) trial. This trial has four arms: RT alone, RT plus concurrent temozolomide, RT plus concurrent and adjuvant temozolomide, and RT followed by temozolomide. This trial, which has not yet closed to accrual, will give us the answer to the never ending question- how much temzolomide is needed? Certainly one of the criticisms of the landmark EORTC paper in glioblastoma[6] was that we still don't know whether the majority of benefit from additional temozolomide is in the concurrent phase of treatment, and whether the sequential phase is actually required. Currently St Vincents is not a registered trial site for the CATNON trial, and for patients who are non-deleted grade III tumours, my preference would still be to give RT followed by six cycles of temozolomide accepting that there will be an out of pocket cost with the temozolomide.

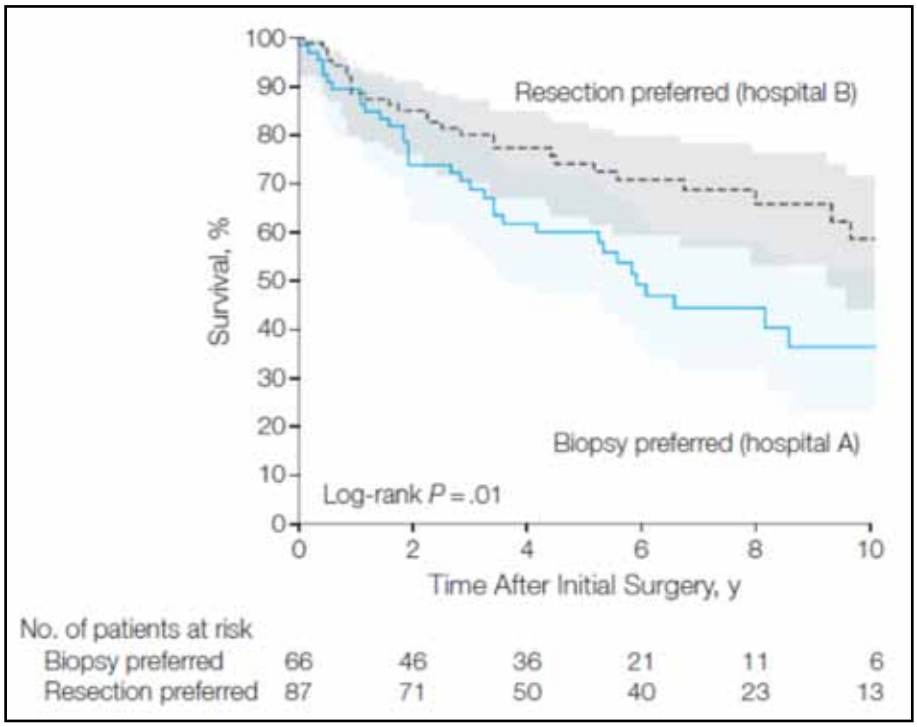

Figure 1. *Survival analysis comparing favoured surgical strategies for low grade glioma (from Jakola et. al.[8] figure 2)*

Glioblastoma In Elderly Patients

Glioblastoma (GBM, WHO grade IV) remains the most common primary brain tumour in adults and continues to carry a poor prognosis despite the addition of temzolomide to adjuvant RT. The optimal treatment pathway for elderly patients remains the most controversial. The landmark EORTC paper[6] limited trial patients to those <70 years and there has remained concerns over the tolerability and efficacy of long-course chemoradiotherapy in elderly patients.

Roa and colleagues[18] conducted a prospective trial of an abbreviated course of RT (40 Gy) versus standard long-course RT (60 Gy) (without the addition of temozolomide in either arm) in elderly patients (>65 years) and demonstrated non-inferiority of the short-course arm. A large international trial of elderly GBM patients (NCIC/EORTC/TROG GBM elderly trial) treated with adjuvant short-course RT (40 Gy) versus the same RT with concurrent and adjuvant temozolomide closed to accrual in late 2013 and the results are eagerly awaited.

I conducted a retrospective study of 109 elderly patients with GBM managed with 60 Gy or 40 Gy RT with or without the addition of temozolomide in 2012[3] and found that patients in the 60-65 year age group should be treated as younger patients would with long-course chemoradiotherapy (60 Gy plus TMZ). Patients older than 75 years demonstrated some (but minimal) benefit from the addition of temozolomide, and are probably best treated with short-course RT alone (40 Gy). Patients in the 65-75 year age group definitely gain benefit from long-course chemoradiotherapy but performance status, social support, and co-morbidities/performance status need also be considered before embarking on this approach.

Are there some elderly patients who are better treated with TMZ alone? The NOA-08 trial by Wick and colleagues (19) was a prospective trial of long-course RT (60 Gy) versus TMZ alone in elderly patients with GBM or grade III astrocytoma and demonstrated non-inferiority of the TMZ alone arm. I feel that patients >75 years who have had subtotal resection or biopsy only with considerable residual disease who are likely to require large-field RT and who are O-6-methlylguaninine-DNA methlytransferase (MGMT) methylated may be better treated with TMZ alone as even short-course RT in this cohort of patients can be quite disabling with lethargy that can be protracted, limit the efficacy of rehabilitation and limit the patient's ability to return to independence.

MGMT methylation testing may be particularly useful in determining which elderly patients will benefit from TMZ but, at present, is not routinely tested. Testing capabilities are only available at selected centres in Sydney and require additional expense for the patient. Results can take up to 2-3 weeks to be reported and this can occasionally delay treatment decisions. In younger cohorts the MGMT status (whilst interesting and prognostic) doesn't change treatment decisions but it can be vital in elderly patients.

Pseudoprogression

Pseudoprogression is a radiological diagnosis of an increase in size of contrast-enhancing lesion(s), or new areas of contrast enhancement immediately after radiotherapy, with subsequent improvement without any further treatment **(Figure 4)**. The underlying pathophysiology is poorly understood and the true incidence, timing, and impact on survival is yet to be determined. In the chemoradiotherapy era the incidence has been reported as anywhere from 3-24 per cent[20] with higher rates in patients who display MGMT promoter methylation.[21] With the increasing use of bevacizumab in clinical practice, either as part of the initial adjuvant treatment paradigm or at the time of suspected recurrence, the identification of pseudoprogression is further complicated. Bevacizumab can improve the "leaky" tumour vasculature subsequently decreasing the observed gadolinium enhancement on T1 MRI images, known as "pseudoresponse", or can effectively treat true radiation necrosis (RTN), further complicating interpretation of MRI images.[20,22]

The criteria used to determine response in brain tumours has evolved over the past decade and continues to evolve partly due to the uncertainty involved with these early post-treatment changes on MRI scans and the question that constantly worries both the clinician and the patient: are the changes on the scan just inflammatory or is there early tumour recurrence? And if so, what do we do next? Novel MRI sequences (such as perfusion imaging and diffusion tensor imaging- DTI) have shown some promise in assisting in determining the difference between inflammation/necrosis and tumour but specificity and sensitivity remain less than ideal. Currently, any early MRI changes within the first three months after completing radiotherapy should not necessitate a change in standard therapy. Only after the three month period if there are ongoing (and confirmed on >1 scan) increasing areas of enhancement should discussions about re-craniotomy/second-line chemotherapy be instituted.

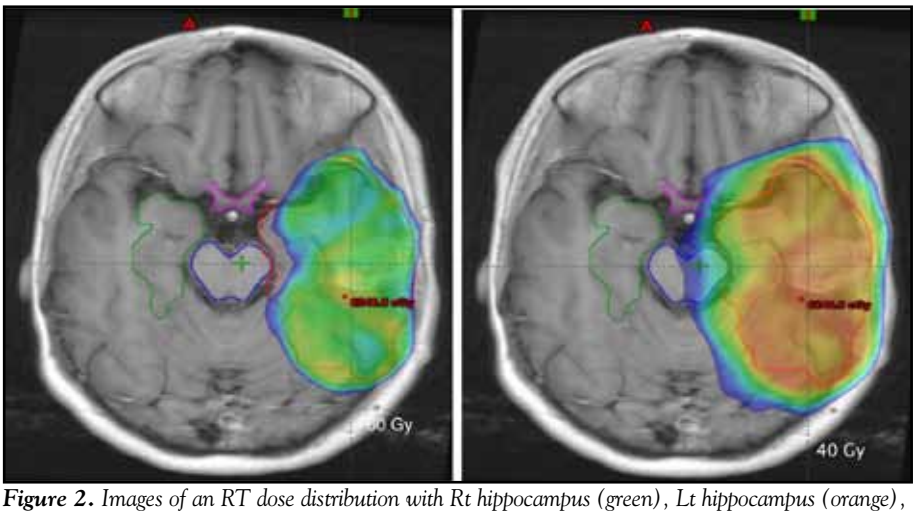

Figure 2. *Images of an RT dose distribution with Rt hippocampus (green), Lt hippocampus (orange), brainstem (dk blue), and optic chiasm (pink) all outlined. The panel on the left shows the distribution of 60 Gray and the panel on the right shows the distribution of lower dose (40 Gray). The Rt hippocamputs is well spared from even low dose of RT.*

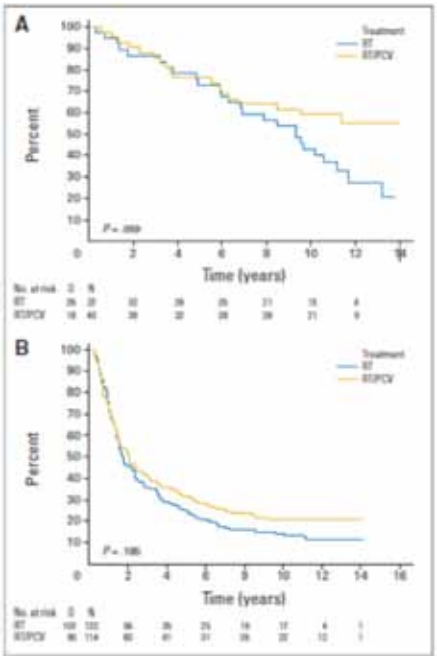

Figure 3. *Overall survival in both treatment arms (A) patients with 1p19q co-deleted tumours, and (B) patients with non co-deleted tumours (from Van den Bent et. al.[17] figure 3)*

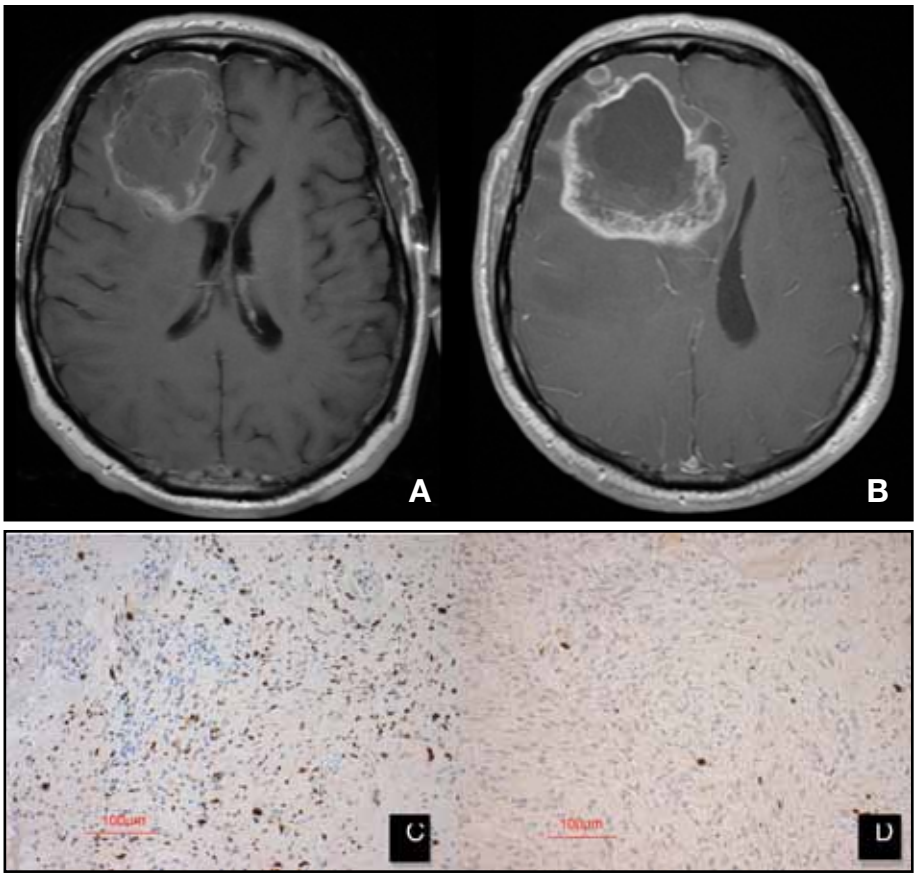

Figure 4. *58 yr old patient with GBM requiring re-operation for symptomatic increase in T1 enhancement not controlled with steroids. Image (A) is T1 + contrast MRI post-operative (prior to RT), (B) is T1 + contrast MRI 1 month after RT, prior to re-operation. This patient had some viable tumour cells on repeat pathology but the Ki67% reduced from 25% (C) to <3% (D). This patient survived for a further 22 months after his second surgery and is representative of outcomes in pseudoprogression.*

Re-irradiation

Previously, high-grade glioma patients with small volume, inoperable relapsed disease would be considered for re-irradiation utilising stereotactic radiosurgery/radiation therapy. These patients would usually have failed second-line chemotherapy and often had more than one craniotomy. However, this targeted radiotherapy was generally limited to lesions of < 3cm.[23] This was due to concern that re-irradiation to larger, overlapping volumes would potentially increase the risk of morbidity with acute oedema or necrosis, thus reducing the therapeutic benefit. However the recent awareness of bevacizumab as a management option for radiation necrosis has expanded the potential for large volume relapses to be managed with re-irradiation, in combination with bevacizumab to minimise the acute morbidity.[22,24] The total dose in these overlapping areas can exceed 100 Gray with minimal toxicity and the use of re-irradiation with concurrent bevacizumab conveys a median survival of approximately 9-10 months.[25]

Conclusion

Improvements in the survival and functional outcome of glioma patients are constantly being made. However, there continues to be controversy within the management for each tumour/grade group of patients that requires resolution. A multidisciplinary approach to the management of these patients is essential to achieve the best possible outcomes.

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New Developments in Cardiac Imaging

Dr James Otton

Introduction

Cardiac imaging and its clinical applications are rapidly expanding. Cardiac MRI and CT, experimental ten years ago, are now in routine clinical use. Echocardiography has morphed from a two-dimensional technique reliant on subjective interpretation to a three-dimensional modality equipped with tools to objectively measure and quantify cardiac function and valve integrity.

The development of these techniques has numerous implications for cardiology but also for a broad range of specialties spanning stroke assessment, pulmonary medicine, endocrinology, haematology and oncology.

This review presents a focused update on novel imaging techniques within cardiology and the broad clinical contexts in which the new techniques may be used. Due to the large number of new techniques, nuclear imaging modalities are not covered within this synopsis.

Echocardiography

While echocardiography has been the mainstay of cardiac imaging for decades, the technique has numerous limitations. Firstly, at least until recently, echocardiography has been a two (and sometimes even one) dimensional imaging technique attempting to monitor a complex three-dimensional structure in motion over time. Standard echocardiography therefore involves a degree of interpolation, assumption or approximation of the true underlying three-dimensional structure.

The second limitation of echocardiography includes the inherently subjective nature of many of the assessments with somewhat poor reproducibility and inter-observer reliability.

A third limitation is the lack of a widely clinically applied measure of contractile function, sufficient to detect small changes as may occur with cardiotoxic medications or even, in some cases, ischemia. All of these limitations have been substantially addressed with recent technological change.

Three-dimensional echocardiography

Advances in ultrasound phase-array design and image processing now enable three-dimensional acquisition of cardiac structures in either real time or over multiple heartbeats with enhanced spatial resolution. In essence, the images are high quality, live and in 3D. An important application of this technique is valve interrogation and in the assessment of structural heart disease, where 3D trans-oesophageal echocardiography can also be applied at the time of the invention to guide device placement.

Complex valvular anatomy, such as leaflet prolapse, clefts or restricted motion **(Figure 1)** may be easily visualised and can assist surgical planning. In the era of percutaneous valve implantation, three-dimensional measurement and visualisation are of even more importance. Studies have clearly demonstrated that two-dimensional echocardiography is unable to accurately size the aortic annulus leading to undersizing or potentially catastrophic oversizing of percutaneous valve devices.[1] By contrast, three-dimensional echocardiography correlates more strongly to CT measurement.[2]

Perhaps the most important application of three-dimensional echocardiography is for the measurement of left ventricular size and ejection fraction. Ejection fraction is a frequently used surrogate for contractility and is the most widely used measure of cardiac systolic function. Nevertheless, the limitations of this technique, both in terms of accuracy and reproducibility, have been poorly appreciated by both cardiologists and the more general medical community. For example in a recent study, even using carefully performed quantitative biplane

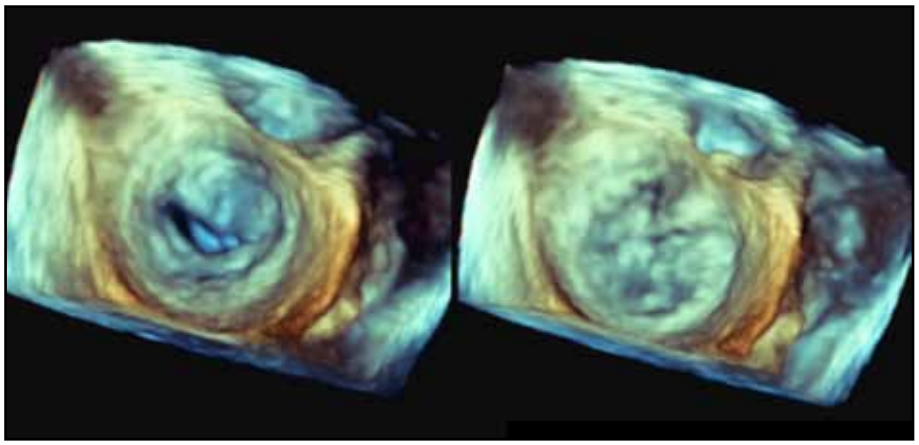

Figure 1: *Three-dimensional trans-oesophageal echocardiogram of the mitral valve in a patient with mitral stenosis.* ***Left:*** *Restricted opening.* ***Right:*** *Closed*

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measurements, the inter-study 95% confidence intervals of ejection fraction by two dimensional echocardiography exceeded ±10 per cent(3). The inability of 2D echocardiography to reliably detect clinically significant deterioration or improvements in cardiac function limits its ability to be used in the settings such as chemotherapy surveillance, transplant assessment and drug treatment effects. In contrast, assessment of cardiac function by three-dimensional echocardiography **(Figure 2)** compares well to cardiac MRI, with confidence limits in the order of six per cent.

Myocardial strain

Strain is a quantitative measure of local myocardial shortening. Strain can be measured within a defined segment or as a global parameter, such as global longitudinal strain (GLS) to provide an indication of myocardial function. Like ejection fraction, strain is not a true measure of contractility and is influenced by loading factors (e.g. fluid status and blood pressure), however strain appears more robust and more sensitive than ejection fraction in certain situations. Changes in myocardial strain have been found in the setting of diabetic heart disease[4] where it may correlate with interstitial fibrosis. Strain imaging is frequently used to assess early chemotherapy toxicity and is the subject of an ongoing multi-centre trial to assess its ability to guide the use of cardio-protective treatment during oncological treatment. Strain measurement has also been applied to stress echocardiography and can be routinely applied in clinical practice.

Cardiac CT

Cardiac CT has already become the favoured tool for imaging coronary anatomy in the setting of low to intermediate risk chest pain. Numerous developments have led to improvements in spatial and temporal resolution and radiation dose has been reduced, in many cases by an order of magnitude compared to a decade ago. All indications are that technological advances in cardiac CT will continue unabated.

Cardiac CT is widely used to exclude or assess coronary disease. In addition to being a non-invasive test, cardiac CT enables the accurate assessment of plaque extent and morphology which are powerful predictors of coronary risk and may guide medical therapy.[5] Several new areas of CT development are likely to have clinical implications in the near future.

Dual energy CT

Dual energy CT utilises simultaneous or near simultaneous beams of x-rays of differing energy (kV) levels to differentiate between constituent materials of the imaged area. As low energy x-rays, above the 33 keV K-edge of iodine, are strongly absorbed by the material, subtraction and manipulation of two different energy images may allow the removal of calcium from an image or the quantification of iodine contrast. For cardiac imaging, the technique has been used to assess the presence of myocardial scar,[6] and to assess the presence or absence of thrombus in the left atrial appendage.[7] The technique may also be useful for CT myocardial perfusion studies.

Computational Imaging

The second area of CT development meriting special attention is computation imaging, that is, the use of computational simulation to assess the effects of cardiac pathology detected by cardiac CT. In early experimental work performed at the Victor Chang Cardiac Research Institute, we have shown that three dimensional computer models constructed from imaging data allow blood flow and pressure to be simulated using computation flow dynamics. In the setting of aortic coarctation or narrowing, the pressure gradient across the lesion may be estimated without invasive procedures **(Figure 3)**. Physical three-dimensional models can also be produced using a 3D printer. Other commercially

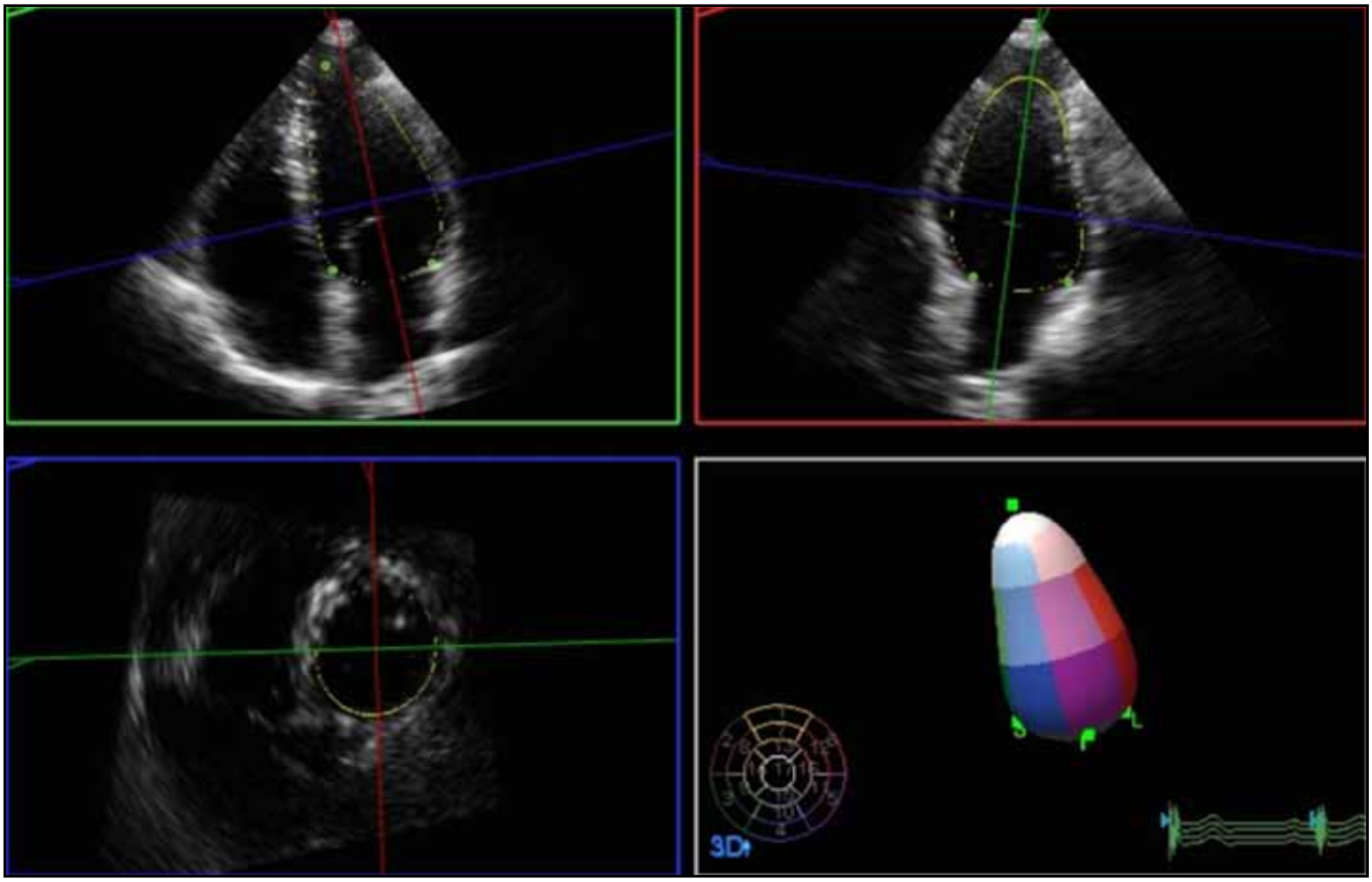

Figure 2: *Three-dimensional echocardiography captures an entire heart volume in motion over time. Slices from any angle may be reconstructed as can a three-dimensional shell, representing the left ventricular volume.*

available techniques utilising computational flow dynamics enable the simulation of the severity of coronary stenosis seen at cardiac CT. This approach has been shown to improve the diagnostic accuracy of CT coronary angiography.

Cardiac MRI

Cardiac MRI is currently widely used for the assessment of cardiomyopathy, arrhythmias, ischemic heart disease and congenital heart disease. The versatility of the technique is such that it may be applied to almost any condition **(Table 1)**. The main advantage of MRI is the clarity of images provided **Figure 4**, the ability to image any area of the heart and the ability to characterise myocardial tissue. This tissue characterisation role of MRI is of key importance. MRI allows oedema of the myocardium to be seen, which may reflect an acute inflammatory process, such as infarction or myocarditis. Myocardial scar may be precisely located and quantified. Fibrosis of the heart can also be measured. Amyloidosis can be detected as can myocardial iron and lysosomal storage disorders.

Cardiac Magnetic Resonance Perfusion

A major advance in cardiac MRI over the last few years has been the demonstration of its role in assessing ischemic heart disease. Cardiac MR perfusion scans are performed with the use of adenosine which results in coronary arterial vasodilation. A gadolinium based MRI contrast agent is administered and the heart is imaged during first-pass perfusion. Recent randomized trials of cardiac MR perfusion have shown the technique to be superior to standard SPECT nuclear perfusion.[8,9] In addition to this accuracy MRI perfusion does not involve ionizing radiation and the scan also provides excellent functional and scar (viability) imaging. More recent perfusion MRI sequences have improved the resolution of the technique further allowing the precise identification and localisation of culprit coronary vessels.

Conclusion

Cardiac imaging techniques have evolved in recent years. Rapid three-dimensional assessment using non-invasive imaging now permits routine and accurate visualisation of cardiac function and morphology, coronary vessels, valve assessment and guides cardiac intervention. Several major developments in echocardiography, cardiac MRI and CT impact upon diagnostic and clinical practice and provide real benefit to patients with heart disease.

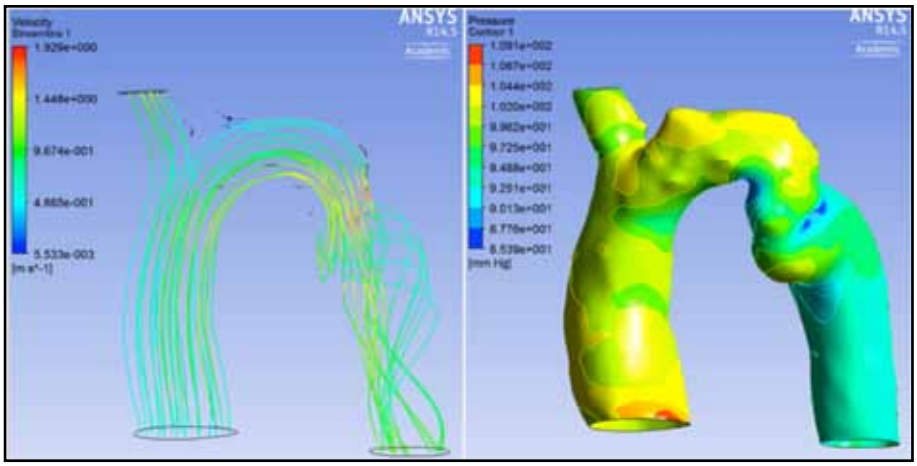

Figure 3: Left: *Computational flow dynamic simulation of blood flow across an aortic coarctation.* ***Right:*** *Corresponding simulated pressure gradient in the aorta.*

Table 1

Clinical indications for cardiac MRI
Cardiomyopathy
Left ventricular hypertrophy
Myocardial viability
Myocardial ischaemia
Myocarditis
Amyloidosis
Lysosomal storage disease
Complex valve disease
Aortic pathology
Pericardial pathology
Arrhythmia

Acknowledgments

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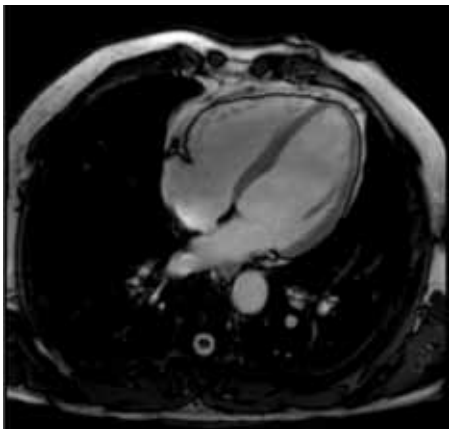

Figure 4: *Cardiac MRI (Four chamber view)*

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Expanding use of the da Vinci Robot at St Vincent's for Treatment of Bladder Cancer: Robot-Assisted Radical Cystectomy and Urinary Diversion

Dr Carlo Yuen
Dr David Ende

Introduction

Robotic surgery has revolutionised cancer treatment over the past decade and has allowed us to perform increasingly complex operations by minimally invasive means.

St Vincent's Private Hospital was the first hospital in NSW to use the "state-of-the art" *da Vinci SI* system to perform Radical Cystectomy (removal of the bladder) with intracorporeal urinary diversion for the treatment of invasive bladder cancer.

Invasive Bladder Cancer and Its Treatment

Each year over 2000 Australians are diagnosed with bladder cancer. There is no screening test for bladder cancer and the most common presenting symptom is blood in the urine. The risk of bladder cancer is associated with increasing age, cigarette smoking, male gender, phenacetin (Bex powder), aromatic amines, aniline dyes and radiation. Whilst most bladder cancers are superficial cancers (non-invasive) approximately 10 per cent-20 per cent are invasive and locally advanced at presentation. Local metastatic spread to surrounding lymph nodes, as well as distant metastases, make it a potentially lethal cancer if not treated early.

Surgery remains the standard of care for muscle invasive bladder cancer and may be used alone or in combination with chemotherapy and/or radiation. Neo-adjuvant chemotherapy has been shown to improve overall survival for locally advanced disease.

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Consulant Urologist

Robotic Cystectomy and Urinary Diversion

Until recently the standard treatment for invasive bladder cancer was to remove the bladder and its lymph glands via a long (15-20cm) midline abdominal incision. The options for urinary diversions include: an *Ileal conduit* (stoma), where a short segment of bowel is used as a conduit to drain urine from the kidneys to an external bag on the patient's abdomen; or a *Neo-bladder*, where a short segment of bowel is used to construct a reservoir which is then anastomosed onto the urethra **(see Figure1)**.

Robot-assisted radical cystectomy is a relatively new procedure that aims to significantly reduce the morbidity of the more traditional open procedure. Standard laparoscopic techniques have been attempted previously. However, due to the limitations of laparoscopic instruments making prolonged intra-corporeal suturing extremely difficult and tedious, the procedure has not been widely performed. In most cases the urinary diversion part has therefore been performed via an open technique as a hybrid procedure, which defeats the purpose of minimally invasive surgery.

Robotic cystectomy utilises standard laparoscopic port sites similar to those used for radical prostatectomy. The technique of robotic cystectomy has been refined with the use of a motorised stapling device to allow improved haemostasis and the *Airseal* insufflation system that can maintain pneumoperitonium even with a significant air leak. This is particularly useful in female cystectomy where the

specimen is retrieved via the vagina, leaving only the port site wounds. In male patients, the specimen is retrieved by enlarging the camera port in the upper abdomen, typically by no more than 3-4cm **(see Figure 2)**. Consequently, the analgesic requirement is significantly less compared with the open procedure.

There are several well defined surgical steps: six small skin incisions are made to allow the introduction of the robotic arms including the 3D camera and laparoscopic instruments; the bladder with the prostate and seminal vesicles (anterior vaginal wall in females) is freed from the surrounding structures by dividing its vascular pedicles; pelvic lymph node dissection is carried out up to the aortic bifurcation; a piece of small bowel is then selected and harvested on its mesenteric pedicle for formation of the conduit or neobladder, with the small bowel being reconstituted using a stapling technique; the ureters are anastomosed to the conduit or neo-bladder; and the stoma is then brought to the skin surface or the neo-bladder anastomosed to the urethra.

Early Recovery After Surgery (ERAS) Protocol

The ERAS is a multimodal care pathway that aims to shorten recovery following surgical procedures by maintaining vital organ function and minimising the stress response following surgery. The key elements include preoperative counselling, optimising nutrition with carbohydrate loading and early enteral feeding, standardised analgesic and anaesthetic regimens including the avoidance of narotics and early mobilisation.

Every effort is made to enhance recovery of bowel function, which is often the main reason for prolonged hospitalisation. We no longer use mechanical bowel preparation before surgery as it has been shown to delay return of bowel function. In addition, the intra- and post-operative fluid regime is also carefully rationalised to avoid over-hydration, which may lead to prolonged paralytic ileus. Early feeding following bowel surgery has also been shown to hasten bowel recovery along with the use of pro-kinetics and chewing gum.

The St Vincent's Robotic Experience

The robotic cystectomy program was introduced a year ago after visiting the University of Southern California (USC) Medical Centre where the technique was developed. Robotic cystectomy is an incredibly complex and sophisticated procedure that is also technically demanding. It should only be performed by high volume surgeons in selected centres where there is a dedicated team. In setting up the program, we drew on our own experience and knowledge of robotic prostate and kidney surgery and we have used this as a platform to ensure the safe introduction of this new procedure.

We have now safely performed over 12 cases of robotic cystectomy with excellent oncological outcomes similar to the open technique. All had negative surgical margins except for one where the tumour was located at the trigone invading into the anterior rectum in the presence of a previous radical prostatectomy for prostate cancer. This series included nine males and three females with a median age of 76 years (range 61-87). The average operative time (console) was 5.9 hours, which is similar to the open procedure. The analgesic requirement was noticeably less and most patients required only oral analgesia by the second postoperative day. The majority of patients went home between days 7-10. One patient stayed for 21 days due to a urine leak that stopped with conservative management and a second patient (aged 85 years) stayed for 24 days waiting for rehabilitation. There were no major complications or unplanned returns to theatre or ICU admissions. One patient was readmitted within 30 days due to dehydration from Clostridium difficile infection. No patient required transfusion. One patient also underwent robotic nephroureterectomy at the same procedure for a concurrent renal transitional cell carcinoma and was discharged on day 7.

Whilst the cost of robotic surgery remains substantially higher than open surgery due to the cost of disposables, it is anticipated that this additional expense will be offset by the potential gain of reduced morbidity, shorter hospital stay and quicker return to normal activities.

Conclusion

Robot-assisted radical cystectomy is a sophisticated and technically demanding operation that requires a dedicated team of highly skilled surgeons to ensure optimal outcomes and should only be performed in high volume centres. We are very proud to be now able to offer this procedure at St Vincent's Private Hospital.

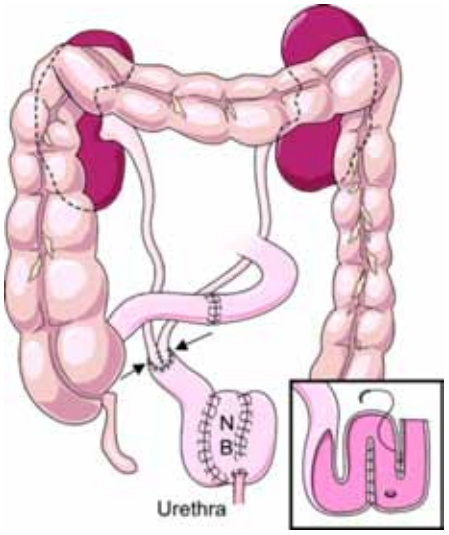

Figure 1. *Neo-bladder construction using a segment of small bowl.*

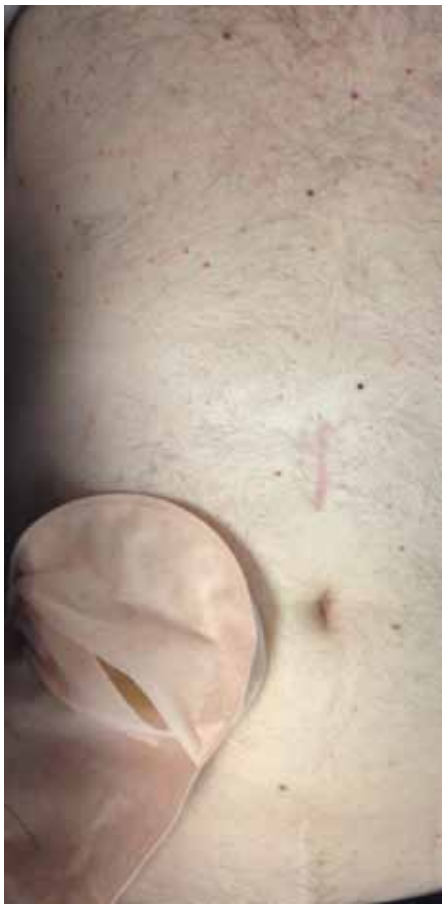

Figure 2. *Abdominal port sites and wounds for Robotic Cystectomy*

Images in Clinical Medicine – Vasculitis

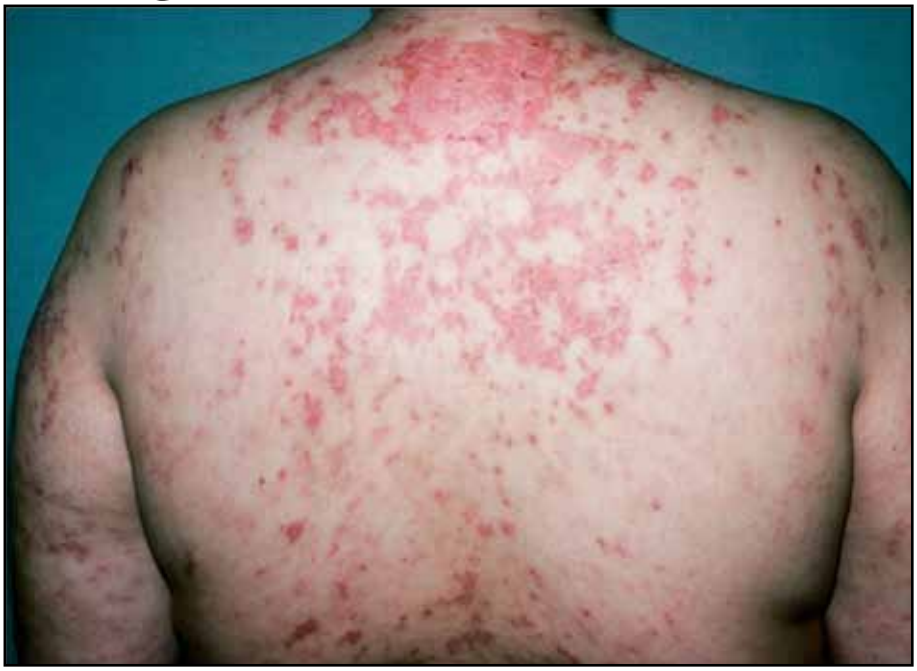

Figure 1: Cutaneous Photosensitivity
Cutaneous Photosensitivity typically occurs in systemic lupus erythematosus either as a diffuse maculopapular rash in sun exposed areas or as a flat, non-scarring, fixed erythematous rash over the cheeks and bridge of the nose.

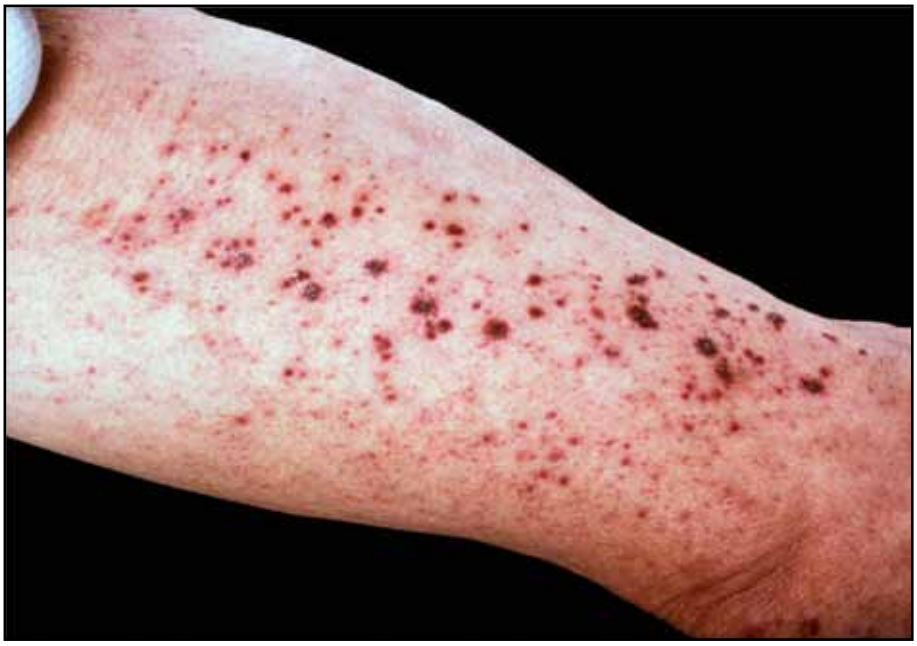

Figure 2: Palpable Purpura
Palpable Purpura is a painless, non-ulcerating and non-scarring purpura with a component of inflammation (hence 'palpable'), typically involving the more dependent regions. This is the clinical expression of vasculitis involving venules, small veins and capillaries, and the histopathology includes evidence of immune complex deposition and leukocytoclasis.

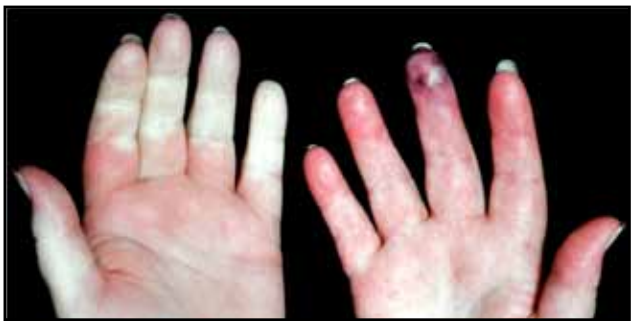

Figure 3: Raynaud's Phenomenon
Raynaud's Phenomenon and other more severe expressions of digital ischaemia in vasculitis (eg SLE, PAN), result from the occlusive inflammatory process targeting small arteries and especially the digital arteries.

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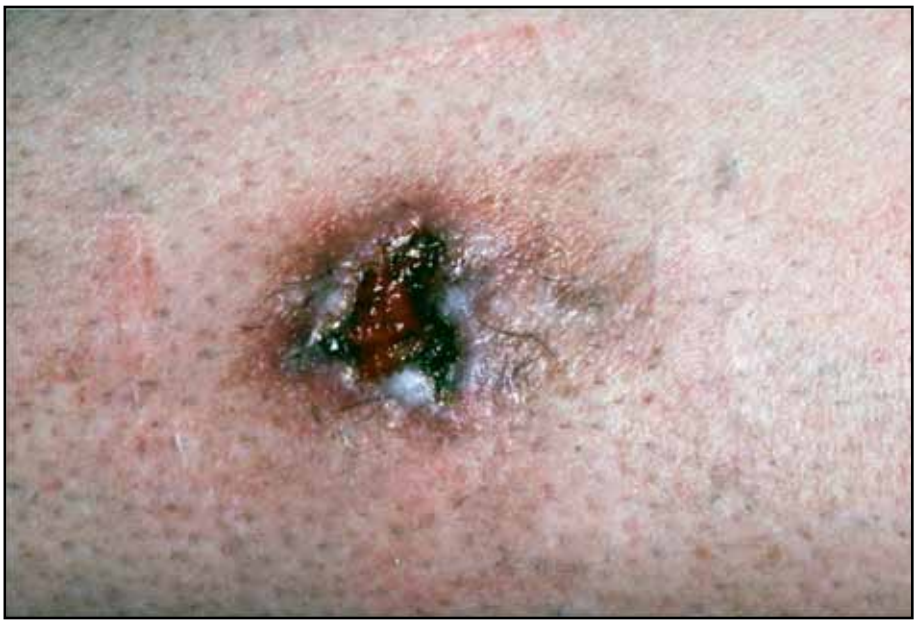

Figure 4: Skin Infarction – Necrosis
Skin infarction caused by vasculitis (eg ANCA - positive arteritis), with occlusion of the cutaneous arteries is expressed clinically as very painful regions of skin necrosis that are slow to heal and result in scarring.

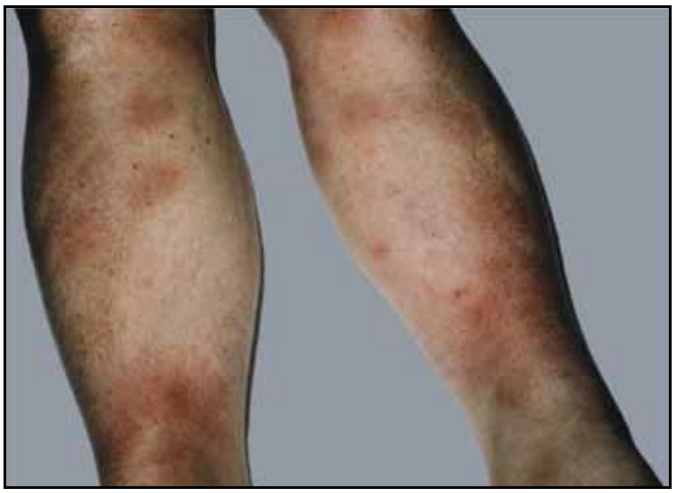

Figure 5: Erythema Nodosum
One of the causes of Erythema nodosum is vasculitis involving small veins within the subcutaneous fat. This localized form of panniculitis results in tender, non-ulcerating, erythematous, sub-cutaneous nodules, usually on the anterior region of the legs.

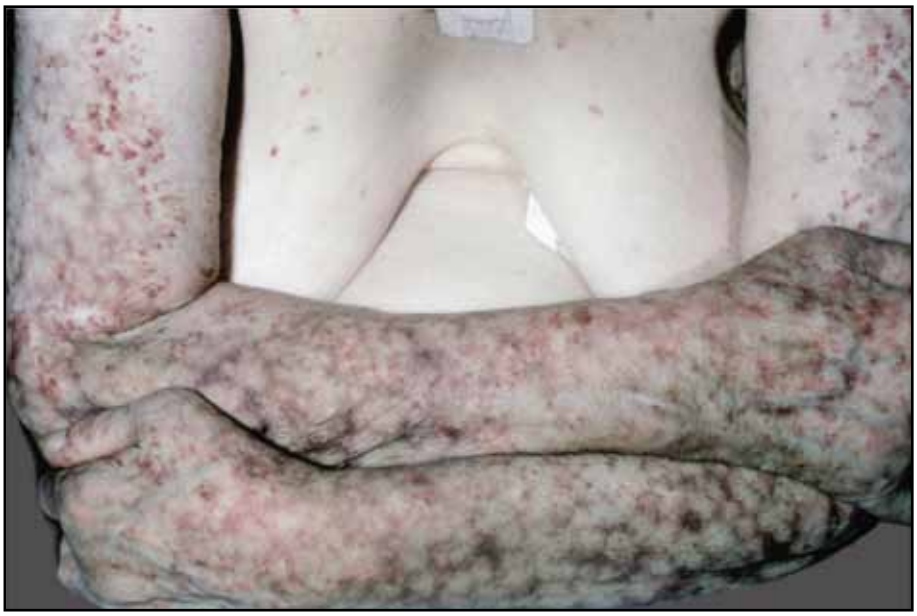

Figure 7: Cryoglobulin
Vasculitis can occasionally be accompanied by a blood cryoglobulin representing an alteration in the serum immunoglobulins, either polyclonal or a monoclonal response. The presence of a cryoglobulin will cause a marked increase in the blood viscosity within the low shear venous circulations and especially in those regions of the skin exposed to the cold.

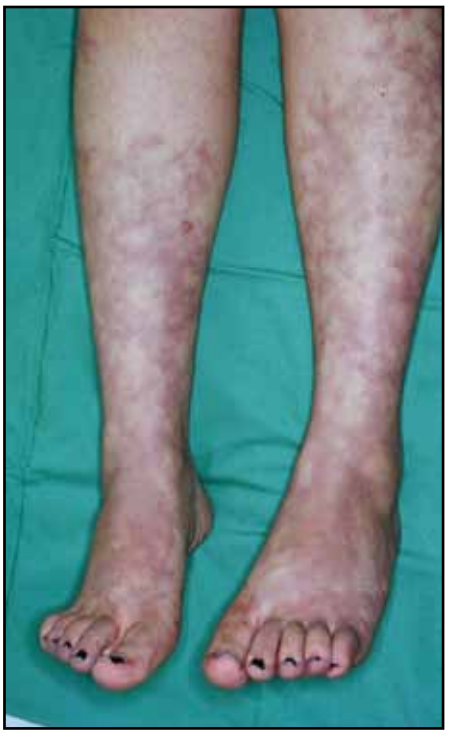

Figure 6: Livedo Reticularis
As in Raynaud's phenomenon, the cutaneous signs of Livedo reticularis can be a primary vasomotor phenomenon, or secondary to vascular disease such as vasculitis. This cutaneous pattern represents altered blood flow in the subcataneous venous plexus. This can develop either by the vasculitic process involving the microvenous circulation directly or by the targeting of the cutaneous arteriolar circulation resulting in slowing of the downstream subcutaneous venous circulation.

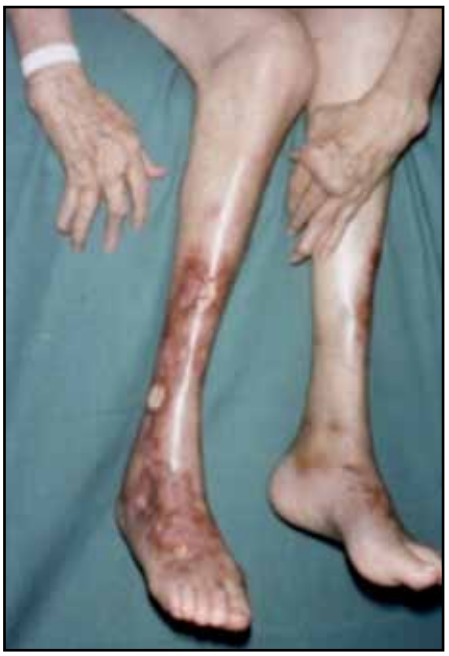

Figure 8: Ulceration
The mechanism of skin ulceration in Rheumatoid Arthritis and other connective tissue diseases is multifactorial. Vasculitis can be a pivotal cause but there can also be contribuutions from non-inflamatory microvascular disorders, the premature atheromatous disease in this group, associated prothrombotic states and novel syndromal states such as pyoderma gangrenosum.

St Vincent's Clinic Foundation – 2014 Grant Recipients

- **SVPHS Ladies' Committee Sr Mary Bernice Research Grant – $100,000**
  A/Prof Diane Fatkin – Victor Chang Cardiac Research Institute
  "A novel zebrafish model of dilated cardiomyopathy"

- **Adult Stem Cell Research Grant – $100,000**
  Prof David Ma – St Vincent's Centre for Applied Medical Research
  "Targeting of Leukaemic stem cells by anti-microRNAs to treat acute myeloid Leukaemia"

- **Tancred Research Grant – $50,000**
  Dr John Moore – St Vincent's Centre for Applied Medical Research
  "Molecular determinants of Haematopoietic Stem Cell Ageing and Rheumatoid Arthritis Pathogenesis"

- **K&A Collins Cancer Grant – $50,000**
  Prof Andrew Carr – St Vincent's Centre for Applied Medical Research
  "Understanding the immune mechanisms underlying spontaneous regression of high-grade anal squamous intraepithelial lesions"

- **Thelma Greig Cancer Grant – $50,000**
  A/Prof Reginald V N Lord – St Vincent's Centre for Applied Medical Research
  "DNA methylation biomarkers for Barrett's oesophagus and oesophageal adenocarcinoma"

- **Di Boyd Cancer Grant – $30,000**
  Dr Helen Tao – St Vincent's Centre for Applied Medical Research
  "Role of ETS-related gene (ERG) in the pathogenesis of transient myeloproliferative disease and leukaemia in human Trisomy21"

- **Combined Froulop Research & Annual Grant – $50,000**
  A/Prof Catherine Suter – Victor Chang Cardiac Research Institute
  "Fetal programming of cardiovascular disease risk"

- **Annual Grant 1 – $30,000**
  Dr Melissa Baysari – St Vincent's Hospital
  "Exploiting new opportunities with an electronic prescribing system to identify prescribers at risk of making prescribing errors"

- **Annual Grant 2 – $30,000**
  Dr Blanca Gallego Luxan – St Vincent's Hospital
  "Identifying hospitalised patients at high risk of potentially avoidable readmission"

- **Annual Grant 3 – $30,000**
  Dr Priya Nair – St Vincent's Hospital
  "Vitamin D dosing study in Intensive Care Unit (ICU) patients with the Systemic Inflammatory Response Syndrome (SIRS)"

St Vincent's Clinic Foundation – 2014 Grant Recipients

- **Annual Grant 4 – $30,000**
  Prof Deborah Marriott – St Vincent's Hospital
  "Bad bugs need well administered drugs"

- **Annual Grant 5 – $30,000**
  Dr Jill Newby – St Vincent's Hospital
  "Development and evaluation of a novel internet-delivered cognitive behavioural treatment for severe health anxiety (hypochondriasis)"

- **Multidisciplinary Patient Focused Research Grant 1 – $25,000**
  Ms Lisa Robins – St Vincent's Hospital
  "Brief intervention for people with Type One Diabetes Mellitus and psychiatric comorbidity"

- **Multidisciplinary Patient Focused Research Grant 2 – $25,000**
  Mr Kenny Vuong – St Joseph's Hospital
  "Reducing falls among people with Huntington Disease"

- **Multidisciplinary Patient Focused Research Grant 3 – $25,000**
  Mrs Jane Rodgers – Nursing Research Institute / St Vincent's Hospital
  "The surgical patients' pressure injury incidence (SPPII) study"

- **Multidisciplinary Patient Focused Research Grant 4 – $25,000**
  Ms Tamra Langley – St Vincent's Hospital
  "Creating the St Vincent's Hospital Online Cardiac Health Centre"

- **Multidisciplinary Patient Focused Research Grant 5 – $25,000**
  Ms Tania Gardner – St Vincent's Hospital
  "The reboot pain management program - is cognitive function a predictor of outcome?"

- **Travelling Fellowship 1 – $10,000**
  Dr James Otton – St Vincent's Hospital
  "Echocardiography Fellowship - Kings College Hospital, London, UK"

- **Travelling Fellowship 2 – $10,000**
  Dr Alina Stoita – St Vincent's Hospital
  "Advanced Endoscopic Ultrasound (EUS) Fellowship, University College, London, UK"

- **2013 Clinical Excellence Award – Scientist – $1,500**
  Ms Tamalee Roberts – St Vincent's Hospital – Technical Officer – Microbiology Department

- **2013 Clinical Excellence Award – Nursing – $1,500**
  Prof Jane Phillips – St Vincent's Hospital – Professor Palliative Nursing, Cunningham Centre for Palliative Care

- **2013 Clinical Excellence Award – Allied Health – $1,500**
  Dr Alishia Williams – St Vincent's Hospital – Director Experimental Research, CRUfAD

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