PROCEEDINGS

St Vincent's Clinic

VOLUME 20 NO: 1 DECEMBER 2012

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PROCEEDINGS

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EDITORIAL

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Consultant Neurologist

Editor, Proceedings

This is the 24th Issue of *Proceedings* which is now in its 20th year of production. I would like to acknowledge both the work of Dr John Roarty OAM as the founder of *Proceedings* and also Mr Chris Thomas who has been the publisher from the time of the first edition in 1993.

The 2011 Sandra David Oration was given by Professor John Shine of the Garvan Institute of Medical Research. His article on "Today's Medical Research" is a synopsis of that Oration. It highlights the major advances in genomics since publication of the human genome sequence in 2000. Increasingly, genetics is allowing accuracy of diagnosis at reduced cost. It is beginning to give rise to targeted therapies and illness prevention strategies based on the knowledge of each individual's genetic and environmental risk factors.

The da Vinci robotic system is being increasingly employed for surgical procedures at St Vincent's. St Vincent's was the pioneer of robotic surgery in NSW. Doctors Brenner and Yuen, Urologists, describe the use of robotic surgery for selected kidney cancers. Dr Gallagher, ENT Surgeon, describes the recent employment of robotic surgery, using a transoral approach, for certain tumours of the head and neck.

Inflammatory Bowel Disease (IBD) is a term to describe two main diseases, Crohn's Disease and Ulcerative Colitis. Dr Alissa Walsh, Gastroenterologist and Dr Gareth Owen, Colorectal Surgeon have combined to produce a comprehensive and scholarly article on the medical and surgical management of IBD. They emphasise the importance of their collaborative approach which optimises the care of patients with complex presentations of IBD.

In Australia, breast cancer now effects one in nine women below the age of 85. Breast reconstruction plays a vital role in restoring a feeling of wholeness and well-being to women after surgery for breast cancer. Drs James Southwell-Keely and Elias Moisidis describe breast reconstruction by both the alloplastic (expanders/implants) or autologous (patient's own tissues) techniques.

An epileptic seizure is a frightening experience for an individual and often even moreso for the family. Assessment of an apparent first seizure is a complex matter requiring an accurate and detailed history. The event has important social as well as medical implications. I have discussed these matters in my own article and have provided reasons why such patients should undergo a specialist neurological consultation following the apparent first seizure.

Surgeons are continuously improving outcomes by incorporation of newer technologies into their practices. The use of robotic surgery has already been mentioned. Lasers play an important role in head and neck surgery. Dr Nigel Biggs describes laser technology in otological surgery and Dr Richard Gallagher its use in laryngeal surgery.

Australia has the highest instance of skin cancer in the world and the most feared type of skin cancer is melanoma. There has traditionally been a nihilistic view on the use of radiotherapy in the management of malignant melanoma. In his article, Dr Gerald Fogarty, Radiation Oncologist, reputes this attitude. He cites recent and continuing trials which indicate radiotherapy may have a currently under-recognised and future important role in the management of certain stages of malignant melanoma.

The St Vincent's Clinic Foundation has this year provided $732,430 in research grants and awards. The Foundation is grateful for the support of Friends of St Vincent's Private Hospital in funding the Ladies' Committee Sr Mary Bernice Grant. The recipients of these grants and their topics of research is shown on pages 32 and 33.

The Sandra David Oration

Today's Medical Research – 'Big Science' and health care impacts

Professor John Shine

Professor John Shine, AO FAA
Executive Director, Garvan Institute of Medical Research

Introduction

In 2000, the first draft of the human genome sequence was announced with great fanfare on both sides of the Atlantic by President Bill Clinton and Prime Minister Tony Blair. At a cost of some $3 billion and taking over 15 years to complete, this achievement was compared to landing on the moon – in hindsight it will prove to be of much greater significance for humanity.

Two quotations at this time illustrate the importance of this development. The first was from the United Nations, in their *Universal Declaration on the Human Genome and Human Rights* - ***"The human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense, it is the heritage of humanity."***

The second was the editorial in the journal *Nature* on February 15, 2001, on the occasion of the first publication of the genome sequence -

"Humans are much more than simply the product of a genome, but in a sense we are, both collectively and individually, defined within the genome. The mapping, sequencing and analysis of the human genome is therefore a fundamental advance in self knowledge; it will strike a personal chord with many people. And application of this knowledge will, in time, materially benefit almost everyone in the world."

The ready availability of all human gene sequences and the development of related technologies have caused a paradigm shift in medical research. The classic "hypothesis based" approach to research has been overtaken by "discovery based" experimental paradigms. For example, by displaying all human gene sequences on a small silicon chip (a gene "array") and incubating the chip with RNA from either a normal breast cell or a breast cancer cell, researchers can rapidly identify any changes in specific gene expression which may be responsible for the cancer phenotype.

An example of one such gene is shown in **Figure 1**. This shows that the level of expression of one particular gene, as evidenced by the levels of its encoded mRNA and hence protein, is very low in normal breast tissue from several patients but is very high in the breast cancer biopsies from some patients, eg TN, but not all, eg EX. This gene, or its protein product, is thus a potential target for the development of new therapeutics and diagnostics for particular subtypes of breast cancer. Such a therapeutic would be expected to be effective in breast cancers where the gene is overexpressed, eg in TN's cancer, but would be ineffective in cancers where it is not active, eg patient EX.

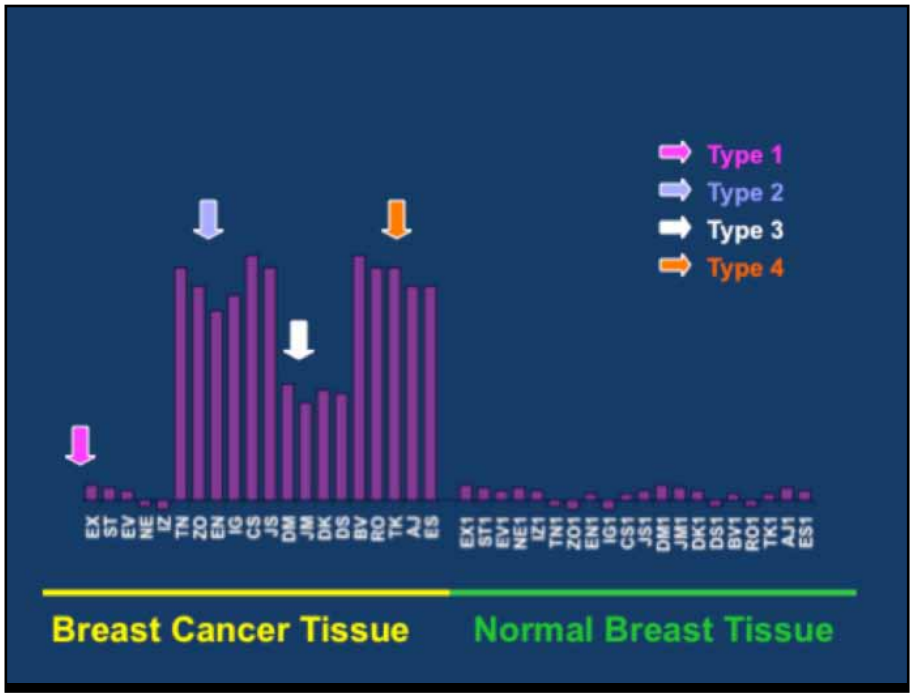

Figure 1: *Histogram of the level of mRNA (and hence protein) encoded by Gene X present in biopsies of breast cancer tissue and normal tissue from different patients. Patients are identified by initials eg EX,ST,EV etc. Gene X is not expressed or "turned on" in normal breast tissue from any of these individuals but is clearly overexpressed in some, but not all, breast cancers*

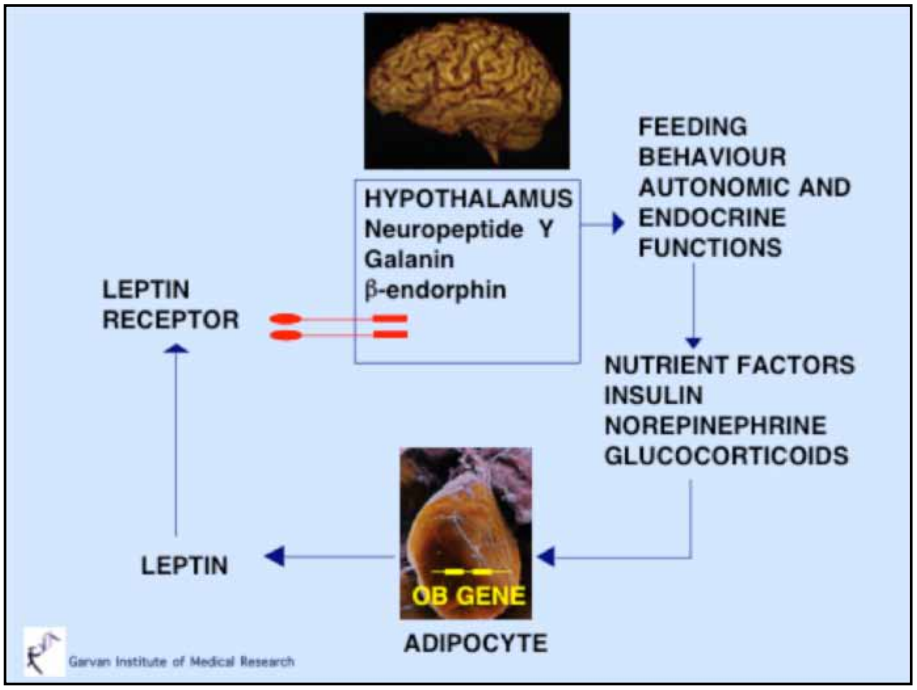

Figure 2: *An individual's obesity "set-point" is determined by a complex feed-back loop involving the regulation of expression of several genes affecting appetite, metabolism, feeding behaviour and fat deposition. Individual polymorphisms (mutations) in these genes result in subtle changes to the feedback loop leading to different obesity set-points in different individuals.*

No "a priori" assumptions are made as to which genes are involved and any changes can then be further studied to elucidate their role in the development and progression of the cancer and their potential as targets for new therapeutic intervention. Such analyses of individual cancers underlie the concept of personalized medicine – where treatment is no longer generic but specifically targeted to the individual cancer.

Another example is our growing understanding of the role of different genes in determining our susceptibility to obesity (and hence the related risks of diabetes and cardiovascular disease). Although we know much about the environmental / lifestyle risk factors for obesity – lack of exercise and poor nutrition, we are only just beginning to understand the corresponding genetic risk factors.

As shown in **Figure 2**, a sophisticated feedback loop determines our normal set-point for body mass/composition. The expression of the OB (obese) gene in fat cells is determined by the amount of stored fat – the more fat, the more the OB gene is turned on and directs the synthesis of the hormone leptin (from Greek, leptos –"thin"). Leptin is released to the blood stream and enters the brain where it interacts with specific receptors, which regulate release of several important neuropeptides, especially neuropeptide Y. These peptides have powerful effects on appetite, preference for different types of food and metabolic rate. This then affects feeding behaviour and metabolism, leading to different levels of fat accumulation and hence different levels of leptin release – completing the circuit.

An individual's predisposition to obesity is influenced by variations (mutations) in any one of several genes in this pathway. For example, a mutation in the gene for the leptin receptor may result in a reduced level of leptin signaling to the brain and increased appetite. Another variation in the gene encoding neuropeptide Y (a powerful appetite stimulant) may increase or decrease appetite and preference for different types of food. Knowledge of which gene in this pathway predisposes any particular individual to increased weight gain suggests that treatment of that individual's obesity would be best targeted to the product of that gene. Such "personalisation" of prevention and treatment is thus becoming more and more possible in a wide range of disorders where both genes and environment play important roles.

While the above examples of breast cancer and obesity focus on direct gene analyses flowing from developments in the human genome project, enormous progress is also being made in cataloging the repertoire of other cellular molecules in normal physiology and in disease. The application of these "big science" databases – the "omics" (genomics – genes, transcriptomics – RNA, proteomics – proteins, and metabolomics – small molecules) is leading to the identification of specific aberrant molecular pathways and networks that are responsible for an individual's risk for developing disease. They also promise to offer exciting new ways to monitor the course of the disease and the optimal treatment and response to treatment for the individual.

International Cancer Genome Project

The implications of these amazing databases for the future are myriad, but one very recent and exciting development illustrates the pace of scientific progress – the International Cancer Genome Consortium.

The Cancer Genome Consortium is an international collaboration involving 11 countries with the aim over the next two years to determine the complete genome sequence of 500 of each of the 50 most common cancers – 25,000 genomes or 80 trillion bits of data. Australia is playing a major role – our task is pancreatic and ovarian cancer.

The consortium will provide a detailed description of every mutation that leads to the development of different forms of cancer, which then provides a targeted road map of how to develop highly specific diagnostics and novel therapies, with minimal side effects, for each individual's cancer.

In 2000, it took over a decade and cost approximately $3 billion to develop the first human genome sequence. With the technology developments that have followed over the past few years, it now takes only a week and $20,000 per genome – with the time and cost still falling rapidly. It is confidently predicted that over the next few years, this will drop to a hundred dollars and a couple of days – levels which will make complete genome sequencing a standard diagnostic procedure.

Not only will this prevent enormous pain and suffering, but it will also dramatically lower the cost to the health care system - as patients are diagnosed earlier, treated far more effectively and kept out of hospital.

We will never prevent the initiation of cancer, as our genes mutate with the normal aging process, but with highly targeted individual therapies we should be able to stop development of cancer in it's tracks and hopefully death from many forms of cancer will be banished into the history books - as previous medical research has done to infectious diseases such as smallpox and polio.

Personalised Medicine

Over the past 100 years, the development of "best practice" treatment has been based on epidemiological studies of large cohorts which have not been able to take account of genetic variability of individuals within the population – a "one size fits all" outcome.

Today, personalised medicine aims to provide improved prevention and treatment options based on genetic/proteomic/metabolic profiling for consideration of individual differences, both in respect of response to, and side effects from, pharmaceuticals. For example, as shown in **Figure 1**, an anticancer drug developed against Gene X should work for patient TN in whose breast cancer Gene X is very active, but would not work as a treatment for patient EX in whose cancer the gene is silent.

Traditionally, the tailoring of medical care to the individual has been based on family history, behaviour, environment and social circumstances. Today, this is being updated to focus on molecular profiling, including genetic testing, proteomic profiling and metabolomic analyses.

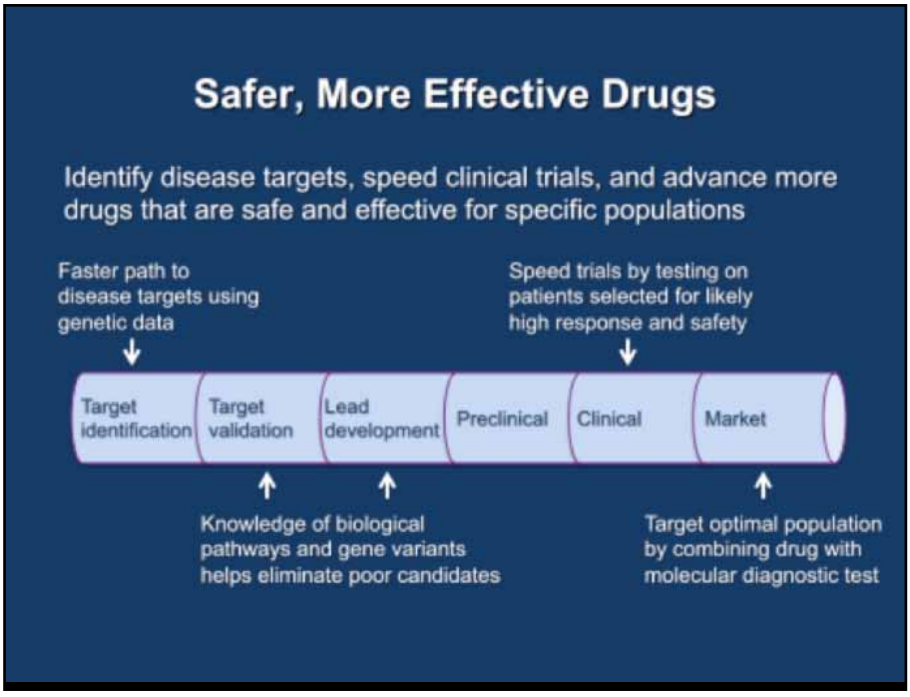

Figure 3

Furthermore, the ability to link drug response to genetic profile is enhancing the value of clinical trials and the effectiveness and safety of new pharmaceuticals. This is illustrated in **Figure 3.**

As illustrated in **Figure 4**, future medical care will incorporate more emphasis on an understanding of the individuals' genetic risk informing an earlier detection of disease and using more specific therapies targeted to the molecular lesion(s) relevant to the individual case. Although this has always been the goal of effective health care, development of cost effective technologies in genomics, proteomics and metabolomics are rapidly making the dream a reality.

Perhaps even more importantly, these same technologies promise to change the focus from treatment to prevention for a wide range of disorders. At the individual level, knowledge of personal genetic risk factors is a powerful incentive to pay attention to the known (and modifiable) environmental risks. For example, if someone is aware that they are at high risk genetically for cardiovascular disease, they are more likely to reduce cholesterol levels, stop smoking and exercise – it is not just a population statistic – it is personal.

The combination of more effective use of such preventative measures and specific monitoring of markers associated with the known genetic risk factors **(Figure 5)** should lead to much earlier detection and intervention in disease progression – preventing the enormous costs, both social and financial, associated with the burden of ill health.

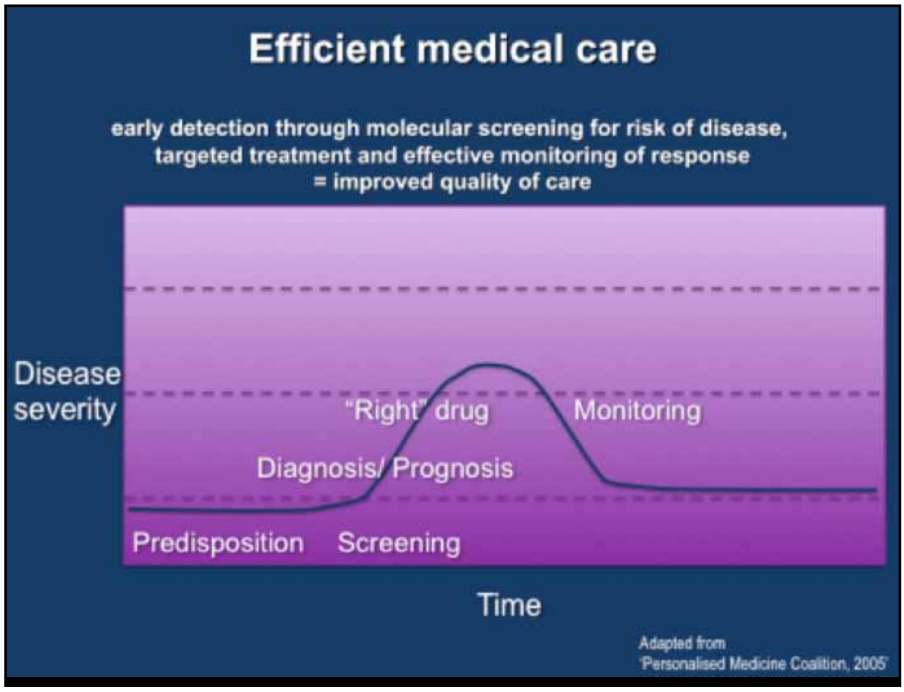

Figure 4

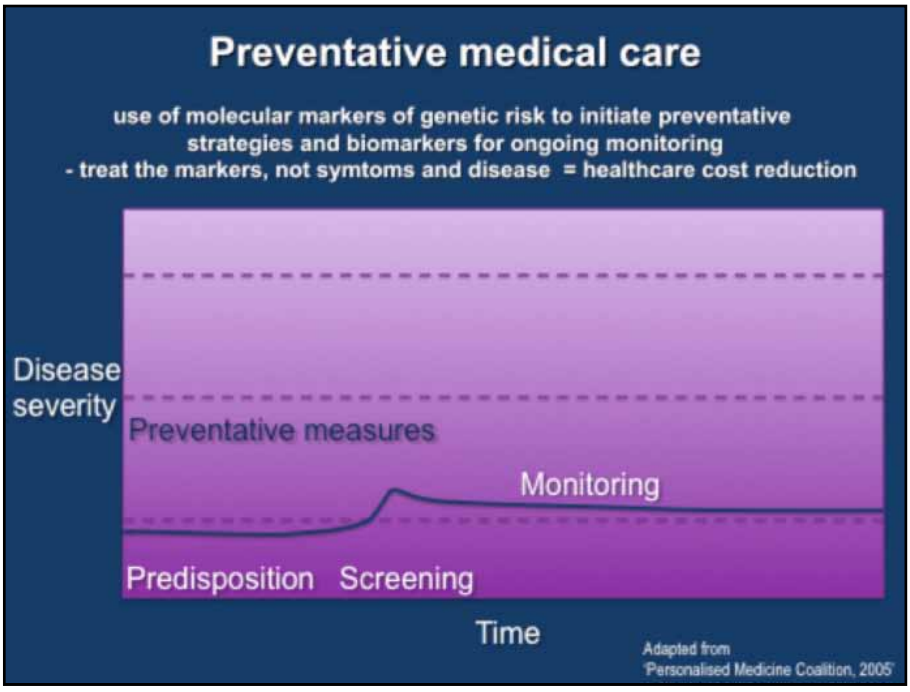

Figure 5

Conclusion

Imagination, based on knowledge, is the key to discovery.

Humanity has always been rich in imagination. In medical research we now have an exponentially growing database of knowledge – we are truly in an age of discovery.

If we look back at history, medical research has underpinned humanity's progress – good health is a prerequisite to community prosperity. Targeted therapies and prevention strategies based on knowledge of an individual's genetic and environmental risk factors are now clearly the future.

Use of the da Vinci Robot at St Vincent's in Kidney and Head and Neck Cancer

Dr Phillip Brenner
Dr Carlo Yuen

Part A: Robotic-Assisted Partial Nephrectomy at St Vincent's for Kidney Cancers

Introduction

Robotic surgery has enhanced our ability to remove kidney cancer while preserving the rest of the kidney and does so in a minimally invasive fashion.

St Vincent's Private Hospital was the first hospital in NSW to use a 'state-of-the-art' da Vinci SI surgical robot which has further refined this surgery **(Figure 1)**.

Dr Phillip Brenner

Dr Carlo Yuen

Figure 1. *The da Vinci Robotic System*

Dr Phillip Brenner, MBBS (UNSW), FRACS (Urology)
Head, Department of Urology, St Vincent's Hospital
Conjoint Senior Lecturer, UNSW.
Fellowship Urological Oncology (Mskcc)

Dr Carlo Yuen, MBBS, FRACS (Urology)
Consultant Urologist
Conjoint Senior Lecturer (UNSW)

Renal Cell Carcinoma and Its Treatment

Renal cell carcinoma is one of the most surgically curable tumours when diagnosed in the early stages. It is relatively resistant to radiation and there is only slight response to some of the new chemotherapeutic agents.

Fortunately, most tumours are diagnosed in the very early stages when found incidentally on ultrasound or computerised tomography (CT) scan being done for other indications. Since the introduction of CT scan and ultrasound, the cure rate for kidney cancer is in excess of 80 per cent and approaches 100 per cent for smaller tumours.

Historically kidney cancer was treated with "radical nephrectomy" ie, removal of the entire kidney through a large incision between the ribs on the side of the body. Often nerves to the abdominal muscle and skin are cut during this process, leaving a bulging and numb area.

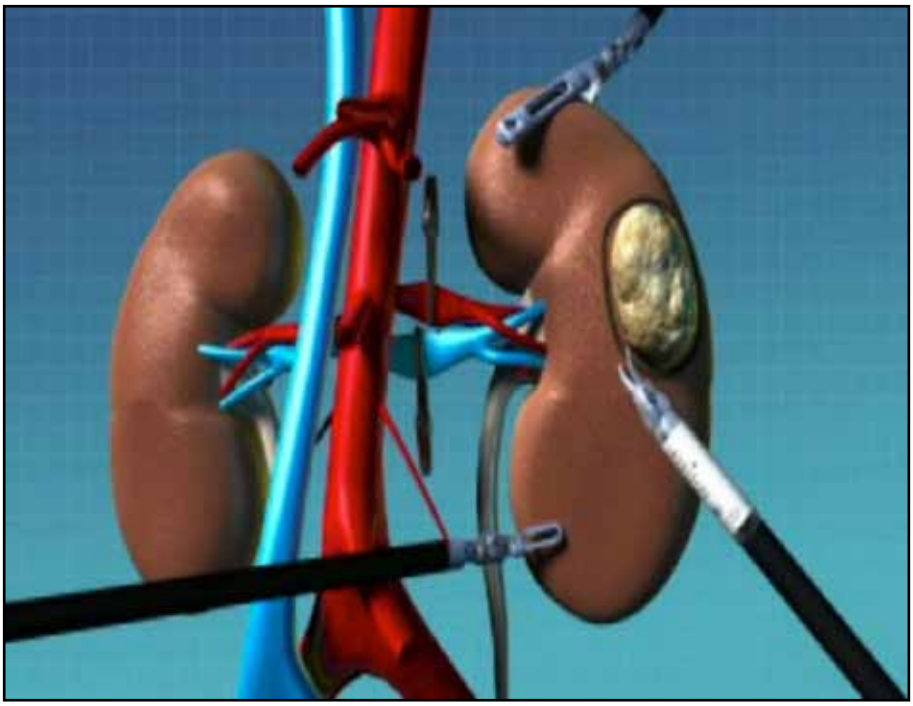

Figure 2
Schematic of tumour of the left kidney. The left renal artery and vein are clamped. The tumour is being excised by the robotic scissors.

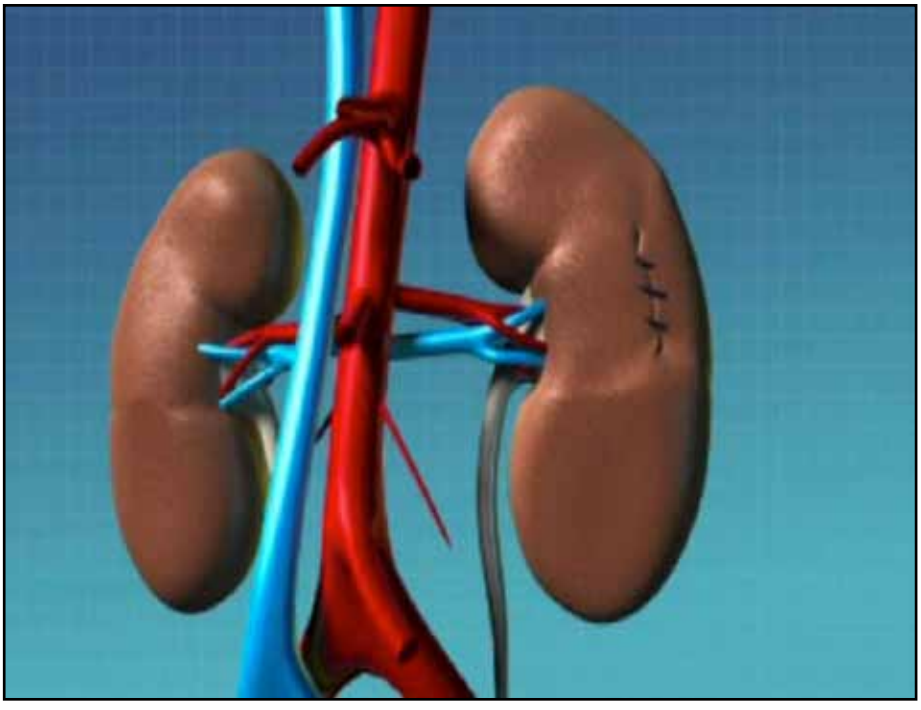

Figure 3
Tumour removed and kidney repaired with sutures.

In the early 1990s, laparoscopic radical nephrectomy was perfected allowing a minimally invasive approach to cure kidney cancer.

In recent years, it has become apparent that removal of the tumour alone (sparing the rest of the kidney) for tumours 5cms and less, has the same cancer cure as radical nephrectomy with less risk of kidney disease and/or dialysis at a later stage. This was also originally done through a large incision between the ribs.

Minimally invasive or laparoscopic partial nephrectomy was developed to achieve both sparing of the kidney and a minimally invasive surgical approach. However, the limits of laparoscopy in terms of dexterity, visualisation and control of bleeding limits the effectiveness of this technique.

I performed a large series of these but the procedure was hindered by being technically difficult and slow - especially while repairing the kidney after removal of the tumour. Because the blood supply of the kidney is interrupted during the excision of the tumour and repair of the kidney, the longer the procedure, the greater the risk of potential damage to the kidney due to lack of blood supply.

The development of the da Vinci Robotic system overcame many of these limitations.

Da Vinci Robotic System And Robotic Partial Nephrectomy

The da Vinci Robot gives a highly magnified three-dimensional view of the operative field using two separate cameras, allowing depth perception and facilitating accurate placement of surgical sutures.

The movement of the robotic arms are "scaled down" so a large movement of the surgeon's hands become a much smaller movement of the surgical instrument, allowing more delicate work. Any surgical tremor is eliminated.

The robotic instruments mimic the human wrist and have seven degrees of movement, increasing dexterity when

compared to rigid laparoscopic instruments. This allows more accurate and rapid surgery, minimising the time the kidney is deprived of blood.

Robotic partial nephrectomy is a sophisticated and technically challenging operation, ideally only performed in selected centres. At St Vincent's, the development of da Vinci robotic-assisted laparoscopic partial nephrectomy was personally preceded by experience in over 850 standard laparoscopic kidney procedures and subsequently a series of 20 laparoscopic partial nephrectomies.

At St Vincent's, robotic training was drawn from over 400 robotically-assisted radical prostatectomies since the introduction of the robot.

There are essentially eight surgical steps: five small skin incisions are made to allow the introduction of the laparoscopic instruments; the kidney is freed from the surrounding organs; the artery supplying blood to the kidney and the vein draining blood from the kidney and the ureter are all exposed; the tumour itself is exposed. This is assisted by intra-operative ultrasound which is incorporated in the da Vinci SI by "Tilepro" technology. The tumour is marked by cautery leaving an adequate margin of healthy tissue; the artery and vein are clamped to allow a bloodless dissection with excellent view of the tumour and normal tissue; the tumour is excised sharply **(see Figure 2)** with scissors to allow appreciation of the tissues so that no tumour is cut through; the defect in the kidney is repaired with sutures to prevent bleeding or urine leakage **(see Figure 3)**. This step is particularly enhanced by the robotic dexterity and view and minimises the time that the kidney is without blood; and the clamp on the renal artery and vein are then removed and blood flow is restored to the kidney.

Post-operatively, patients are expected to be in hospital for two nights. Most will return to work within 1-2 weeks and will return to normal sporting activities in six weeks.

The St Vincent's Robotic Experience

We now offer robotically-assisted laparoscopic partial nephrectomy to suitable patients with small (< 5cm) tumours if the tumour is in a favourable position.

Table: OPERATIVE RESULTS

Patient Number	Tumour Size	Ischaemic Time	Blood Loss
1	14x12x12	20 min 56 sec	Negligible
2	15x15x12	24 min	Negligible
3	40x35x18	16 min	Negligible
4	20x15x22	25 min	Negligible
5	21x16x13	20 min	Negligible
6	24x20x20	16 min	Negligible
7	50x48x45	30 min	Negligible
8	55x55x40	10 min	Negligible
9	40x35x30	12 min 30 sec	Negligible
10	18x15x15	15 min	1000cc
11	28x23x24	8 min	Negligible
12	35x35x24	9 min	Negligible
13	39x49x46	4 min	Negligible
14	20x20x28	16 min	Negligible

This initial report of the first fourteen (14) patients indicates excellent early results **(see Table)**. Patients had tumour adequately removed with a cuff of normal tissue. In only one patient was tumour found in a small vein at the point of resection – no extra treatment was required. Most patients had blood flow interrupted for less than 20 minutes and none had blood flow interrupted for more than 30 minutes. All but one patient have retained excellent function in the affected kidney. Very few complications have been encountered with one patient developing deep venous thrombosis (having had this after previous surgery as well) and one patient requiring a further laparoscopy to exclude possible complications (no complication was found).

Conclusion

Da Vinci robotic-assisted laparoscopic partial nephrectomy should now be regarded as the gold standard for smaller renal tumours, both in terms of cancer control, preservation of kidney function and excellent functional results due to the minimally invasive nature of the surgery.

Use of the da Vinci Robot at St Vincent's in Kidney and Head and Neck Cancer

Dr Richard Gallagher

Part B - Transoral Robotic Surgery: A New Paradigm in the Management of Head and Neck Cancer

Introduction

Dr Richard Gallagher

Robotic surgery has evolved over the past 20 years from initial development by NASA to commercialisation and development of the first true surgical robot by Intuitive Surgical. The da Vinci Robot was orginally applied to cardiac valve surgery. Its application to prostate surgery led to more rapid uptake and development.

In 2007 Weinstein and O'Malley from the University of Pennsylvania reported and developed Transoral Robotic Surgery (TORS). This has led to an evolutionary change to access to the oropharynx and laryngopharynx. Transoral laser surgery has been practised since the mid-70s. It is however time consuming and cumbersome to remove cancers of the tonsil, tongue base, supraglottic larynx and hypopharynx. Access was often

Figure 1. *The robotic theatre set- up is demonstrated with the surgical assistant and scrub nurse at the head of the table viewing the procedure on high definition screens.*

Dr Richard Gallagher FRACS
Otolaryngology - Head & Neck Surgery
St Vincent's Hospital Sydney

difficult or impossible. The da Vinci robot overcomes most of these problems allowing a new approach to the management of these tumours.

The superior visualisation achieved by the use of a 3-D camera system and surgeon immersion in the operative environment combined with precision instrumentation allows en-bloc excision of tumours unique in the field of Head and Neck Surgery.

The Procedure

Surgery is performed under general anaesthesia usually with an oral endotracheal tube. A skilled anaesthetist familiar with upper airway work is required so as to avoid airway complications, particularly at the end of the procedure.

The procedure begins with the surgeon exposing the relevant surgical site with a variety of different mouth gags and retractors. The patient cart is then docked at the bedside next to the patient's head. The 3-D camera and two robotic arms are then positioned in the patient's mouth. A bedside surgical assistant is required to provide further retraction, suction and to help manage haemostasis **(Figure 1)**. A specifically trained Scrub Nurse is essential.

The surgeon then controls the camera and robotic instrumentation from the console using both foot and hand controllers. Motion scaling and tremor filtration enable precise movements of the 5mm endowrist instruments. These instruments also have seven degrees of movement whereas the human wrist has only five. This enables more complex resections in small spaces.

Presently TORS has been successfully applied to tumours of the tonsil, tongue base, palate, parapharyngeal space, supraglottic larynx and hypopharynx **(Figures 2 and 3)**.

There also appears to be a future role for TORS in the management of obstructive sleep apnoea.

The main application for TORS is in the management of oropharyngeal tumours, particularly human papillomavirus associated carcinomas of the tonsil and tongue base **(Figures 4**

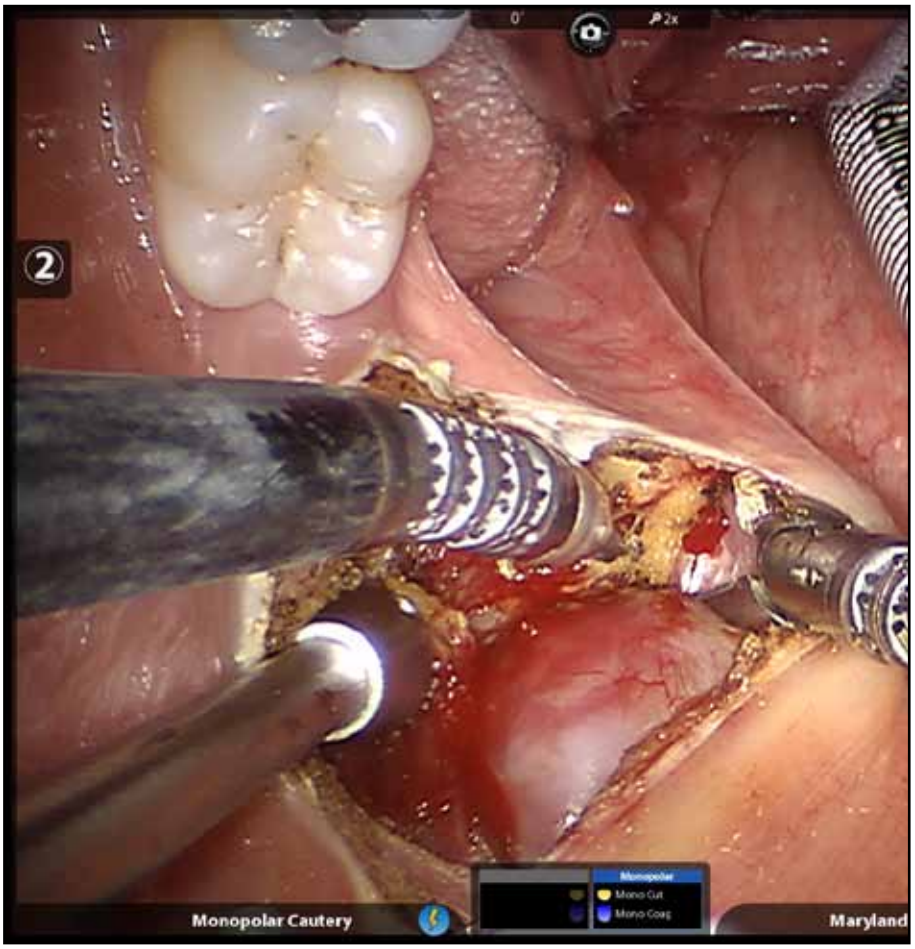

Figure 2. *A transoral view of a left parapharyngeal space tumour being exposed for excision.*

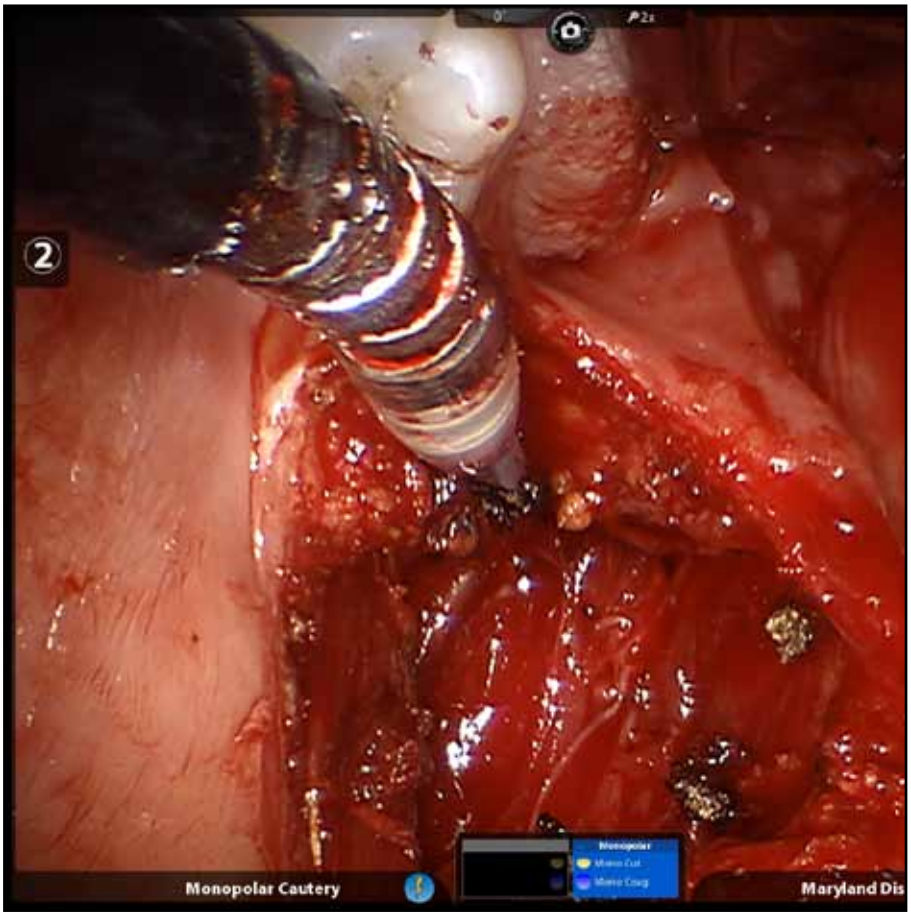

Figure 3. The surgical bed following excision of the tumour.

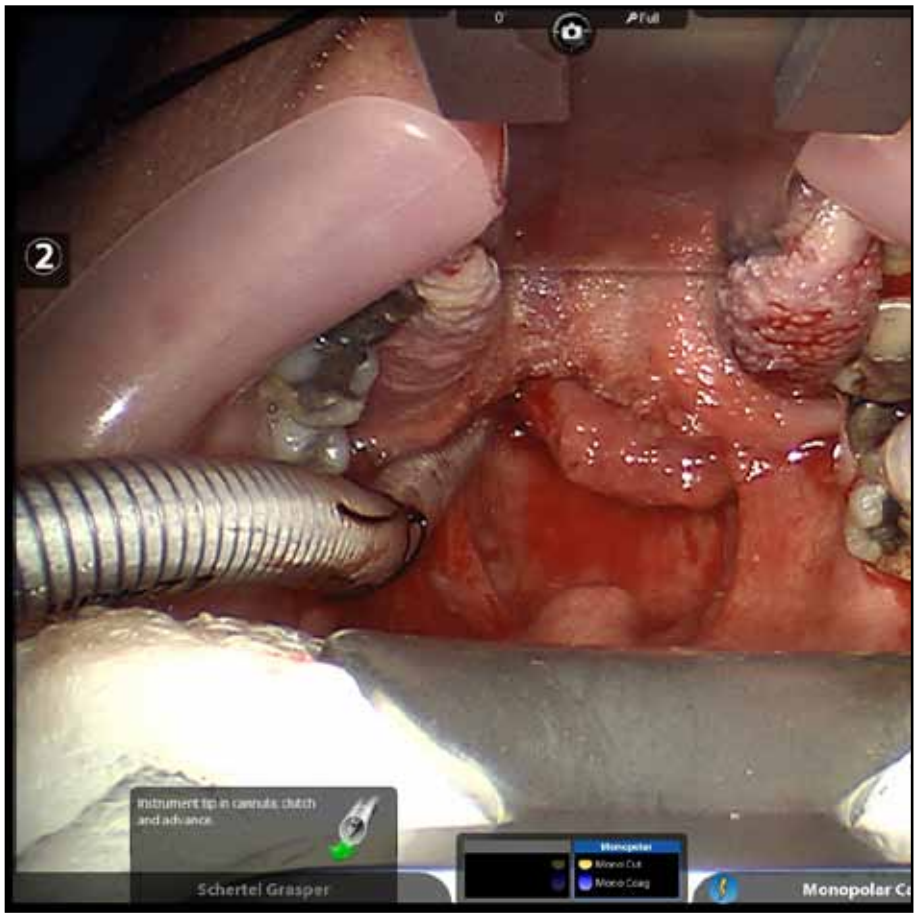

Figure 4. This image demonstrates a large right tongue base tumour at 1 o'clock. The uvula is at 6 o'clock.

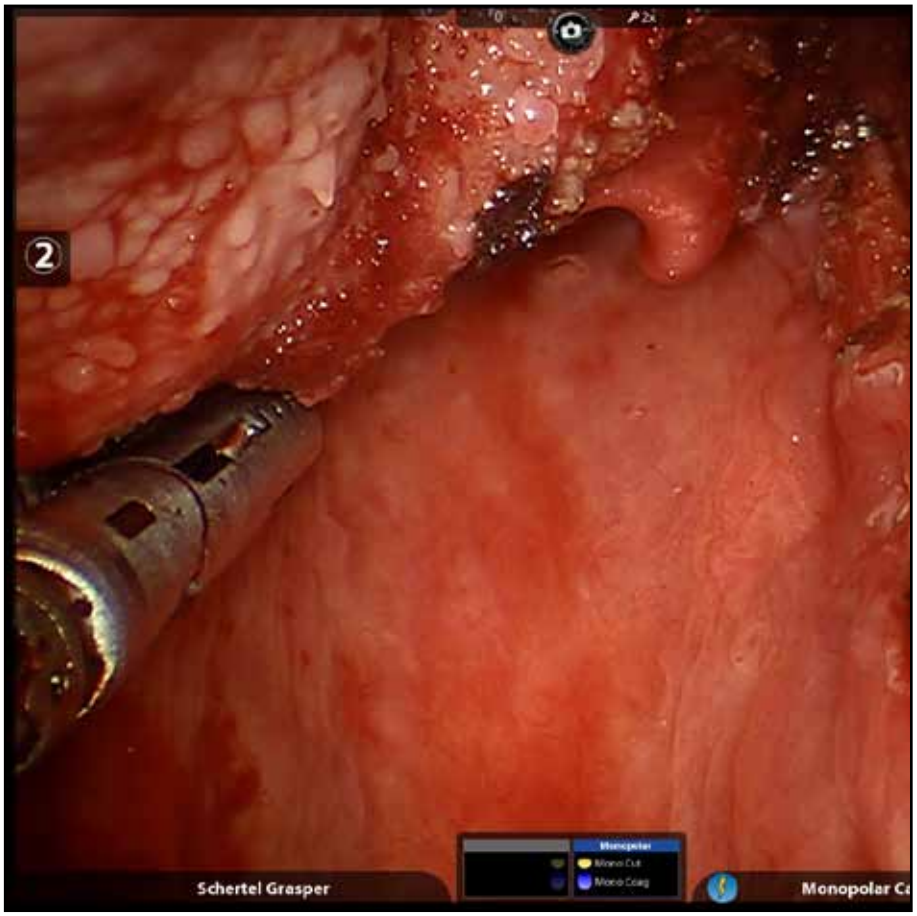

Figure 5. Following removal the epiglottis is seen and the large surgical excision achieved.

and 5). Conventional access to the oropharynx is via external approaches requiring tracheotomy, skin incisions, extensive dissection (often splitting the mandible) and free flap repair. TORS avoids the morbidity associated with these approaches.

There are several other advantages which include shorter operative times, less blood loss, no need for or reduced intensive care bed time and shorter hospital stays.

Human Papillomavirus Related Oropharyngeal Cancer

Tumours of the oropharynx (tongue base and tonsil) have been increasing in incidence over the past 15 years, particularly in young men who are non-smokers. These tumours are typically poorly differentiated squamous cell carcinomas (SCC's) presenting at an advanced stage due to nodal disease.

Initially it was not clear what was occurring to explain the explosion in these cancers. A change in epidemiology had occurred. Viral oncoproteins E6 and E7 were over-expressed in these cancers and it became apparent that the human papillomavirus (HPV) was associated with these tumours. HPV-16 which is also associated with cervical and anal cancers is the causative serotype.

HPV related head and neck squamous cell carcinoma (HNSCC) is being recognised as a distinct clinical entity which responds well to treatment. The presence of nodal disease does not have the same implication for survival as it does in the traditional non-HPV smoker/drinker cohort. Over the past 10 years these young patients have increasingly been treated with radiotherapy and chemotherapy rather than surgery. There has been an increase in morbidity associated with this treatment with long term implications for swallowing and the possible development of radiation related cancers.

This has led to the recognition that this large group of patients are potentially being over-treated. TORS offers the ability to de-intensify treatment. There are now a critical number of series

published that demonstrate increased local control and survival utilising a TORS paradigm. They demonstrate low morbidity compared to traditional open approaches. It is also important to stress that the neck has to be addressed surgically whether node negative or node positive. It is hoped that this approach will help large numbers of patients avoid adjuvant therapy, and when required can be treated with lower doses of radiotherapy and chemotherapy.

St Vincent's Experience

The development of a TORS programme at St Vincent's (the only centre in NSW providing this service) has required a significant amount of co-operation between the hospital administration, theatre and ward nurses as well as speech therapy. The programme is expensive to establish however the long-term benefits to patients and the hospital are enormous. The learning curve for surgeons is steep. To date 39 patients have been treated for a variety of problems **(see Table 1)**. In all cases blood loss has been less than 50ml. Operative times and hospital stay have gradually decreased. The main morbidity has been related to tongue retraction which has decreased as operative times have come down. One patient has required a tracheotomy immediately postoperatively due to airway obstruction.

Conclusion

Transoral robotic surgery offers a new minimally invasive approach to the management of tumours of the upper aerodigestive tract. It has particular utility in the management of HPV-associated oropharyngeal tumours which are rapidly increasing in number, particularly in younger age groups. This disease is likely to require less intense treatment and it is evident surgery will play an increased role. As with any evolving surgical technique the use and indications for TORS will increase with experience.

Table 1

Tonsil SCC	10
Tongue Base SCC	13
Palatal SCC	1
Hypopharyngeal SCC	1
Nasopharyngeal SCC	1
Parapharyngeal Space Tumours	6
Supraglottic Tumours	2
Obstructive Sleep Apnoea	6

Table 1: *Different Pathologies Treated by Transoral Robotic Surgery at St Vincent's*

Dr Alissa Walsh
Dr Gareth Owen

The Medical and Surgical Management of Inflammatory Bowel Disease

Dr Gareth Owen

Dr Alissa Walsh

Introduction

Inflammatory bowel disease (IBD) is a term used to describe two main diseases, Crohn's disease (CD) and ulcerative colitis (UC). These are chronic inflammatory conditions of the gastrointestinal tract. The peak incidence of IBD is between 20-24 years and the overall incidence in Australia is 30 per 100,000, among the highest reported internationally.

CD can involve the entire gastrointestinal tract. It is characterized by transmural, patchy inflammatory changes. CD involves the terminal ileum in 30%, the large bowel in 30%, both the ileum and large bowel in 30% and the proximal small bowel in 10% of cases. Of all of these, one third of patients develop perianal disease. Common symptoms include abdominal pain, diarrhoea and weight loss.

UC only involves the large bowel, characterized by inflammation of the colonic mucosa. It always begins in, and involves, the rectum. It then progresses for a variable distance more proximally in the colon. The inflammation is confined to the mucosa and submucosa. Symptoms of UC include bloody diarrhoea, urgency, nocturnal diarrhoea and incontinence.

The care of a patient with inflammatory bowel disease (IBD) can be either medical or surgical in nature or, in many patients, a combination of both. Surgery plays an important role in the treatment of both CD and UC and one that is evolving with time. Indeed, around 50% of all patients with IBD will require at least one surgical procedure at some stage. The need for surgery and it's timing are best decided upon in a multi-disciplinary approach involving the gastroenterologist, surgeon and patient.

Laparoscopic surgery is now emerging as an alternative approach to traditional open surgery and in many instances is becoming the surgical technique of choice. There is now significant convincing evidence of the benefits of laparoscopic surgery and laparoscopic colectomy. These benefits include: improved cosmesis, reduced postoperative pain, earlier return of gastrointestinal function and earlier tolerance to diet. These factors in turn contribute to a faster recovery of the patient with reduced use of hospital resources, reduced costs and earlier return to function and work of the patient. What is important however is that it has been shown that laparoscopic surgery, especially in IBD, should only be performed by experienced surgeons with an extensive background in laparoscopic training.

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Medical Management of IBD – the "step up approach"

The management algorithm is dependent on whether the diagnosis is CD or UC. The medical approach for patients with IBD is both symptomatic care (i.e., relief of symptoms) and mucosal healing following a stepwise approach to medication, with escalation of the medical regimen until a response is achieved. The two goals of therapy are the achievement of remission (induction) and the prevention of disease flares (maintenance). In the treatment of both CD and UC, the treating physician needs to consider both the distribution and severity of disease as this will best guide management. Flare–ups of IBD are usually managed in an outpatient setting however hospitalisation is occasionally necessary.

Available conventional treatment options for the gastroenterologist include: 5 aminosalicylates (5ASA), corticosteroid therapy (prednisone, budesonide or intravenous hydrocortisone), immunomodulators (azathioprine (AZA), 6-mercaptopurine (6MP), methotrexate (MTX), and anti-Tumour Necrosis Factor alpha (TNFα) agents (infliximab and adalimumab).

Medical Treatment of Crohn's Disease

A lifestyle change that may benefit patients with CD is smoking cessation. Tobacco use has been linked to increases in the number and severity of flares of CD and smoking cessation alone is occasionally sufficient to achieve remission of refractory CD.

5ASA agents can be effective for mild Crohn's disease although these agents are more commonly used for UC.

Steroids are rapid-acting anti-inflammatory agents. These medications are indicated for acute flares of disease only and have no role in the maintenance of remission. They may be administered by various routes depending on the location and severity of disease. Steroids may be administered intravenously (i.e., hydrocortisone), orally (i.e., prednisone, budesonide), or topically (i.e., enema, suppository, or foam preparations). Corticosteroids are limited by their adverse effects, particularly with prolonged use.

Budesonide (Entocort EC), a synthetic corticosteroid, is used for ileal or ileocaecal CD. Budesonide has extensive first-pass metabolism, which limits systemic adverse effects. However, some absorption occurs over a prolonged period of exposure. Budesonide is less effective than prednisone for the treatment of ileal CD and has not demonstrated efficacy in maintaining therapy beyond 12 months.

The most common starting dose range for moderate flares of IBD is oral prednisone at 40 mg/day. Once a clinical response is seen, the dose is tapered. Inability to taper down the steroids without recurrence of symptoms should trigger discussion regarding the use of alternative drugs (immunomodulators or anti-TNF therapy).

Patients who are concerned about immunosuppressive therapies, including immunomodulators or anti–TNF agents, should be educated about the potential greater incidence of complications occurring with long-term steroid use and with undertreated disease. The potential complications of corticosteroid use include fluid and electrolyte abnormalities, osteoporosis, avascular necrosis, peptic ulcers, cataracts, glaucoma, neurologic and endocrine dysfunctions, infectious complications, and occasional psychiatric disorders (including psychosis). Periodic assessment of bone mineral density is recommended for patients taking steroids for more than 3 months. Agents used for osteoporosis prevention and treatment (e.g., the bisphosphonates) are useful for preventing the bone loss associated with corticosteroid use.

The concept of deep mucosal healing, particularly in CD, is becoming increasingly advocated. There are several studies, primarily involving anti-TNFα agents and immunomodulators that have shown that the elimination of inflammation (as demonstrated by endoscopic and histologic criteria) results in a decrease in the rate of surgery, the use of corticosteroids, and the rate of hospitalisation. This supports the use of immunomodulators or one of the anti-TNFα agents earlier in the course of IBD.

Patients are candidates for immunomodulators (6-MP, AZA, MTX) if flares are frequent (>1-2 times/year), if the duration of steroid use is prolonged, if reduction of the steroid dose causes recurrence of symptoms (steroid dependent) or if steroids do not appear to be working (steroid refractory).

Immunomodulators have a slower onset of action (typically, a 2- to 3-month lag) and therefore it is important to consider these agents early in order to avoid prolonged treatment with steroids.

When prescribing a thiopurine medication, the American Gastroenterological Association (AGA), in accordance with the US Food and Drug Administration (FDA), recommends that patients undergo assessment of the thiopurine methyltransferase (TPMT) genotype or phenotype before starting therapy with AZA or 6-MP. Individuals who have low enzyme activity or are homozygous deficient in the TPMT mutation are at risk of very severe leukopenia, with potential septic complications, and may not be good candidates for therapy with these drugs. About 11% of individuals with heterozygous TPMT activity respond well to therapy but are prone to myelotoxicity, although this can be minimized with the use of lower doses. These patients, as well as those with wild-type TPMT activity, require monitoring for complications.

The cytopenic effect is typically dose dependent, although some patients are more sensitive than others. Use of immune modifiers mandates monitoring of blood parameters. Development of neutropenia or elevated liver function tests warrants a dose reduction or discontinuation.

The typical AZA dose is 2-2.5 mg/kg/day, whereas the dose of 6-MP is 1-1.5 mg/kg/day. After a stable dose has been reached, it is becoming increasingly common to check thiopurine metabolite levels in order to ensure that the correct dose is being used. Other adverse effects of the immune modifiers include fever, rash, infectious complications, hepatitis, pancreatitis, and bone marrow depression. The most common reason for discontinuing the immune modifiers within the first few weeks is the development of abdominal pain. Occasionally, a biochemically demonstrable pancreatitis occurs.

Concerns have been raised about the development of malignancy in patients taking 6-MP and azathioprine. These agents have been associated with a 2- to 4-fold greater incidence of lymphoma

and an increase in nonmelanoma skin cancers, but there is a 3.5-fold decrease in colorectal carcinoma.

Methotrexate has not been as widely studied in IBD as the thiopurines as this medication is generally avoided in the childbearing years due to its teratogenicity. This medication can be used for both CD and UC if thiopurines have failed. It is best used via the subcutaneous route (weekly dose) due to variable oral bioavailability. Folic acid supplementation is required.

The anti-TNF agents available for the treatment of CD in Australia are infliximab (Remicade®) and adalimumab (Humira®). Currently, these agents are funded through the pharmaceutical benefits scheme for CD (both luminal and fistulising).

Infliximab is administered intravenously at weeks 0, 2, and 6, followed by infusions every 8 weeks for maintenance of remission. Adalimumab is administered subcutaneously every fortnight after a loading dose of 6 injections over 4 weeks.

Before anti-TNF agents are administered, screening for opportunistic infections should be performed.

Adverse effects are uncommon but can include hypersensitivity and flulike symptoms. There have been rare reports of lupus-like reactions and lymphoproliferative malignancies, although whether the malignancies are related to the drug or to the underlying disease process remains uncertain.

Surgical Treatment of Crohn's Disease

Unfortunately, surgery is not curative for CD and it therefore needs to be used selectively. Despite advances in medical treatment somewhere between 70%-90% of patients with CD will still need surgical intervention at some stage. Surgery is mainly performed for complications of CD. These include stricture formation and subsequent obstruction, fistula formation or medically refractory disease. Perforation, malignancy and certain extra-intestinal manifestations of disease are other indications for surgery. Skin, mouth, eye and joint disorders tend to mirror gastro-intestinal disease activity. In contrast, hepatic, vascular, haematologic, pulmonary, cardiac and neurological manifestations act independently and do not necessarily improve following surgery.

Laparoscopy for CD has been slow to gain widespread acceptance. Laparoscopy is technically challenging in CD because of associated inflammatory adhesions, inflammatory phlegmons and hypervascular tissue. Because of these technical challenges operative times are often significantly increased and conversion rates greater than for other laparoscopic procedures.

Despite this, laparoscopy is an increasingly used surgical technique and indeed may be significantly beneficial for young patients who not uncommonly require re-resection. Re-resection is needed in up to 40%-75% of patients and previous laparoscopic resections may help reduce difficulty in subsequent surgical procedures by reducing adhesion formation.

In addition to potentially aiding future surgical procedures, laparoscopic resection in CD has been proven to improve time to resumption of intestinal function and oral intake. It has also been proven to lead to a shorter length of stay and hence the overall cost of the laparoscopic procedure is lower than that of an open operation. Other possible advantages of laparoscopic surgery are that the incidence of incisional hernia has been shown to be less and also small bowel obstruction requiring hospitalization has also been shown to be significantly less.

Small Bowel Crohn's Disease

The most common procedure for small bowel CD is resection, but stricturoplasty, bypass or ileostomy can also be performed. A philosophy of conservatism is paramount due to the recurrent and panenteric nature of CD. Recurrence rates increase with time and multiple operations may eventually lead to short-gut syndrome.

To support a philosophy of conservatism are studies that have randomised patients to different macroscopic resection margin lengths. There has been shown to be no statistically significant difference in the recurrence rate of CD despite differences in macroscopic margin at operation. The type of anastomosis may be important in regards to reducing recurrence. There is some evidence to suggest that a stapled, side-to-side anastomosis is less likely to stenose and hence obstruct, than a hand-sewn end-to-end anastomosis. Despite these technical considerations however, overwhelmingly the most important factor in reducing recurrence rates is smoking cessation in those patients that continue to smoke at the time of initial operation.

Unfortunately recurrence rates in CD are quite high. It is almost universal to have a degree of endoscopic recurrence at an anastomosis 12 months following surgery. Surgical re-intervention has then been reported in up to 30% of patients at 5years and 50% at 15 years.

Colonic Crohn's Disease

The indications for surgery in colonic disease are similar to those for small bowel disease. Dysplasia or colorectal cancer along with toxic colitis, are site specific indications. The risk of malignancy in CD was initially thought to be less than that in ulcerative colitis, however recent publications have indicated it is similar. As with UC, the risk of malignant transformation increases with duration of disease and extent of disease. Surgery is indicated in colonic CD with proven malignancy, high-grade dysplasia or Dysplasia-associated Lesion or Mass (DALM).

The surgical options for colonic disease are still of some debate. A segmental resection for isolated disease versus a total colectomy and ileo-rectal anastomosis is still a decision that has not been definitively defined. There is conflicting evidence, with some studies suggesting no significant difference in recurrence rates, complications or the need for permanent ostomy between the two procedures. These studies have shown a longer time to recurrence in the total colectomy group however. On the other hand some earlier evidence had suggested that total colectomy with an ileo-rectal anastomosis had led to a slightly higher recurrence rate. In general most surgeons now would recommend a segmental resection in limited disease and a total colectomy in more extensive disease, or when more than one segment is involved.

Unfortunately, most patients with rectal disease requiring surgery end up with a permanent colostomy or ileostomy.

Results from patients who have rectal involvement and an attempted restorative procedure in CD are very poor.

Anorectal Disease

Around 10 per cent of patients with CD have disease limited to the anorectal region but around 90 per cent of all CD patients have some degree of anorectal involvement. This can be manifest as fissures, fistulae or abscesses. Once again it is important to manage anorectal disease with a degree of conservatism, as damage to even a small amount of the anal sphincter can lead to significant morbidity.

Unfortunately fissures and fistulae are often atypical and significantly more complex than those that present in patients without evidence of CD. Control of sepsis and prevention of future sepsis, along with preservation of continence is of utmost importance. Incision and drainage of collections, often with insertion of seton's (that may be permanent) is the first step in management. Diversion of the anorectum is something that not infrequently has to be undertaken to help control ongoing symptoms.

Medical Treatment of Ulcerative colitis

5ASA therapy is central in the treatment in ulcerative colitis.

The 5ASA preparations available for use in Australia are sulfasalazine, mesalamine (Pentasa, Salofalk, Mezavant), balsalazide (Colazide) and olsalazine (Dipentum). Enema and suppository formulations are also available. The major differences between these medications are in the mechanism and site of delivery. Some of these agents also have unique adverse effects lacking in other agents of this class.

None of the aminosalicylates has been proven to have greater efficacy than any of the others for the treatment of UC and all can be used to induce and maintain remission. In treating ulcerative proctitis, rectal 5-ASA is preferred over rectal steroids. Oral 5-ASA therapy also has a role in decreasing the risk of dysplasia and colorectal cancer in patients with UC.

Oral steroids (prednisone) are used for mild to moderate UC not responding to 5ASA therapy or for severe disease. As in CD, prednisone should not be used as maintenance therapy. Inability to taper prednisone or need for recurrent courses of prednisone should trigger discussion regarding the use of immunomodulators. For acute severe ulcerative colitis, the patient should be admitted to hospital and treated with intravenous steroids.

The use of thiopurines is similar to CD. There is good evidence for both the induction and maintenance of remission in UC. There is less evidence for methotrexate in UC however this is often used if the patient has failed or is thiopurine intolerant. Other medications such as tacrolimus and mycophenolate can be used.

With respect to the use of anti-TNF therapy in UC, there is good evidence that when used in patients with moderate to severe disease it is associated with significant reductions in hospitalisations and surgeries. In Australia, both Infliximab and adalimumab are licensed for use in UC however they are not currently funded under the pharmaceutical benefits scheme. This limits their use as the cost is prohibitive. Infliximab is commonly used in Australia for treatment of acute severe ulcerative colitis for those patients who have not responded to intravenous hydrocortisone. A recent European randomised study has shown that Infliximab is equally efficacious to Cyclosporin for this indication.

Surgical Treatment of Ulcerative colitis

Medical therapy is directed toward symptom control but is not curative for UC. Surgery for UC is curative. It eliminates the possibility of developing cancer. Around 35% of patients with UC will eventually need a colectomy, either for a complication of disease or inadequate symptom control. Surgery also allows patients to eliminate long term anti-inflammatory and immune-modulating medication usage.

Surgical treatment is looked at from two aspects, emergency and elective surgery.

Worsening colitis with greater than 8 bloody stools per day, fever, tachycardia, anaemia, raised CRP, abdominal distension with tenderness or colonic dilatation on X-Ray can all predict a possible need for emergency surgery. In the acute setting however, medical therapy will allow 80% to avoid an operation. Most people would suggest that if there is no improvement within 3-4 days surgery should be contemplated.

Toxic megacolon, defined as the transverse colonic diameter greater than 6cm with fever, is almost an absolute indication for surgery. Perforation is also an absolute indication in the acute setting. The development of haemodynamic instability or multi-organ failure also warrants an emergency colectomy. Unfortunately, up to a 70% mortality has been described in acute UC with multi-organ failure, which only further demonstrates the severity of this disease.

Surgery in the acute setting is designed to remove the inflamed bowel whilst minimizing morbidity. A total colectomy with end ileostomy is the procedure of choice in this situation. It removes the majority of diseased bowel whilst avoiding complications involved with either a pelvic dissection or an anastomosis. The complication rate is relatively low (20 to 30 per cent) and it has a low mortality. The rectal stump can either be left intraperitoneal or exteriorized.

Proctectomy is rarely needed for symptomatic emergent relief and as these patients are usually nutritionally deplete, anaemic and on high-dose steroids, pelvic dissection with or without an anastomosis significantly increases the complication rate.

The most frequent indication for elective surgery in UC is failure of medical management. Inadequate symptom control, despite optimal medical management, chronic disability, or symptom control with therapy that has a high probability of long-term morbidity, all fall into this category.

The risk of developing malignancy, or indeed development of actual malignancy, is a further indication. The overall incidence of malignant transformation is not well defined but it increases with both the duration of disease and severity of disease. It has been quoted at 20 per cent after 30years of disease.

An established carcinoma certainly requires surgery, but the indication for surgery in dysplasia is less well defined. High grade dysplasia (HGD) or DALM have a high incidence of synchronous cancer and most surgeons and physicians would consider this an indication for surgery. Studies have reported a 43% incidence of synchronous tumours in HGD and DALM.

The management of low grade dysplasia (LGD) is much less well defined. Studies looking at the progression to HGD and cancer formation are widely variable. Many surgeons will still advocate surgery in the setting of LGD as there are studies reporting a reasonably high progression to HGD or a high incidence of synchronous tumours. In addition, surgery will eliminate the need for ongoing medical therapy and colonic surveillance.

Patients who develop strictures should proceed to surgery as up to 25 per cent of strictures are malignant, despite biopsies that may suggest otherwise.

Finally, elective surgery should be considered for severe extra-intestinal manifestations. Arthritis, uveitis and iritis are often improved with surgery. Unfortunately, primary sclerosing cholangitis, ankylosing spondylitis and sacroiliitis are not improved.

There are a number of surgical options offered for UC. The most widely accepted "standard" procedure offered today is a total proctocolectomy and ileal pouch anal anastomosis. This was first described in 1978 by Parks and Nichols. This procedure involves removing the colon and rectum and creating an ileal reservoir. This reservoir, or pouch, is then anastomosed to the anal canal. A variety of "pouch" designs have been described, however a J-pouch configuration is the most commonly preferred design. The reason for this is that it uses less bowel to create the pouch, it empties reliably and is relatively easy to construct. Once constructed most surgeons would "defunction" the anastomosis with a loop ileostomy as the pelvic sepsis rate due to an anastomotic leak can approach 20-25 per cent. The defunctioning ileostomy is then reversed at a later date.

Other surgical options include total proctocolectomy and end ileostomy, subtotal colectomy and ileorectal anastomosis or even colectomy with ileostomy followed by proctectomy at a later date.

Infertility is a problem in around 50 per cent of women who have undergone pouch surgery and it is not unreasonable to offer women who wish to conceive the option of a colectomy and end ileostomy, with completion proctectomy after they have completed their family. This avoids the initial pelvic dissection, which is what leads to infertility, almost certainly by pelvic adhesions. The pelvic dissection can then be performed after the family is complete.

Pouch function is an important issue for patients considering undergoing a restorative procedure. One of the largest studies looking at function was from the Mayo Clinic. It found that nearly 80 per cent of patients had complete continence. Only two per cent of patients had frequent episodes of incontinence. Most patients experienced between 4-6 motions daily with an additional 1-2 motions overnight. Long-term pouch loss was around 10% and most was related to pouchitis in the long term or sepsis in the short term. Most studies looking at patient satisfaction weigh very heavily in favour of significant patient satisfaction following a restorative procedure.

Inflammatory Bowel Disease Management at St Vincent's Hospital

Management of IBD patients at St Vincent's Hospital is very much a multi-disciplinary approach. Patients are regularly discussed in multi-disciplinary meetings involving gastroenterologists, surgeons, specific IBD nurses and others. This has allowed patient management to be streamlined and allow the best management option to be arrived at, as a group, rather than relying on an individual practitioner to bear the brunt of the burden of making all decisions. The medical management at St Vincent's is led by gastroenterologists with extensive IBD experience from large units around the world. An IBD clinic has recently been developed with the aid of an experienced IBD nurse specialist and this is an important point of contact for patients. From a surgical perspective, St Vincent's hospital has surgeons with a vast range of experience including highly trained laparoscopic surgeons and those with special interests in pelvic floor disorders for complex anorectal disease management. Complex cases are often operated on by more than one consultant surgeon to help with intra-operative decision making. The aim of the multi-disciplinary approach is to ultimately improve the patient's long-term outcome.

Breast Reconstruction After Mastectomy

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Breast Reconstruction After Mastectomy

Breast cancer remains the most common cancer and the second most common cause of cancer related death in Australian women. Statistics from Cancer Australia state that one in nine women will develop breast cancer before the age of 85.[1] While breast-conserving surgery remains the first choice of the treatment in many cases, mastectomy is still a mainstay for surgical management of the disease.

Mastectomy also has a place in risk reduction for patients who are BRCA1 and BRCA2 gene positive, conveying a genetic predisposition to breast cancer. Finally, contralateral prophylactic mastectomy is becoming increasingly popular with these patients citing piece of mind as the main motivation for surgery.[2]

The mastectomy defect can have a profound physical and psychological impact on the patient.[3] Breast reconstruction aspires to create symmetrical breast mounds that are soft to touch and natural in feel, thereby restoring a feeling of wholeness to the patient. In broad terms, the reconstruction can be performed using alloplastic (expanders/implants) or autologous (the patient's own tissues) techniques. Respective techniques will be more or less appropriate for an individual patient according to characteristics specific to the individual. Patients often present to their plastic surgeon with strong preferences for a particular type of reconstruction based on advice from friends, internet searching, online forums and published literature. Much of this advice can be confusing and inappropriate for the individual. While the patient will make the ultimate decision on choice of technique, this decision is best reached through open discussion between the surgeon and the patient. The best results in breast cancer treatment and breast reconstruction are obtained in a multidisciplinary care setting where treatment planning is optimised and individualised for the patient.

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Breast reconstruction is usually a procedure performed in two or three stages, with each stage spaced several months apart. The initial operation is invariably the longest and involves recreating the breast mound. Subsequent procedures improve the shape and symmetry of the breasts, with the creation of a nipple being left until last. An immediate breast reconstruction is performed during the same operation as the mastectomy, while a delayed reconstruction takes place during a separate operation, some time after the mastectomy. Both alloplastic and autologous techniques can be applied in the immediate or the delayed setting. A critical factor in deciding the timing of reconstructive surgery is the likelihood a patient will require post-operative radiotherapy. A delayed procedure is more prudent in patients likely to require radiotherapy because of the unpredictable deterioration in cosmesis caused by external beam radiotherapy treatment.[4-6]

Alloplastic Reconstruction

Modern breast implant technology allows for excellent cosmetic results with an ever-decreasing side effect profile. From the perspective of breast symmetry, implants are best suited to patients with smaller breasts requesting unilateral reconstruction and patients requiring bilateral reconstructions **(Figure 1a and b).**[7]

In unilateral implant-based breast reconstructions for patients with larger breasts, it can be difficult to match the ptosis and suppleness of the contralateral, native breast7. Also the position of the breast on the chest wall can be difficult to replicate as the device is placed in a submuscular pocket and has a tendency to rise superiorly on the chest wall. Contralateral mastopexy improves symmetry but rarely matches it precisely and, with the passage of time, the two breasts will age differently due to their different tissue characteristics8. Another option is contralateral augmentation to improve symmetry **(Figure 2a, b and c)**.

There are many advantages to expander-implant-based breast reconstruction including shorter

operating times, quicker recovery times and no donor site morbidity. Disadvantages include the firmer feel, capsule formation and risk of leakage. Implants also have a finite life span (usually 10-20 years) and as such patients must be educated on the likely future need for implant exchange.

Options

Expanders and implants require adequate tissue coverage to minimise extrusion, capsule formation and palpability. Where skin flaps are particularly thick, the device may be placed directly below the skin, however in most cases it needs to be buried beneath muscle. The pectoralis major muscle is elevated off the chest wall to cover the upper two thirds of the expander with the lower third being covered by the elevated serratus anterior muscle.[9] An alternative technique uses an acellular dermal matrix to provide the lower third coverage.[10] The use of autologous dermal flaps may be considered in select patients and offers the potential for complete implant coverage with a dermal-muscle (pectoralis major) layer.

Technique

Expanders are chosen according to the base diameter of the mastectomy defect and the required fill volume. Modern expanders are anatomical or tear-drop shaped to better replicate the natural breast with the lower half of the device projecting more than the upper half. They have a port for external, percutaneous filling that is either incorporated in the expander or sits in the subcutaneous tissues a short distance from the device. Expanders have a textured surface to minimise capsule formation and superior migration. Expansion usually commences two weeks after insertion and proceeds with weekly or second weekly filling sessions. The filling process is performed in the doctor's rooms or the outpatient clinic and takes less than 5 minutes. No local anaesthetic is required. A needle is inserted through the skin and into the expander's filling port. Filling stretches the overlying muscle and skin causing some short-lived discomfort. Between 50-100ml of normal saline can be instilled at any one time according to a patient's pain tolerance and the tolerance of the tissues to stretching. Having filled the expander to the desired volume it is left in situ for a further four to six weeks before returning to the operating theatre to exchange it for a fixed volume implant. Implants can be silicone gel or saline filled according to patient preference, however the silicone implants have a more natural feel in the reconstructed breast.

Autologous Reconstruction

Autologous breast reconstruction uses the patient's own tissues to create a new breast mound. Plastic surgery principles divide the human body into a series of vascular units of tissue that may be moved from one position to another to reconstruct defects, be they congenital, post-traumatic or post-surgical. These vascular units are referred to as flaps. There are many different flaps that can be used for breast reconstruction. Flap-based surgery is well suited to both unilateral and bilateral breast reconstruction. In unilateral cases, surgery to the contralateral breast may be required to improve symmetry but both breast mounds are more likely to age in a similar fashion than is the case with a unilateral implant-based reconstruction due to the greater similarity in the tissue characteristics between the native and reconstructed breasts.[11]

There are many advantages to autologous breast reconstruction including the softness, suppleness, warmth and natural ptotic appearance of the reconstructed breast. Disadvantages include longer operating times and hence longer recovery times, donor site morbidity including extra scarring and a small but real risk of partial or complete flap necrosis necessitating further surgery.

Options

Abdominal flaps form the mainstay of breast reconstruction and provide an excellent skin colour and texture match to the patient's own breast. An additional advantage is the concurrent abdominoplasty necessary for harvesting the abdominal tissue. There are many variations of abdominal flap that preserve more or less of the underlying rectus abdominis muscle. The more the muscle is disturbed, the greater is the risk of post-operative hernia formation. CT angiogram images assist in the pre-operative planning of these cases allowing for visualisation of the flap source and perforating vessels, so increasing the speed and the accuracy of intra-operative decision-making.[12]

Other common donor sites include the back, the buttocks and the inner thighs. The latissimus dorsi muscle can be elevated off the posterior chest wall and transferred to the anterior chest wall to recreate a breast. Traditionally this technique has been used in combination with an implant but the latissimus dorsi flap can be used in isolation for small volume reconstructions.[13] The buttocks can provide ample tissue for the purpose of breast reconstruction with well-concealed scars, however the dissection can be challenging and the source vessels short resulting in technical difficulties

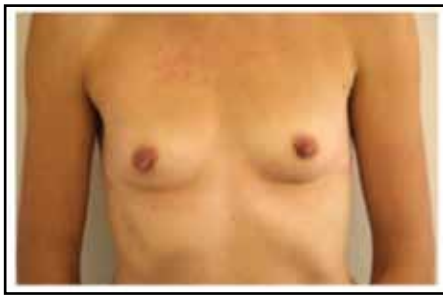

Fig 1a. *BRCA1 gene positive patient prior to surgery for left breast cancer requesting bilateral mastectomies*

Fig 1b. *Immediate bilateral expander/implant reconstruction with nipple reduction for droopy nipples*

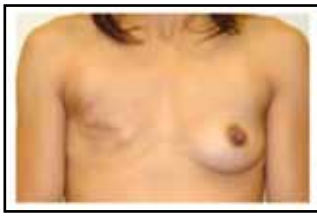

Fig 2a. *Patient with a right mastectomy awaiting delayed implant breast reconstruction*

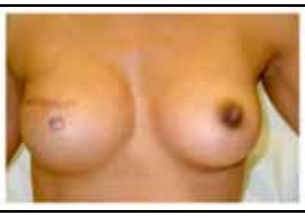

Fig 2b. *After expander/implant breast reconstruction with contra-lateral breast augmentation*

Fig2c. *The right breast after creation of a nipple and nipple/areola tattooing*

not encountered to the same degree in other flaps.[14] The gracilis muscle provides another reliable flap option for breast reconstruction and can be harvested with the patient supine, unlike the latissimus dorsi and the buttock flaps that require patient turning during the operation.[15] The resulting scar is situated in the superomedial aspect of the thigh, where it is well hidden. While there are still other flaps that have been employed in breast reconstruction those mentioned above form the most commonly used autologous options.

Technique

Abdominal free flap surgery involves elevating the redundant anterior abdominal wall pannus on it's vascular pedicle, namely the deep inferior epigastric artery and vein, whilst at the same time performing an abdominoplasty to close the resulting abdominal wound. The ipsilateral and half the contralateral pannus will reliably survive the transfer. Transverse rectus abdominis myocutaneous (TRAM) flaps remove part or all of the rectus abdomins muscle **(Figure 3)**. Harvesting deep inferior epigastric perforator (DIEP) flaps involves incising the rectus sheath to mobilise the pedicle vessels but preserves the rectus abdominis muscle. An advantage of the DIEP over the TRAM flap is reduced abdominal wall morbidity, most notably abdominal hernia, as no muscle is removed, however the dissection is technically more difficult and partial flap loss is more common.[16,17]

Numerous other free flaps are available for breast reconstruction, including tissue from the buttocks (superior or inferior gluteal flaps), the hip (Rubens flap) and the thigh (transverse upper gracilis or lateral thigh flaps). Irrespective of the free flap chosen, the tissue must be detached from the patient and transferred to the chest to recreate a breast. For the free flap to survive in its new location the circulation must be promptly re-established. Under the operating microscope the flap vessels are anastomosed to recipient vessels, most commonly the internal thoracic or thoracodorsal vessels. This stage of the operation is time dependent. If the flap remains unperfused for an excessive time, the tissue will not survive. The latissimus dorsi flap presents yet another reconstructive option. It is not a free flap and as such requires no microsurgery to re-establish perfusion. The surgical incision can be hidden within the outline of a bra.

Free flap complications tend to be minimal but are occasionally devastating. The most serious is total flap loss. The literature reports this occurring in up to five per cent of cases.[18] At St Vincent's campus, the rate is closer to one per cent due to the high volume of free flap surgery performed by the Plastic Surgery unit. The most common cause for flap necrosis is venous thrombosis, which occurs twice as commonly as arterial thrombosis.[18,19] As for the initial microvascular anastomosis, free flap vascular compromise is time dependent. Salvaging the compromised flap necessitates an urgent return to the operating theatre.

Donor site complications are not uncommon but are usually more of an inconvenience than a significant clinical problem and can often be managed by conservative means. Such complications include seroma, haematoma, infection and delayed healing.

Conclusion

Breast reconstruction is a commonly performed procedure that aims to restore a feeling of wholeness to the patient after mastectomy. With so many different surgical techniques available the patient and surgeon must together decide what is most appropriate for the individual.

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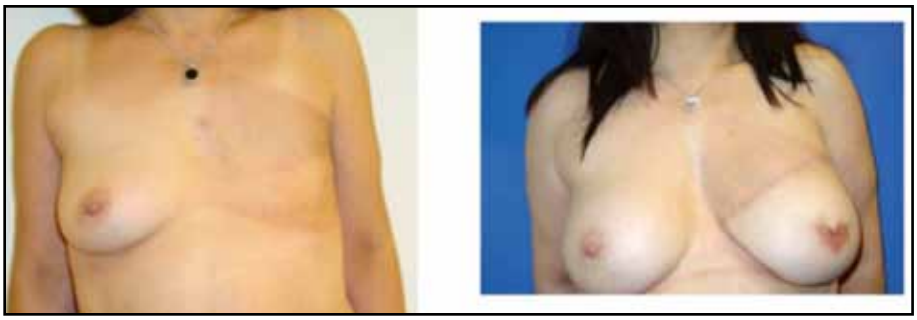

Fig 3a. *Pre-operative view of patient having undergone left mastectomy and radiotherapy awaiting delayed TRAM flap breast reconstruction*

Fig 3b. *Post-operative TRAM flap breast reconstruction with creation of a nipple and contralateral breast augmentation for symmetry*

Assessment of the Apparent First Seizure

Dr John O'Neill

Introduction

An epileptic seizure is the clinical sequel to a sudden, excessive, rapid (electrical) discharge of grey matter. It may be generalised within the brain or focal to a segment of it.

Epilepsy refers to a usually stereotyped (in any one patient) symptom complex arising from recurrent, apparently unprovoked, epileptic seizures. In other words, a diagnosis of epilepsy requires a history of two or more unprovoked seizures.

From a definition viewpoint, it should be noted that multiple seizures in the first 24 hours of presentation still constitute a single seizure. A patient will sometimes have a seizure leading to presentation and then a second or third seizure in quick succession, often witnessed in the Emergency Department. This situation must be differentiated from the much less common but life-threatening condition of status epilepticus in which prolonged and persistent seizure activity results in loss of consciousness or altered awareness over a period exceeding thirty minutes.

The first witnessed seizure is often a frightening event for the beholder. The patient is often assessed by a junior doctor in the Emergency Department or a General Practitioner working under time constraints in a busy practice, yet the event has major medical implications. For over 50 per cent of patients, it will be the beginning of living a life with epilepsy with its associated health and social implications.

Whilst the management of established epilepsy is relatively clear cut, what should be the approach to the apparent first seizure which initially brings the patient to seek medical attention? The word "apparent" is specifically used here as a careful history may reveal that the sentinel seizure (first bringing the patient to medical attention) is in fact part of an existing but previously unrecognised syndrome of epilepsy.

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Clinical Assessment of the Apparent First Seizure

In assessing an apparent first epileptic seizure, the history is all important. It should be obtained both from the patient and a reliable witness.

Typically, in the case of a generalised tonic/clonic seizure (grand mal seizure), the patient has little or no warning. If witnessed, the patient will typically regain consciousness with concerned bystanders or ambulance officers in attendance. The patient will often be confused in time and place for some minutes after the event. There may have been self-injury including tongue biting and urinary incontinence. Typical orthopaedic injuries in generalised seizures include spinal fractures and posterior fracture/ dislocations of the shoulder. There will typically be post-ictal tiredness (the patient often wishes to sleep) and there may be some generalised aching of the musculature.

The witness will typically describe a (strangled) cry or moan, a fall to the ground with loss of consciousness associated with generalised rigidity. There will often be description of a cyanotic hue, clenching of the teeth, foaming from the mouth and the rigidity will give way to generalised convulsive movements of the body. This will typically occur over a period of some (three to five) minutes before the body relaxes and there is transition to deep breathing and return of consciousness.

When a history such as that just described is obtained, it is very difficult for the doctor to arrive at any incorrect diagnosis.

Perhaps the most common mistake in diagnosis occurs when convulsive activity arises in the setting of vasodepressor syncope.

Though sometimes quick in onset, in vasodepressor syncope the loss of consciousness is typically preceded by a warning in the form of a feeling as though the patient is going to faint or requires fresh air. Patients may describe feeling hot, light-headed and they may describe blurring of vision or noise becoming distant. They will usually want to sit or lie down. There may have been a precipitant event such as prolonged fasting on a hot day or the experience of trauma (often minor, including such things such as venepuncture). There may be a family history of fainting. Especially if a well-meaning bystander prevents the patient from becoming supine, the primary physiological changes of bradykinesia and hypotension can be prolonged to the point where there is reduced cerebral perfusion and secondary convulsive activity of the body, simulating a seizure to the inexperienced eye. In typical vasodepressor syncope, the patient will usually slump to the ground without rigidity or convulsive activity. The eyes are often observed to roll back in the head and there may be facial pallor and sweating. The loss of consciousness is usually brief (thirty seconds or so) and there is no subsequent confusion. Such events are common in young thin women with relative hypotension.

It is also important for the clinician to be aware of the possibility of pseudo-seizures (non-organic functional seizure activity) and the history of abnormal illness behaviour or psychiatric illness may be an early clue.

It is important to determine if the seizure which first brought the patient to

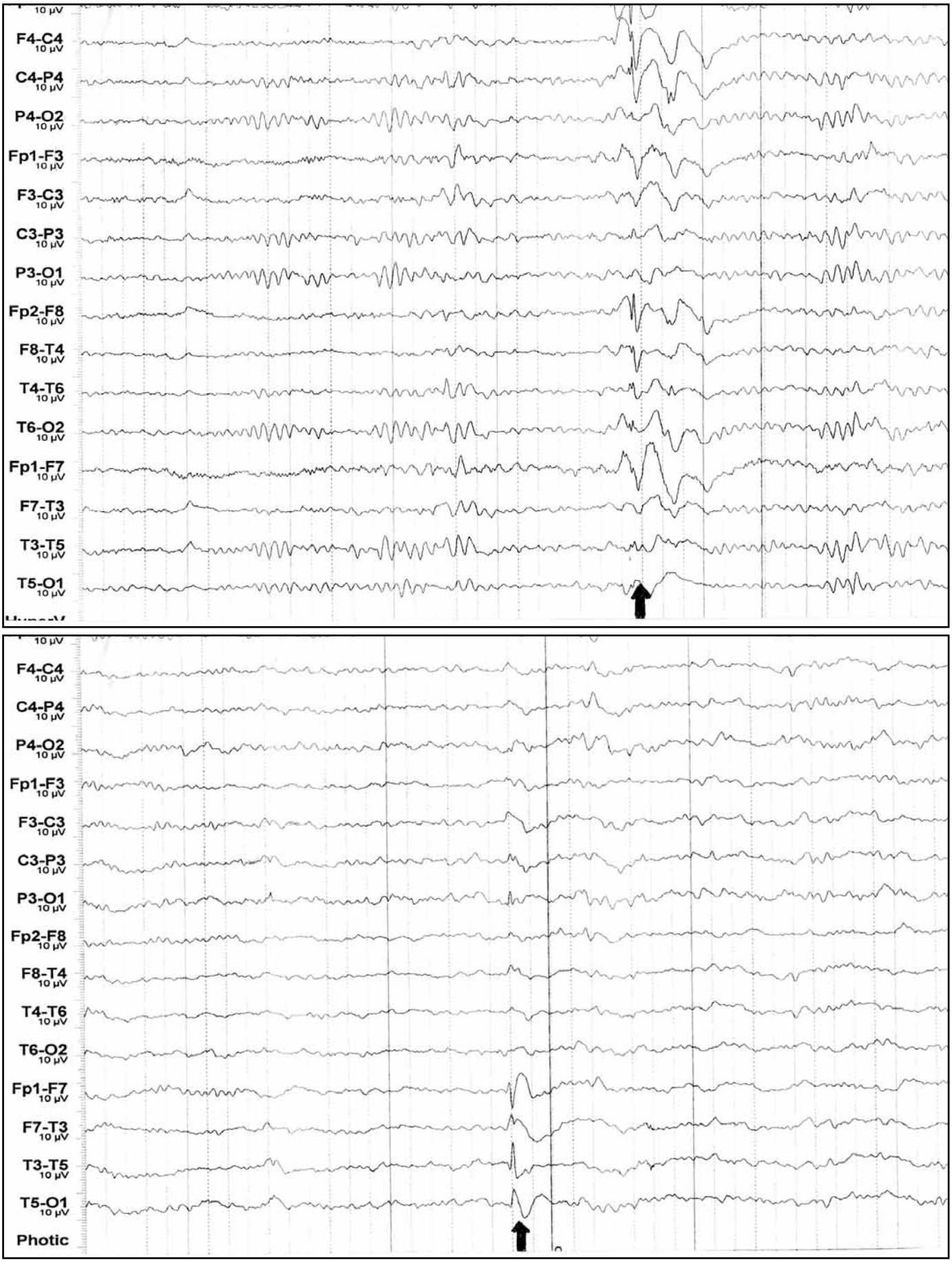

Figure 1

Top: *Dysrhythmic record with a generalised spike and slow wave discharge in a patient with Juvenile Myoclonic Epilepsy;*

Below: *Left temporal spike and slow wave discharge in a patient with a history of herpes simplex encephalitis and subsequent complex partial seizures of temporal lobe origin.*

medical attention was, in fact, the first manifestation of previously unrecognised epilepsy which had been manifest in more subtle ways.

It should be asked whether the patient has previously experienced unexplained and unwitnessed episodes of nocturnal incontinence or tongue biting (which might represent nocturnal generalised seizures).

It should be asked whether the patient is prone to involuntary limb jerks (outside the physiological setting of falling asleep), especially in the setting of tiredness or around the time of menstruation. Such a history is more concerning if the described jerks are such that it leads the patient to drop an object they might be holding or buckle at the knees.

It should be asked whether the patient has ever been observed to suddenly and briefly "switch off' so that they may stop what they are doing and stare (and/or repetitively blink) often for only a few seconds but sometimes frequently on a daily basis.

The myoclonic jerks and absences (usually seen in pre-adolescence) described above are themselves epileptic events so that the signature (apparent initial) generalised seizure is actually a manifestation of a pre-existing epilepsy. Such a combination is typical of a common genetic form of epilepsy, Juvenile Myoclonic Epilepsy **(Table 1)**.

Patients should also be asked about previously unexplained episodes of altered awareness, especially if such an event immediately preceded the apparent initial generalised seizure. Again, in such a situation, the patient may already have epilepsy in the form of complex partial seizures which are always stereotyped in any individual patient. These events reflect focal seizure activity arising from a focal region of the brain. In the case of a seizure of temporal lobe origin, a patient may lose awareness in the setting of a feeling that is typically difficult to define but which may be frightening, uncommonly pleasant and often described as a familiar (deja-vu) sensation or alternatively, one of unreality. Such complex partial seizures (with secondary generalisation manifesting as a grand mal seizure) constitute the most common form of epilepsy in adults.

Once established that the patient has had an isolated seizure, it is also necessary to determine whether there might be a relevant antecedent risk in the form of a family history of epilepsy or a past history of birth trauma, febrile convulsions, serious head trauma or a previous neurological insult such as meningoencephalitis or tumour. The history should identify any other neurological symptoms which might indicate that the seizure was symptomatic of a current, active neurological condition such as a tumour.

On the other hand, an isolated seizure is unlikely to be repeated when induced by a reversible common metabolic disturbance (such as hypoglycaemia, hyponatraemia, hypocalcaemia or hypomagnesaemia) or substance abuse (especially alcohol or benzodiazepine withdrawal) wherein the offending substances can potentially be avoided in the future.

It cannot be emphasised enough that an accurate eye-witness account and thorough history is critical to the diagnosis and management of the apparent first seizure.

Investigating the Apparent First Seizure

From an investigation viewpoint, in the case of an unwitnessed loss of consciousness, a seizure is more likely to have taken place if there is a temporary elevation in the leucocyte (and neutrophil) count or creatinine kinase (only after a generalised seizure) or the prolactin level, which might increase within 10 to 20 minutes of either a generalised or complex partial seizure.

Though usually performed, it is rare without an appropriate history, to find a metabolic disturbance such as severe hyponatraemia, hypoglycaemia, hypokalaemia, or hypomagnesaemia.

A CT brain scan is usually sufficient to exclude a tumour but MRI is clearly more sensitive in excluding the possibility of underlying structural pathology of the brain.

An electroencephalograph (EEG) is mandatory in all patients after a seizure. The finding of a focal abnormality or a general epileptiform disturbance on EEG **(Figure 1)** independently increases the risk of a second seizure. The likelihood of such an abnormality on EEG is greatest when the record is taken within 24 hours of the seizure and subsequently a sleep-deprived record also increases the risk of an abnormal EEG. These investigations are summarised in **Table 2**.

Table 1: Juvenile Myoclonic Epilepsy

- 5-10% of epilepsies
- 25-50% affected relatives
- Onset late childhood or adolescence
- Absences (40%) may antedate myoclonus
- Myoclonus (100%) may precede generalised seizures (seen eventually in 80-90% of cases)
- Greater than 60% have abnormal EEG with 4-6 cps spike/polyspike and slow wave discharges
- Highly responsive to valproate
- Lifelong treatment required - 90% relapse with drug withdrawal

Table 2: Investigation of the first seizure

- FBC
- Urea, electrolytes, BSL
- Calcium and magnesium
- CK and prolactin
- CT (±MRI) brain scan
- EEG (preferably within 24 hours of the seizure)

Medical Management of the Apparent First Seizure

If the history established that the history leading to presentation was, in fact, a confirmation of the presence of epilepsy in the that patient had a past history of previously unrecognised nocturnal generalised seizures or complex partial seizures or had a generalised epilepsy syndrome (with preceding myoclonus and/or absences) then there is no question about the need for commencement of effective anticonvulsant medication.

What, on the other hand, should be done about the first seizure with no such antecedent history? Is the patient to be confined to long-term anticonvulsant cover despite not, by definition, having epilepsy?

Statistically, after a first seizure, some 50 per cent of patients will have a second seizure within 3 months and up to 70 per cent within 6 months. The risk increases with a positive family history, symptomatic seizures, presentation with status epilepticus and a positive EEG **(Table 3)**. It is in such patients that I would usually commence anticonvulsant treatment.

Quantitative issues also play a part in decisions on treatment. An anxious patient or family may not want to risk a second event, especially if the first seizure was associated with serious injury. The very small risk of death associated with an epileptic seizure has to be explained to the patient and taken into consideration. There are also social implications for driving and often the workplace.

The commencement of treatment does reduce the risk of a second seizure and delays the onset of such an event if it were destined to occur, but how long should such treatment continue if the diagnosis of epilepsy is uncertain?

Patients are always concerned about driving. Whether treated or not, the recommendation by AUSTROADS 2012 is that a patient cannot commence driving a private vehicle until they have been seizure –free for a period of six months and a commercial vehicle until they have been seizure-free for 5 years. If a patient takes the initial decision to commence medication but later wishes to be taken off it then it must be pointed out that that patient will again have to cease driving for a period of 3 months after a period of anticonvulsant withdrawal as the risk of a further seizure (were it destined to occur) is greatest in the first 3-6 months after medication withdrawal.

In the case of young women, commencement of medication may carry the risk of an interaction with the oral contraceptive pill and an unwanted pregnancy unless the need for a full-dose oestrogen pill is emphasised. If pregnancy is under consideration by the patient there is the risk of a possible increased teratogenic risk with introduction of medication.

Other arguments against treatment of the first seizure are the cost of medication and the potential side-effects of the chosen drug.

In practical terms, especially in the setting of an unwitnessed seizure in a young patient, that patient is often reluctant to accept the serious nature of the situation (even after full explanation) and will not be compliant with any prescribed medication. Especially in young patients, it is not uncommon for there to have been several seizures before the patient accepts the diagnosis of epilepsy and the need for compliance with treatment including appropriate changes in lifestyle.

In general, taking all these matters into account, neurologists are reluctant to treat the first seizure, especially when there is no clear predisposition to a second event and hence the diagnosis of epilepsy.

Table 3: Risk of epilepsy after an apparent first seizure

- Greater than 50% progress to a second seizure, usually in the following 3-6 months
- Risk increases with:
  - Positive family history
  - Juvenile Myoclonic Epilepsy or other epileptic syndrome
  - Partial seizures identified on history
  - Seizures symptomatic of underlying brain disease
  - Status epilepticus at presentation
  - An abnormal EEG
- Risk is low with:
  - Alcohol withdrawal seizures
  - Other drug-induced seizures
  - Correctable metabolic disturbances

Conclusion

Assessment and management of the apparent first seizure is complex and time consuming. It requires specialist follow-up by a neurologist.

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The Use of Lasers in Head and Neck Surgery

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Introduction

As modern surgery has evolved there has been a drive to maximise technical success and minimise complications. Many different instruments have been trialled to achieve this aim and lasers have become a commonly used device within various fields of surgery.

Otolaryngology, Head and Neck Surgery and Urology are the fields in which lasers are most widely utilised. St Vincent's Private Hospital boasts an array of lasers for use in this field and is the leading hospital in New South Wales when it comes to laser surgery.

Lasers in Otology

The advent of laser technology has always been of interest in Otology given the very small scale of the work required, performance under the microscope and desire for accuracy to avoid complications. Early work with lasers in Otology started in the late 1960s and early 1970s (Sataloff 1967; Stahle, Hogberg et al. 1972). Stapedotomy was of particular interest as removal of a stapes superstructure with a width of 1mm and performing a fenestra through the oval window in the range of 0.4mm to 0.8mm requires very fine instruments and technical skill. Perkins (1980) was the first to use laser for stapedotomy clinically. Initial work was with the Argon laser with a wavelength of 514 nm. KTP (Potassium Titanyl Phosphate) lasers are also within the visible spectrum (532nm). Both of these lasers are able to be delivered via a fibreoptic cable and focussed on a spot size of less than 100um. Due to the laser's short wavelength, pigmented tissues or substances (eg. haemoglobin) provide excellent absorption and energy release.

Carbon dioxide (CO2) lasers (wavelength 10,600 nm) are invisible, require an aiming beam and are usually delivered via a coaxial delivery system on a microscope. CO2 lasers have less scattering and penetration of energy, but may cause more charring of affected tissues. CO2 lasers have been less widely used in otology due to difficulty in maintaining absolute accuracy between the aiming beam and the laser itself. More recently, however, CO2 lasers have been adapted to a fibreoptic system, enabling use within the middle ear (Vincent, Grolman et al. 2010).

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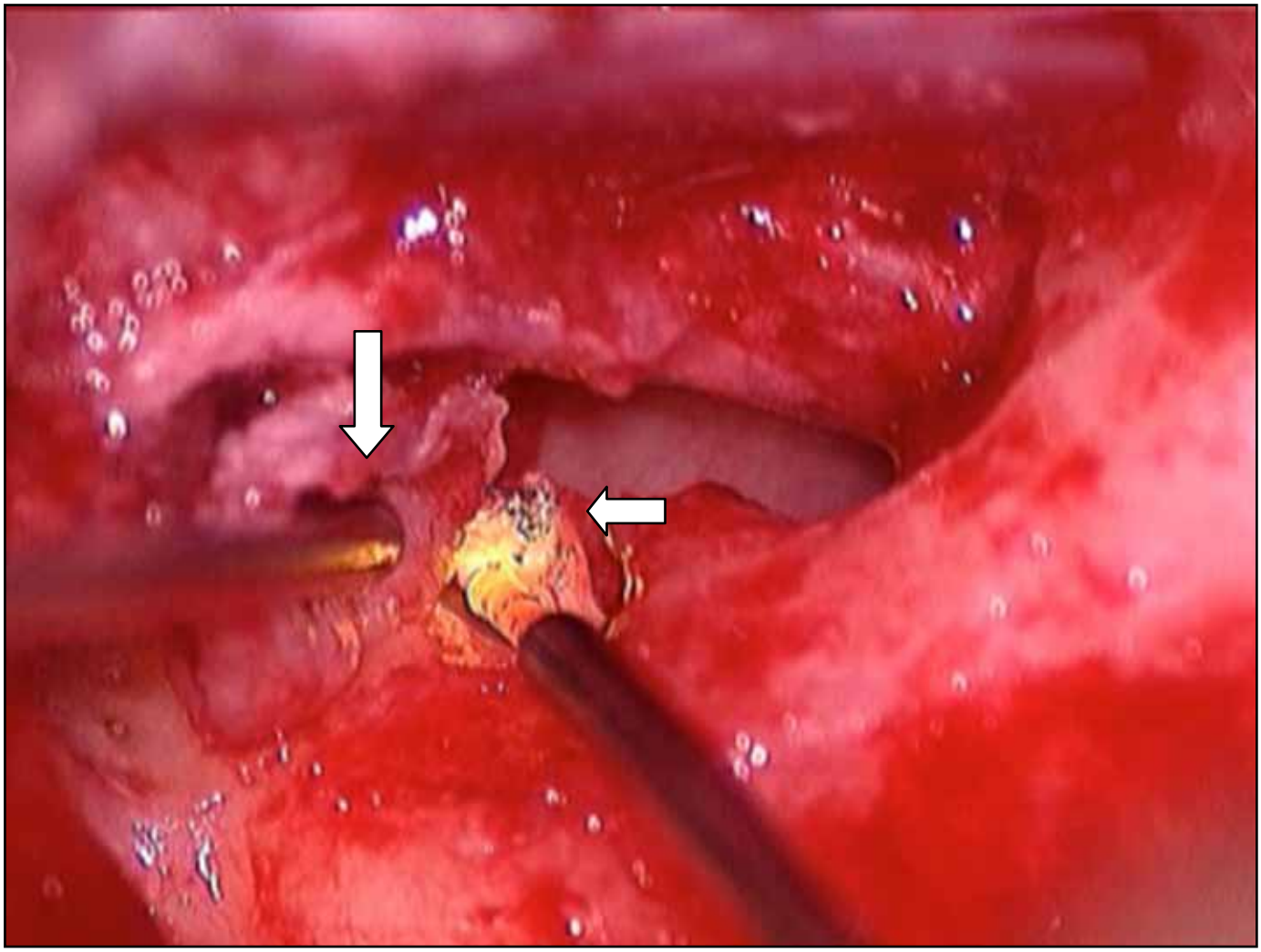

Figure 1. *Image of a 0.4 mm diameter KTP laser fibre being used to excise cholesteatoma (vertical arrow) off a stapes superstructure (horizontal arrow).*

Care needs to be taken with deeper penetration of lasers and thermal injury particularly in stapes surgery where the vestibule is opened and the deeper structures of the inner ear (saccule or utricle) may be exposed. A number of studies have shown no difference in thermal changes or likelihood of inner ear structure injury between the different laser types (Kodali, Harvey et al. 1997; Lundy 2009).

Stapedotomy with the KTP laser is the most commonly performed otologic procedure at St Vincent's Private Hospital with approximately 100 procedures undertaken per year. It allows division of the incudo-stapedial joint, stapedius tendon and stapes structure without applying torsional forces on the stapes footplate which may result in inadvertent mobilisation. The laser also reduces bleeding which compromises visualisation of the stapes footplate and may compromise positioning of the prosthesis. More recent use of memory metals (nitinol or nickel-titanium alloy) which change shape with heating have allowed the manufacture of self-crimping pistons onto the incus. The laser provides an excellent method to temporarily heat these pistons without causing thermal injury to surrounding structures.

In revision stapedotomy, the laser enables fine division of adhesions around the stapes prosthesis without manipulating the prosthesis itself. These advantages reduce the risk of sensorineural hearing loss which is a more significant risk in revision surgery. As a result, use of the laser has almost become standard of care for revision stapedotomy procedures.

Other otologic procedures in which the KTP laser is useful include ossicular chain reconstruction and cholesteatoma surgery, particularly for middle ear cholesteatoma that is draped over the stapes superstructure **(Figure 1)**. In the latter situation, the laser can ablate squamous epithelium off the stapes without manipulation or damage which may further compromise hearing.

The acquisition of a KTP laser by St Vincent's Private Hospital following the donation of funds by a generous benefactor has improved patient outcomes by reducing the risk of known complications in certain otologic procedures and has led to the Department of Otolaryngology, Head, Neck and Skull Base Surgery having the greatest experience in the use of lasers in NSW.

Lasers in Laryngology

The carbon dioxide (CO2) laser is the workhorse laser of laryngology. It has been used for both benign and malignant disease, including management of airway stenosis, laryngeal papillomatosis , supraglottic cysts, laryngeal and hypopharyngeal carcinomas, and pharyngeal pouch diverticulotomy. The advantages of laser surgery in laryngology are significant.

Traditional open procedures used in the management of laryngeal malignancy require a tracheotomy and the breach of multiple tissue planes. This is avoided with laser resection.

The laser has traditionally been mounted onto an operating microscope so any surgery is line of site. The CO2 laser offers precise, repeatable surgeries with good haemostasis. This does however require appropriate instrumentation to provide access, manipulation and haemostasis.

It requires cooperation between surgical, anaesthetic and nursing staff. There is an ever present danger of airway fire. This requires the use of a variety of anaesthetic techniques. Laser proof tubes are frequently used. Their disadvantage is that they are expensive and occupy a significant part of the airway. Jet ventilation has distinct advantages using either small tubes for distal ventilation or no tube using proximal ventilation.

The utility of laser in the management of glottic malignancy has been demonstrated repeatedly over the past decade. It is especially valuable in the management of early disease, avoiding the use of radiotherapy and it's associated morbidity while keeping radiotherapy in reserve for future management.

Operative techniques vary according to the underlying pathology. Laryngeal papillomas can be excised or laser ablated depending on location. Carcinomas require increased expertise and understanding of behaviour within the larynx. Tumours may need to be removed in a planned piecemeal fashion so as to establish tumour depth and enable complete resection. This is especially relevant to more advanced carcinomas. Early carcinomas of the mid vocal cord lend themselves to en-bloc excision **(Figure 2 and 3)**. Bleeding is managed with suction diathermy or the use of ligaclips.

Today many patients can have their cancer treated in a day surgery setting. Vascular lesions such as papillomas which were previously removed piecemeal and imprecisely (resulting in significant damage to underlying structures) can be dealt with in a bloodless fashion avoiding significant morbidity.

It is expected that the introduction of fibre based lasers will lead to further advancements.

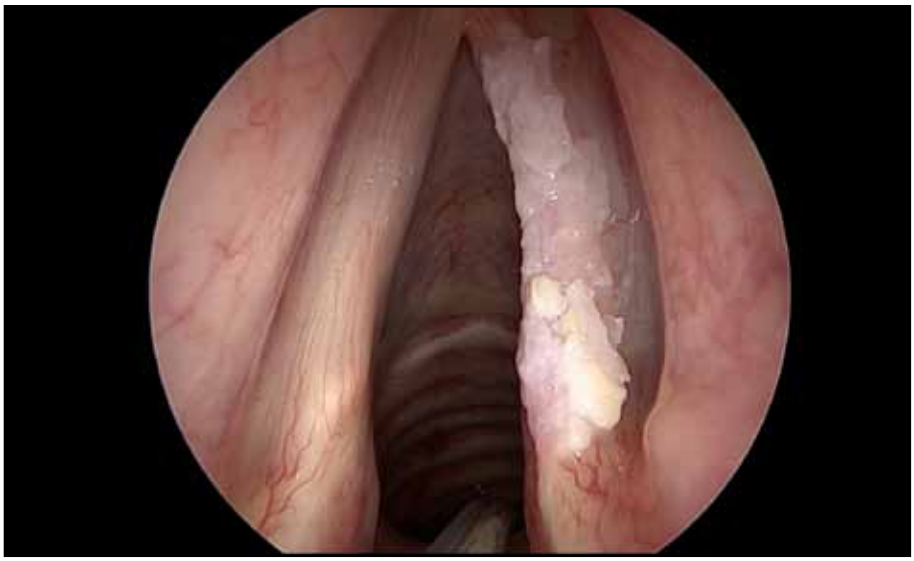

Figure 2. *Intro-operative photograph of an early right vocal cord cancer.*

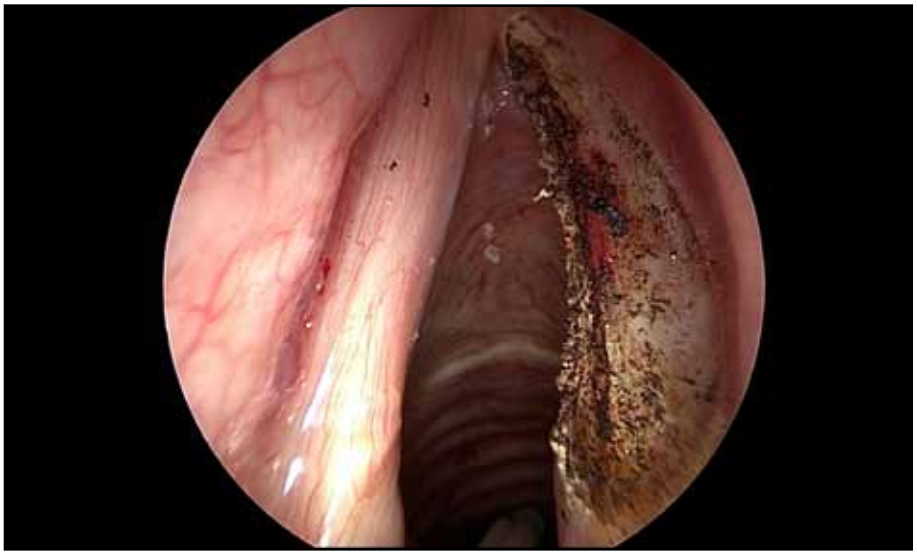

Figure 3. *The appearance at the end of the procedure demonstrating the surgical bed with an intact vocal ligament.*

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The Emerging Role of Radiotherapy in Melanoma is being defined by High Quality Australian Clinical Trials

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Introduction

Australia has the highest incidence of skin cancer in the world, at nearly four times the rates in Canada, the United States and the United Kingdom. The incidence of skin cancer is five times that of any other cancer in the country (Staples et al., 2006). Skin cancer is the most expensive Australian cancer. Most Australian Government funding allocated to cancer care is spent on skin cancer. In 2001, it was estimated the treatment of non-melanoma skin cancer cost $264 million and melanoma $30 million ("Cancer Council Australia - Skin Cancer Facts and Figures," 2011).

Melanoma is a serious skin cancer that can lead to death. Melanoma is a cancer of melanocytes. These cells produce the dark pigment, melanin, which is responsible for the color of skin. They predominantly occur in skin, but are also found in other parts of the body, including mucosa of the oral cavity, anus, and the orbit eg choroidal melanoma. The primary cause is ultraviolet light, especially in Caucasians found in sunny climates. 160,000 new cases of melanoma are diagnosed in the world yearly. Melanoma is not as common as other skin cancers but is much more dangerous if it is not found early. There are 48,000 melanoma related deaths occur worldwide per year. It causes the majority (75%) of deaths related to skin cancer.

Prognosis is related to depth of invasion of the primary, ulceration and spread to lymph node and other organs. **Table 1** describes the current staging of malignant melanoma.(ref: Balch et al, 2001)

The content of this article won the prize for best oral presentation at the 6th Melanoma Centres Meeting/8th Meeting of the European Association for Dermato-Oncology held in Barcelona Nov 14-18, 2012.

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On an annual basis, over 10,600 Australians will develop a melanoma (Australian Institute of Health and Welfare, 2010). The mortality is increasing. From 1984 to 2005, the number of deaths in Australia per year doubled for melanoma, from 640 to 1,273; (Australian Institute of Health and Welfare, 2008). This incidence of melanoma is increasing on a global scale also (Little, 2012). It is only fitting that therapeutic advances in skin cancer care, particularly in melanoma, should progress with at least Australian participation and collaboration.

Radiotherapy (RT), along with surgery and chemotherapy, is an established anti cancer modality in many cancer types. However, the general perception in the medical community is that melanoma is radio-resistant (MacKee, 1946). How did this perception come about? There are no laboratory of clinical studies which support this. In fact, the opposite is true.

Historically, laboratory (Rofstad 1986, Stevens 2006) results suggested that large radiation doses per fraction were necessary. Hypo fractionated regimes became popular. Gray (Gy) is a measure of radiation therapy being delivered. The total dose of RT is usually delivered in small doses or "fractions". One regime for high risk postoperative patients in which most gross disease had been resected was 21 Gy in 3 fractions of 7 Gy each, delivered on days 1, 7, and 21(Million, 1984). This gave greater than 90 per cent local control at four years. Ang et al gave 30 Gy in five x 6-Gy fractions to patients with primary node-negative cutaneous melanoma of the head and neck in the post operative setting who were at high risk for local-regional relapse. In 174 patients the actuarial 5-year local-regional control (LRC) and survival rates for the whole group were 88 per cent, better than the 50 per cent observed in historical controls treated without RT. Sause et al conducted a randomised trial. One hundred thirty-seven patients with

measureable lesions were randomized. Treatment was given over four weeks. The arms were either 8.0 Gy once weekly to a total dose of 36Gy, or 2.5 Gy x 5 days a week for a total dose of 50Gy. There was no difference between arms. Response rate overall was complete remission 23.8 per cent, partial remission 34.9 per cent.

The problem with these techniques was that total dose needed to be reduced when large fraction sizes were given. This may compromise disease control and perhaps survival. Unfortunately large fractions sizes are also associated with increased late side effects, which are dominated by fibrosis. Bad side effects include lymphoedema and telangectasia. Therefore, those that did survive had complications, giving RT a bad name. At the same time, surgical techniques improved. Surgery also results in a histopathological diagnosis on what is resected. The histopathology is important in melanoma for prognostication and to decide whether further theories are warranted. Surgery won the ascendancy, and radiation oncologists, in the main, retreated from the field. Those cases referred for RT then became those referred as a last resort. These were usually large symptomatic lesions that had progressed through other therapies. They generally were treated with palliative intent, and often did not respond anyway, just reinforcing the pessimism.

There is no need for this nihilistic attitude. There is no laboratory or clinical data which demonstrates that radiation does not work in melanoma. The place of radiotherapy in melanoma needs to be defined. Otherwise, melanoma patients may not be getting the full range of treatments they need.

Australian radiation oncologists want to have better evidence to guide treatment and are leading research in this area. The role of RT in melanoma is being defined by high quality Australian research. This effort is being led by the ANZMTG based at the Mater, assisted by other groups, such as the Trans Tasman Radiation Oncology Group (TROG) and the Melanoma Institute of Australia (MIA). These RT trials are discussed below.

The Trials

The ANZMTG 1-02/ TROG 02.01 trial is a randomised clinical trial of surgery versus surgery plus adjuvant radiotherapy following completely resected macroscopic nodal melanoma. This first trial has been completed and published (Burmeister & Henderson, 2012). In 248 patients, the addition of radiotherapy of 48 Gy in 20 fractions following lymphadenectomy was associated with a significant reduction in disease recurrence from 32 per cent to 18 per cent as compared with observation over a two year period (HR 0.47; p<0.005). However there was no difference in relapse free survival and overall survival, as this patient population is at high risk of distant metastatic disease. The quality of life data is still being analysed. A similar trial was attempted in the US but was closed due to poor accrual (Creagan ET, 1978).

The second trial ANZMTG 1-07 / TROG 08-05 is a trail looking at the utility of Whole Brain Radiotherapy (WBRT) following local treatment of intracranial metastases of melanoma (WBRTMel) (Fogarty, 2012). It is examining the role of whole brain radiotherapy (WBRT) with at least 30 Gy in 10 fractions following local intracranial treatment of up to three melanoma brain metastases (BMs). The use of WBRT in this scenario is controversial. BMs are a common cause of death in patients with melanoma. Proponents say that radiotherapy to prevent or delay neurological decline from further metastases and their treatment is worthwhile palliation. Opponents argue against radiotherapy as there has never been a survival benefit demonstrated and there is a risk of neurotoxicity. These opinions are based on studies in other malignancies. There are no randomised clinical trials for this specific scenario in patients with metastatic melanoma. The anecdotal impression among some clinicians that melanoma is radioresistant has not helped. As a result, current clinical practice varies widely even within the same Australian cities, with some units

Table 1: *Melanoma staging*

Melanoma staging	5 year survival rates
Stage 0: Melanoma *in situ* (Clark Level 1)	99.9%
Stage I/II: Invasive melanoma, T1a: Less than 1.00 mm primary tumor thickness, without ulceration, and mitosis <1/mm2 T1b: Less than 1.00 mm primary tumor thickness, with ulceration or mitoses ≤ 1/mm2 T2a: 1.00-2.00 mm primary tumor thickness, without ulceration	85-99%
Stage II: High risk melanoma T2b: 1.00-2.00 mm primary tumor thickness, with ulceration T3a: 2.00-4.00 mm primary tumor thickness, without ulceration T3b: 2.00-4.00 mm primary tumor thickness, with ulceration T4a: 4.00 mm or greater primary tumor thickness without ulceration T4b: 4.00 mm or greater primary tumor thicknes with ulceration	40-85%
Stage III: Regional metastasis N1: Single positive lymph node N2: Two to three positive lymph nodes or regional skin/in-transit metastasis N3: Four positive lymph nodes or one lymph node and regional skin/in-transit metastases	25-60%
Stage IV: Didtant metastasis M1a: Distant skin metastasis, normal LDH* M1b: Lung metastasis, normal LDH* M1c: Other distant metastasis or any distant metastasis with elevated LDH*	0-15%
*LDH – Lactate Dehydrogenase	

strongly encouraging WBRT while others rarely offering it. The primary endpoint is distant intracranial failure at 12 months. This trial has robust assessment of neurocognitive function. 200 patients are needed, with 90 so far having been randomised over three years, including 25 from Norway. An interim analysis will take place one year after 100 patients are randomised. It is still accruing.

The third trial, ANZMTG 1-09 / TROG 08-09 - A randomised phase III trial of postoperative radiation therapy following excision of neurotropic melanoma of the head and neck (RTN2) is evaluating whether radiation therapy has a role in the local management of resected primary melanoma of the head and neck showing histological features of neurotropism. The use of RT in this scenario is controversial. The primary endpoint of the trial is time to local relapse. This trial is also a collaboration with TROG, involves a number of Australian Melanoma centres and there is strong international interest in this study. 15 of a needed 100 patients have been randomized within one year which is a solid achievement for a trial which requires patients with this particular diagnosis.

The following two trials are in development. The first is a randomised controlled trial of imiquimod versus radiotherapy for inoperable lentigo maligna (LM). LM is a form of melanoma in situ that occurs on exposed sun-damaged skin of elderly people (Ackerman, 1993). Australia has the highest incidence of LM in the world and with an aging population, LM rates are likely to increase (Youl et al., 2012). There is up to a 50 per cent life time risk of progression from LM to invasive melanoma (McKenna et al. 2006). Surgical treatment is the preferred option when possible but margins of 5 mm are inadequate in 50 per cent of LM (McKenna et al. 2006). Surgery may be contraindicated due to the extent of disease, co- morbidities that make the patient inoperable or as a result of patient preference for a more conservative approach. Significant morbidity can result from wide surgical excisions (de Berker 1991). Radiotherapy, cryosurgery and other medical treatments, such as the topical treatment, imiquimod, have been proposed to treat a larger field, in the hope of decreasing recurrence rates and reducing cosmetic issues. Imiquimod is an immune response modifier. Studies have reported clearance of 77-100 per cent. (Powell et al. 2009) (Buettiker et al. 2008). An unpublished review of radiotherapy by the trial management team shows a recurrence rate of nine per cent at an average follow-up of three years. The two treatments have never been compared and there has never before been a prospective trial of radiotherapy in LM. The LM will be regularly monitored and mapped with reflectance confocal microscopy (RCM). A total of 260 patients will be required.

The second trial in development will be a prospective phase II single arm trial investigating radiotherapy followed by nodal dissection for high volume nodal melanoma (REFORM trial). It will evaluate preoperative radiotherapy for patients with high volume nodal disease (Stage IIIb (N2b), Stage IIIc (N3) and select Stage IV excluding BMs). All patient will undergo a pre-treatment PET scan and receive radiotherapy (48-50Gy in 20#) followed by repeat PET scan and a planned nodal dissection thereafter. The primary end point of the trial is regional control rate at 12 months. Patients who already have metastatic melanoma to other sites by the time of operation may be spared unnecessary surgery.

Conclusion

The current medical perception that melanoma is radio-resistant is not evidence based. In fact a recently published Australian trial has reported a significant advantage in the addition of radiotherapy for regional control following surgery. Radiotherapy may have an important role in melanoma treatment. Five more trials are accruing or in development under the auspices of ANZMTG and these will help to define the role of RT in melanoma. The emerging role of radiotherapy in melanoma is being defined by ongoing high quality trials lead from Australia. Melanoma centres around the world may need to include radiation oncologists, and radiation oncologists need to answer the call so that melanoma patients can access effective evidence-based treatments.

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St Vincent's Clinic Foundation – 2012 Grant Recipients

Ladies' Committee Sr Mary Bernice Research Grant – $80,000
Prof David Ma – St Vincent's Centre for Applied Medical Research
"Identification of MicroRNAs that predict treatment success in patients with acute Myleloid Leukaemia"

Adult Stem Cell Research Grant 1 – $30,000
Dr Robyn Lukeis – St Vincent's Hospital
"Improving the scope and sensitivity of donor chimerism monitoring post stem cell transplant by fluorescence in situ hybridisation (FISH) using cell separation and deletion polymorphism detection"

Adult Stem Cell Research Grant 2 – $50,000
A/Prof Anthony Dodds – St Vincent's Centre for Applied Medical Research
"Role of microRNAs in Haematopoietic Stem Cell Differentiation and Acute Leukaemia"

Di Boyd Cancer Research Grant & K&A Collins Cancer Research Grant – $80,000
Prof Richard Epstein – Garvan Institute of Medical Research/Kinghorn Cancer Centre
"Creation of 'cancer-proof' cells using genetic engineering to vary the mutational stability of human TP53 gene"

Tancred Trust Research Grant – $50,000
Prof Peter Macdonald – Victor Chang Cardiac Research Institute
"Esmolol cardioplegia as an alternative to hyperkalaemic cardioplegia: Using a rodent model of brain death to assess a novel preservation solution in cardiac transplantation"

Froulop Research Grant – $28,000
A/Prof Rajesh Subbiah – St Vincent's Hospital / Victor Chang Cardiac Research Institute
"Beat to beat variability of QT interval and stratification of risk for sudden cardiac death in long QT syndrome"

Annual Grant 1 – $28,000
Dr Mark Danta – St Vincent's Hospital
"Medicare usage in chronic hepatitis C (MUCH-C) study"

Annual Grant 2 – $30,000
A/Prof Jane McCrohon – St Vincent's Hospital
"Non-invasive detection of cardiac transplant rejection using advanced cardiac MRI and ultrasound techniques – Correlation with biopsy"

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Ms Melissa Baysari – St Vincent's Hospital
"Reducing hospital prescribing errors by enhancing the effectiveness of computerised decision support"

Annual Grant 4 – $30,000
Dr Kersten Koelsch – St Vincent's Centre for Applied Medical Research
"GALT in health (GIS) study"

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"A longitudinal investigation of the effects of centrifugal continuous flow left ventricular assist devices (LVAD) on haemostatic parameters"

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Annual Grant 8 – $30,000
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"Investigation of the role of KCNH2 Isoforms in Schizophrenia"

Travelling Fellowship – $10,000
Dr Camilla Wainwright – Cardiology Department – St Vincent's Hospital
"Cardiac Research Fellow & PhD Candidate – University of Oxford, UK"

Travelling Fellowship – $10,000
Dr Rowan Gillies – Plastic & Reconstructive Surgery Department – St Vincent's Hospital
"Fellowship in Reconstructive Microsurgery – Bellevue Hospital, New Yoork, USA"

Multi-Disciplinary Patient Focused Research Grant – $30,000
Ms Zoe Potgieter – St Vincent's Hospital
"Impact of advanced liver disease clinic study"

Multi-Disciplinary Patient Focused Research Grant – $20,000
Mr Daniel Behan – St Vincent's Hospital
"Towards reducing blood product usage in cardiothoracic surgery"

Multi-Disciplinary Patient Focused Research Grant – $25,000
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