Much progress has been made in the treatment of patients with breast cancer. It is beyond the scope of this review to cover all of these advances. This review will address the most practice changing and clinically relevant progress that has been made that impacts on current treatment decisions.

**EXTENDED ADJUVANT AROMATASE INHIBITION (AI)**

Adjuvant endocrine therapy is an important treatment option in the management of hormone receptor (HR) positive early breast cancer. Tamoxifen has been shown to provide a survival and recurrence free benefit with extended treatment of 10 years over 5 years. Due to the improved recurrence free survival of AIs over Tamoxifen in post menopausal woman, AIs are more commonly used in this patient group. The results from the MA.17R trial showed that extended AI had a 4% reduction of breast cancer recurrence and contralateral breast cancers, though survival was similar, and a slight deterioration in bone density and fracture risk was seen.

The B-42 study evaluated 3,923 postmenopausal women diagnosed with early-stage, hormone-receptor-positive breast cancer who had taken 5 years of tamoxifen or AI and were randomized to another 5 years of letrozole vs placebo. This confirmed an additional 5 years of letrozole reduced the risk of breast cancer recurrence, contralateral breast cancer but no overall survival benefit. There was no difference in fracture risk.

These studies have demonstrated small benefits with extended AI treatment in those patients who were able to reach the 5 year milestone on therapy. There may be selected groups of patients who are more likely to benefit, such as those with higher risk tumours, higher Ki-67 scores, luminal B histology, Her2 +ve, extensive lymphovascular invasion and less of a benefit in those having had bilateral mastectomies. The toxicities are great for some women and the impact of bone health is not insignificant.

The role of extended adjuvant AI therapy needs to be discussed on a case by case basis with each patient, taking into account the breast cancer risk, prior toxicity, bone health, patient perceived benefit and quality of life.

**ROLE OF CDK4/6 INHIBITION**

Post menopausal women with HR +ve metastatic breast cancer have a number of treatment options available to them depending on the extent of disease, rate of progression, symptoms, visceral involvement, prior therapies, age and comorbidities. Often treatment involves the utilization of AIs. Inhibition of Cyclin Dependent Kinases 4 and 6 (CDK4/6) may delay or overcome resistance to endocrine inhibition. Agents in this class include ribociclib, palbociclib, and abemaciclib. These agents have been trialled in various stages and combinations in post menopausal patients with HR +ve, her2neu –ve, metastatic breast cancer. The first trial combined fulvestrant with palbociclib/ placebo in woman having progressed on prior aromatase inhibition. This study showed a clinically and statistically significant delay in progression of 9.5 months vs 4.6 months. Sixty-seven percent of women had a clinical benefit with tumour reduction or stabilisation compared with 40% in the control group (fulvestrant/placebo). A delay in commencement of chemotherapy, by about 9 months, was also shown. Palbociclib was well tolerated with the main toxicities being leucopenia and fatigue.

Ribociclib, another selective inhibitor of CDK 4/6, was tested in the first line setting in combination with letrozole compared with letrozole alone. A randomised controlled trial of 668 HR+ve, HER-ve, metastatic post menopausal patients demonstrated a significant increase in progression free survival and response rate with manageable side effect profile.

Similar benefits were seen with abemaciclib. CDK4/6 inhibitors have been shown to be effective in delaying or reversing endocrine resistance in this specific patient population. Although currently not yet available on the PBS, these agents highlight a potential future treatment option and the value of a better understanding of the hormone receptor and development of resistance in designing future clinical trials and treatments.

**NEOADJUVANT TREATMENT FOR HER2 +VE BREAST CANCER**

Neoadjuvant therapy is increasingly being used for locally advanced, triple negative or Her2 +ve breast cancer. A number of advantages include: improved local treatment options, early introduction of systemic therapy and “in vivo” chemotherapy sensitivity assessment.

In Her2 +ve disease Trastuzumab (Herceptin) has been well established as an active agent in the adjuvant and metastatic setting. Recent data have shown that the addition of pertuzumab, a monoclonal antibody against the Her receptor, has improved survival in the addition of pertuzumab, a monoclonal antibody against the Her receptor, has improved survival in...
Many positive advances have been made in cancer management, in particular in the area of chemotherapy. Innovative drugs and delivery vehicles have evolved but most still require venous access for delivery.

Historically venous access was predominantly via peripheral intravenous catheters. New technology allowed the use of Peripheral Intravenous Central Catheterisation (PICC) to deliver cytotoxic drugs into high flow large volume central veins thus reducing the complications.

Direct central venous catheterisation with Hickman or Broviac silastic catheters allowed longer term usage of central catheters but were still cumbersome for patients and external with limited longevity.

Further innovation now allows us to insert central venous catheters with accessible ports that are completely subcutaneous, making management of venous access less complicated, more enduring and less confronting for the patients.

The aim of central venous catheterisation is to allow the delivery of cytotoxic chemotherapy into high flow large vessels thus decreasing the risk of local toxicity and superficial venous thrombosis.

Portacaths or similar devices constitute a sealed reservoir attached to a silastic delivery catheter in varying sizes. The combination allows the reservoir to be sited subcutaneously and to remain in place indefinitely as an inert reservoir.

The port or hub is secured subcutaneously on the chest wall. The port has a silastic plug which is accessed with a "non coring" Huber needle allowing infusion of drugs and blood taking.

Once inserted the port is flushed and locked with Heparin and this is repeated after each episode of access and every 4 weeks to prevent occlusion.

The advantages of a portacath over peripheral cannulation are:
- Self contained with no external catheter or 'tail'.
- Can be left in indefinitely if Heparin locked.
- One-off insertion as distinct to need for repeated cannulation with intravenous cannulation repeatedly.
- Low-infection risk.
- Ease of management for patients who can shower, swim and resume normal physical activities.

Access of the port is better tolerated by patients, and in addition Emla cream can be applied to the access site.

Complications of portacath insertion are low at approximately < 3 % but may include:
- Wound or catheter infection that may require removal of portacath.
- Occlusion of the catheter.
- Pneumothorax at the time of insertion.
- Flipping or malposition of the port.
- Vessel damage at the time of insertion.

A portacath is a safe reliable central venous access device, well tolerated by patients, and easily managed for the long term delivery of chemotherapy.

A portacath is usually removed under local anaesthetic when its use is no longer required, minimising the need for repeated heparin locking.

References available on request.
Phyllodes tumour

Phyllodes (cystosarcoma phyllodes) tumours are an uncommon breast neoplasm representing less than 1% of all breast tumours. The name 'phyllodes,' taken from the Greek language, means 'leaflike' and refers to the leaflike pattern of cellular growth. These tumours present a challenge in relation to diagnosis, classification, behaviour and clinical management.

Phyllodes tumours tend to occur in a younger age group (compared to breast cancers) with a median age of the fifth decade of life. They are almost exclusively seen in females but there are rare case reports in males. They are generally regarded as primary breast lesions derived from periductal and specialised lobular stroma. They are classified into 3 lesions derived from periductal and specialised lobular stroma. They are generally regarded as primary breast sarcomas or spindle cell metaplastic carcinomas. As a result, these tumours often represent a challenge in relation to diagnosis, classification, behaviour and clinical management.

Phyllodes tumours tend to occur in a younger age group (compared to breast cancers) with a median age of the fifth decade of life. They are almost exclusively seen in females but there are rare case reports in males. They are generally regarded as primary breast lesions derived from periductal and specialised lobular stroma. They are classified into 3 lesions derived from periductal and specialised lobular stroma. They are generally regarded as primary breast sarcomas or spindle cell metaplastic carcinomas. As a result, these tumours often represent a challenge in relation to diagnosis, classification, behaviour and clinical management.

Phyllodes tumours tend to occur in a younger age group (compared to breast cancers) with a median age of the fifth decade of life. They are almost exclusively seen in females but there are rare case reports in males. They are generally regarded as primary breast lesions derived from periductal and specialised lobular stroma. They are classified into 3 lesions derived from periductal and specialised lobular stroma. They are generally regarded as primary breast sarcomas or spindle cell metaplastic carcinomas. As a result, these tumours often represent a challenge in relation to diagnosis, classification, behaviour and clinical management.

Figure 1: Fibroadenoma - curvilinear ducts; no stromal expansion or atypia; smooth, demarcated border.

Figure 2: Phyllodes Tumour - stromal heterogeneity – important clue to diagnosis of PT; Left: stromal expansion, increased cellularity and leaf like pattern; Right: fibroadenoma-like areas.

Figure 3: Phyllodes Tumour - stromal expansion and overgrowth; increased stromal cellularity; no heterologous elements.

References available on request.
It is well established that after breast conserving surgery for breast cancer, radiotherapy to the remaining breast tissue reduces risk of local recurrence from 30% to under 10%. However, after mastectomy, is radiotherapy still required? And if so, which patients would benefit most from post-mastectomy radiotherapy (PMRT)?

**LOCALLY ADVANCED (T3/4) DISEASE**

When breast cancer is large, especially when it has invaded the underlying chest wall or overlying skin (T4 disease), there is a high risk of local recurrence, even after a mastectomy, and thus, PMRT is recommended. The St Gallen International Expert Consensus of 2015 recommended radiotherapy after mastectomy in patients with tumour size 5cm or greater (T3/4).

Of interest, PMRT based on size alone can be controversial. A study from Massachusetts General Hospital, Yale, and M.D. Anderson Cancer Centre found that in breast cancer that is larger than 5cm but has no involved regional nodes, nor invaded adjacent chest wall or skin (pT3N0), the long-term local-regional failure rate was less than 10% after mastectomy and chemotherapy. However, local-regional failure rate was 21% when lympho-vascular invasion was also present.

**NODE POSITIVE (N+) DISEASE**

When lymph nodes are found to be involved at mastectomy and axillary nodal dissection, the loco-regional recurrence risk can be 23% at 5 years (Early Breast Cancer Trialists’ Collaborative Group [EBCTCG] 2005 Meta-Analysis). PMRT reduces this risk to 6%, which in turn also reduces breast cancer mortality and all-cause mortality.

However, does “how many nodes” matter? The EBCTCG reviewed their data again in 2014. They found that when 1-3 nodes were involved, the 10-year rate of isolated local-regional failure was 21%. PMRT reduced this to 4.3%. When 4 or more nodes were involved, the 10-year rate of isolated local-regional failure was 31.5%. PMRT reduced this to 13.6%.

In 2001, the American Society of Clinical Oncology (ASCO) Guidelines recommended PMRT in patients with:
- Breast cancers with 4 or more axillary lymph nodes involved (N2+) or
- Node positive breast cancers of 5cm or larger (T3-4N+).

The 2016 ASCO Guidelines Update recommended consideration of PMRT to also include node positive breast cancer smaller than 5cm (T1-2N1).

Of note, the local-regional failure rates in the 2014 EBCTCG meta-analysis are considerably higher than those in many contemporaneous and later trials. Multiple studies from North America and Europe of patients with 1-3 positive nodes treated after 1990 have found 5- to 10-year actuarial loco-regional failure rates of 4-10% (rather than the 21% found in the 2014 EBCTCG meta-analysis). This reduction has largely been attributed to improvements in systemic therapy. Thus, the absolute benefits of PMRT today for patients with 1-3 nodes positive are likely to be smaller than those reported in the meta-analysis.

Thus, the ASCO 2016 Guideline highlights the need to individualise therapy in patients with pT1-2N1 disease. The panel suggest omitting PMRT when the risks of toxicity outweigh the benefits, for example in patients above 40-45 years, those with comorbidities that may reduce life expectancy, or pathological findings indicative of a lower tumour burden such as T1 tumours, small size of nodal involvement, absence of lympho-vascular invasion, low grade, strong hormonal sensitivity, or evidence of greater efficacy of systemic therapy. Similarly, the St Gallen International Expert Consensus 2015 recommended PMRT in patients with 1-3 involved nodes only when adverse pathology present. Both highlight the importance of multi-disciplinary discussion and decision making.

We await the findings of the SUPREMO trial (Selective Use of Postoperative Radiotherapy after Mastectomy) looking at PMRT for patients with 1-3 positive nodes. This trial has just completed recruitment in 2013.

**NODE POSITIVE DISEASE AFTER NEOADJUVANT CHEMOTHERAPY**

Discussion so far has examined use of PMRT based on histopathology results from surgery without prior systemic treatment. However, there is now increasing use of systemic therapy before surgery. This will alter histopathologic findings at surgery. Role of PMRT in this setting has been unclear.

The ASCO 2016 Guideline recommends patients with axillary nodal involvement that persists following neoadjuvant systemic therapy should receive PMRT. It is less clear when there has been a complete pathological response in the nodes after neoadjuvant chemotherapy. We await the findings of the NRG Oncology Group trial 9953 opened in August 2013, randomising patients with biopsy confirmed positive axillary nodes prior to chemotherapy, who then have negative nodes at surgery, to either no irradiation or PMRT.

**POSITIVE SENTINEL NODE BUT NO AXILLARY DISSECTION**

In recent times, there has been an increasing trend to perform sentinel node biopsy rather than a full axillary nodal dissection at surgery to reduce toxicity to patients. The St Gallen International Expert Consensus of 2015 recommended that patients with a positive macro-metastatic sentinel node biopsy but no axillary dissection planned should have PMRT (and radiotherapy to include low axillary nodal stations). If no radiotherapy were planned, such patients are recommended to have axillary dissection.

The ASCO 2016 Guideline on the other hand recommended that patients with T1-2 tumours with a positive sentinel node biopsy who elect to omit axillary lymph node dissection should receive PMRT only if there is already sufficient information to justify its use without needing to know that additional axillary nodes are involved.

**POSITIVE MARGINS**

Current literature surprisingly does not show clear evidence to support the routine use of PMRT when surgical margins are positive. The largest study to-date from British Columbia in 2004 showed that a positive margin only had a substantial impact on the risk of local recurrence when found in combination with other risk factors for patients with pT1-2N0 cancers.

**CONCLUSION**

Breast cancer management is complex and progressing rapidly. A collaborative multi-disciplinary approach to individualise therapy is important to achieve the best outcome for each individual patient.

References available on request.
Surgical advances in breast cancer treatment
(a historical perspective)

DR TREVOR CURRER MBCHB, FCS, FRCS, MMED(SURG), FRACS
Dr Trevor Currer is a general surgeon at the Sydney Adventist Hospital, with interests in hernia, colorectal and breast surgery.

P: 02 9487 4444

The changes in the surgical treatment of breast cancer in the last five decades can be captured in one word: ‘less’. Since the mid-1970s, the surgery for breast cancer has become progressively more conservative, with lesser surgery providing the same survival and disease-free intervals, as provided by the more extensive procedures of the previous era. However, stage for stage, allowing for the improvements in peri-operative care, there has been no additional survival benefit from the lesser procedures. The benefit is seen in the reduction in morbidity and the greatly improved cosmetic outcomes.

The improved survival in breast cancer in the last fifty years can be attributed to screening and to systemic treatments. Screening in breast cancer has been proven to ‘save lives’ due to the early detection of disease. Many of the systemic and surgical advances in the treatment of breast cancer were initiated at the European Institute of Oncology, Milan. In the mid-1970s Gianni Bonnadonna changed the focus in breast cancer treatment. His premise, which was both original and transforming, was that the disease should be considered as ‘systemic’ from the outset. Bonnadonna, who passed away recently in September 2015, can be regarded as the father of modern chemotherapy in breast disease.

Closely linked to the systemic treatment are the astounding advances in the last fifty years which have occurred in the understanding of the pathology of the disease. The extensive research has been directed to answer one question: how will the individual tumour behave? The decisions about adjuvant systemic treatments are based on the predicted behaviour of the tumour as well as the presence of molecular biological markers which may be targeted. It has become clear that the molecular and genetic signature of the disease is of greater importance than the lymph node status. The progressive enlightenment into the molecular biology and genetics will continue to dominate the treatment advances and will be responsible for the improved outcomes in years to come.

The modern era in medicine commenced in the last two decades of the 19th Century. The gold standard in breast cancer surgery was established through the work of William Halsted (1852-1922) and Willie Meyer of the Columbia Presbyterian Medical Centre, New York. The surgery was based on the concept that the breast tumour spread initially to the proximal and then the distal axillary lymph nodes before entering the circulation. This concept led to radical and super-radical mastectomies (Jerome Urban and Saul Livingston), with entry into the thorax. It was understood that the greater the surgery, the greater the chance of cure. This concept of the pathology was challenged in the 1970s. In 1981 the NSABP B-06 trial was published by Umberto Veronesi of Milan, showing no survival difference between the Halsted mastectomy and breast conserving quadrantectomy. Veronesi, who passed away in November 2016 aged 90, can be regarded as the pioneer of conservative breast surgery. The results of the early studies, challenging Halstedian principles, were initially resisted by the surgical establishment, particularly in North America. Subsequently, Bernard Fisher of Pittsburgh published similar results in 1985, with a more limited tumour resection. Subsequently, even lesser resections have been shown to be oncologically safe. The current understanding of a ‘clear margin’ is the absence of the pathologist’s ink on the tumour, sometimes less than 1mm clearance being sufficient.

The sentinel lymph node biopsy (SNB) was based on the hypothesis that the SN accurately predicts the status of the entire axilla. The interest in a more conservative approach to the axilla was sparked by the NSABP B-04 trial results published in 1977, showing that mastectomy patients not undergoing axillary dissection were at no greater risk of metastatic disease than those undergoing a full dissection. The sequelae of axillary dissection have always been a great concern: lymphoedema, pain, stiffness and reduction of limb function. The minimally invasive SN procedure was shown in the 1990s to reliably predict the axillary status.

The first study assessing the feasibility of SNb was published by Armando Giuliano in 1994 and the first clinical trial in breast cancer surgery was conducted by Veronesi and published in 2005 and the reliability and safety of the procedure has been verified by several other studies. Recent studies have shown that even in the presence of a positive sentinel node, axillary dissection is not always necessary. The IBCSG 23-01 trial (Lancet 2013) showed that axillary dissection conferred no advantage if only micro-metastases (foci up to 2mm) were present in the SN. The earlier Z0011 trial (JAMA 2011) had indicated that axillary dissection could be safely omitted if the macro-metastatic disease burden was moderate (1-2 positive SNs). The San Gallen Panel 2013 endorsed these findings but advocated axillary dissection in this setting, in pre-menopausal, triple negative patients. An ongoing study (Sound trial) is addressing the possibility of omitting any form of axillary dissection in suitable patients with invasive disease, who have a negative axillary ultrasound examination.

Neoadjuvant chemotherapy (pre-operative) in proven node positive younger patients is becoming the standard of care and this pertains particularly to HER2 (human epidermal growth factor receptor 2) positive pathology. Three trials (ACOSOG Z1071, Sentina and the Canadian SN study) have addressed the approach to the axilla in patients who underwent neoadjuvant therapy for node positive disease. A full axillary dissection can now be avoided in these patients, provided that the previously involved sentinel node is rendered negative by the neoadjuvant chemotherapy. In contradistinction to the lesser surgical procedures described above, there are situations where the surgery for breast disease has been enhanced. The two obvious examples are breast reconstruction and prophylactic breast surgery. Skin and nipple-sparing mastectomy have become more common place and are appropriate in selected patients, providing good oncological control, together with a superior cosmetic outcome. Contralateral prophylactic mastectomy (CPM) rates continue to rise in Western societies worldwide. This is despite the fact that the overall risk/benefit has failed to show a significant survival advantage for CPM in most women with unilateral breast cancer. The possible exceptions to this would include patients carrying the BRCA mutation and younger women with triple negative breast cancer.

The foundations of breast cancer surgery include conservation surgery, mastectomy (with or without reconstruction) and evaluation of the axilla. The surgery for breast cancer will continue to evolve, respecting the priorities of oncological safety and the personalised needs of the patient.

References available on request.
The concepts of multidisciplinary patient care and multidisciplinary teams (MDTs) are not new. However, they have evolved quite dramatically over the last 20 years, particularly in cancer care. There are quite a number of models for the make-up and workings of MDTs. The San Breast MDT was established over 10 years ago, and was the first MDT at the San. Over 3000 patients have been presented and their management plans discussed and an extensive data base has been maintained.

Established models of the MDT process were assessed to design a model that best suited both our patients and our team members. The model has proven to be highly effective in resolving management issues, definitive treatment planning, “clinico-radiopathological” correlation and team education. Furthermore, through the efforts of members preparing for the multidisciplinary meetings (MDMs), the group discussion is highly efficient. The outcome for our patients is that they receive the opinions of a range of cancer specialists without physically having to see them all. The MDT process emphasises the importance of personalised care. It ensures that each patient’s presenting consultant is their primary contact and remains the person responsible for communicating MDM recommendations, in a private and considered setting.

Further advantages of the MDM process for patients include review and oversight of diagnostic information, the early recognition and management of process issues that could impact on a patient’s experience and the use of the team’s collective knowledge and wisdom to ensure that the most contemporary management options are being considered. The involvement of nursing and allied health professionals is crucial to providing truly holistic and longitudinal care to patients. The meeting of all health professionals involved in breast cancer care at the MDM is a team building exercise that enhances collegiality, teamwork and communication. The team is always working together to look at ways that the service can be improved and developed.

Strong scientific evidence supporting the MDT process is limited because there is no matched comparator cohort to compare outcomes. Pillay et al. (2016) have conducted the most comprehensive systematic review to date - “The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings”. The article’s abstracted results were as follows:

Twenty-seven articles met inclusion criteria. There was limited evidence for improved survival outcomes of patients discussed at MDT meetings. Between 4% and 45% of patients discussed at MDT meetings experienced changes in diagnostic reports following the meeting. Patients discussed at MDT meetings were more likely to receive more accurate and complete pre-operative staging, and neoadjuvant/adjuvant treatment.

There are many confounding factors in an analysis such as this that may dilute or obscure the true impact that the MDT process can have. The main problem is the heterogeneity of the MDT process and the lack of prospectively gathered, well defined and comprehensive outcome measures that reflect not only disease related outcomes but also psychosocial, economic, educational and morbidity outcomes. MDMs will have the greatest impact if there is broad participation, availability of accurate and comprehensive patient related information, an effective means of efficiently communicating treatment plans to all stakeholders and there is an outcome review process.
Breast Cancer Patient Navigators at the San help cancer patients ‘navigate’ their way through various cancer tests, treatments and services and provide emotional and practical support for patients and their families.

They provide a central point of contact and their role includes:

- Initiating contact with patients prior to or on admission - and assessing their needs
- Setting expectations and goals for admission and discharge; organising rehabilitation if appropriate
- Offering resources - such as the My Journey Kit and My Care Kit (free Berli bra) and information booklets from BCNA or the Cancer Council

- Visiting patients on the ward post-op and at any other time they are admitted
- Providing a silky pillow and a support pack from the Cancer Support Centre
- Providing drain education for patients going home with a drain - with referrals to the San Outpatient Clinic for drain care and removal; or community nursing if needed.
- Following up patients after discharge
- Visiting patients in Day Infusion if doing chemotherapy
- Keeping patients informed about their options - e.g. the San Day Infusion Centre now has four cold caps available for suitable women who are interested in trying to keep their hair during chemotherapy
- Developing a rapport and relationship with each patient to provide the best support, individualised care and information
- Encouraging follow up with the physiotherapist for patients at risk of lymphoedema
- Referring on to other health professionals - e.g. counsellor, psychologist, dietitian
- Liaising with other health professionals and GPs where appropriate
- Promoting healthy lifestyle choices such as diet, exercise and rest
- Taking a pro-active approach to future care and support needs.

Breast Cancer Patient Navigators available Monday - Friday 8.00 - 4.00pm on 9480 4873
There have been major changes in the technology of genetic testing. In particular, the cost of testing has declined sharply. For example, a germline BRCA test has dropped from $1650 in 2015 to $425 now. This has made genetic testing more accessible, particularly for private patients. It has also changed the way genetic testing is used.

All cancer is genetic: it is caused by spelling errors that build up in the DNA of cells as they divide. These errors are called somatic mutations. They have occurred in a particular cell. They weren't inherited and they aren't passed on.

In breast cancer, tests such as Oncotype Dx, EndoPredict and Ensigna are used to stratify cancers. They combine specific somatic mutations in an individual’s cancer with factors like tumour size and grade. They help to determine effectiveness of chemotherapy (predictive information) as well as risk of early and/or late recurrence (prognostic information).

The best known somatic tests in breast cancer are for the oestrogen and progesterone receptors. Similarly, ‘ISH’ testing of the tumour can detect overexpression of the HER2 gene, allowing targeted therapies such as Herceptin and Herceptin combination with endocrine therapies.

Somatic genetic testing can be used more broadly. This testing used to cost $10,000. Now, around 400 genes with known or potential treatments can be screened for around $3000. It is referred to as genomic testing and is more commonly used in cancers like lung or colon cancer where knowing the specific pathways that have been switched on or off is essential to guide cancer treatments.

When most people think genetic testing, they are thinking of inherited (germline) genetic changes (mutations). The best known breast cancer related genes would be BRCA1 and BRCA2 but there are several others. Some have a phenotype such as mucosal pigmentation of the lips and buccal mucosa (STK11) or macrocephaly and trichilemmomas (PTEN). Others cluster with specific cancers (eg sarcomas with the TP53 gene).

Germline genetic testing screens the DNA code of a certain gene or genes. I explain genes to patients in the following way: “A gene is a code or recipe. Most of our genes make proteins. In the case of BRCA1 and BRCA2, the proteins work together to make a spellchecker. The TP53 protein is involved in quality assurance, while the PTEN and STK11 proteins encourage growth. When a gene has a spelling error (technically, a ‘pathogenic mutation’), the protein isn’t made or doesn’t work. This results in cells growing when they shouldn’t, not dying when they should and, in the case of spell checker or quality assurance genes, rapidly building up errors in other important genes. That’s Cancer.”

Most inherited cancer syndromes are autosomal dominant, meaning that there is a 50% chance of offspring, siblings and/or parents being at risk. Most of these genes, such as BRCA1 and BRCA2, are stable. That is, it is very rare to be the first person in the family with a germline mutation. (This is the reason why taking a family history and asking about Jewish heritage is so important!). Some genes have a high rate of de novo mutations. This is true for the TP53 gene which causes Li Fraumeni syndrome and is associated with very young onset, HER2 positive breast cancer and a very high risk of cancer in general.

When a pathogenic mutation is detected, predictive testing is offered to blood relatives. This testing is inexpensive (~$200) and black and white: you either carry it (positive) or you don’t (negative). Relatives who are negative are usually at average risk for cancer and can follow population based screening guidelines. A positive individual at high risk may elect to have extra screening (breast MRI from age 30) or surgery (eg bilateral mastectomies). For example, a woman diagnosed with a BRCA1 mutation and breast cancer in her 30s has a 60% chance of a contralateral breast cancer.

Most people associate the BRCA genes with breast cancer. A bigger concern is ovarian cancer. The lifetime risk is between 10% and 60%. There is no effective screening and removal of the tubes and ovaries is strongly recommended by age 40 for BRCA1 mutation carriers and age 45 for BRCA2.

And the future? As costs fall, more people will have testing. We will learn more about cancer penetrance not just for specific genes but also specific mutations within genes, allowing more accurate risk estimation and more focused risk reducing strategies. Families may consider pre-implantation genetic diagnosis in the setting of IVF to prevent a known mutation being passed on. More somatic testing will teach us about how cancers develop and grow as well as increasing targeted therapies (like PARP inhibitors, currently funded for use in BRCA+ ovarian cancer). We will also be able to test for modifier genes: low risk genes that may significantly increase cancer risk if several are inherited. Watch this space!

References available on request.
Breast cancer is estimated to become the most commonly diagnosed cancer in Australia in 2017 replacing prostate cancer (declining incidence). It is estimated that there will be 17,730 new cases in 2017 with a lifetime risk for females of approximately 1 in 8. It is the fourth most common cause of cancer death (3,114 deaths per year).

Screening and early diagnosis plays a vital role in reducing the morbidity and mortality associated with breast cancer. Breast MRI is a non-invasive imaging technique using the superior contrast resolution of MRI for morphological assessment as well as the dynamic contrast enhanced kinetic characteristics to assess for neo-vascularity associated with most cancers. This is in addition to the benefits of multiplanar cross sectional imaging free from ionizing radiation.

Currently MRI is the imaging technique with the highest sensitivity (77-100% vs mammography 25-40%) although with a slightly lower (< 5%) specificity of 81-95% when compared to mammography.

**ROLE IN SCREENING**

As a relatively expensive screening tool this traditionally limits its use to groups at higher risk for breast cancer namely mutation carriers, untested first degree relatives of mutation carriers and women with a lifetime risk > 20% (based on family risk models). While traditionally MRI screening for average risk (<15 % lifetime risk) in women has not been recommended by most major medical societies and evidence based reviews, a recent study from Germany shows that screening breast MRI improves early diagnosis in all women (not only those at high risk) with a supplemental detection rate of 15.5 cancers/1000 women over mammography +/- ultrasound.

This is especially true in women with dense breasts, the subject of which is now becoming a hot topic. The relative risk for women with heterogeneously dense breasts compared with the average women is 1.2 and 2.1 with extremely dense breasts. This relates to the masking effect of dense breast tissue as well as density as an independent risk factor although the statistics would suggest routine MRI in women with dense breast tissue remains controversial. While the relative risk of breast tissue density is much smaller than other major risk factors, the relatively common number of women with dense breast tissue (50 % of the screening population) makes this an important factor by virtue of the number of women affected.

It is important to note with regard to screening, breast MRI is an adjunct to mammography, not a replacement.

**CANCER STAGING & PREOPERATIVE WORKUP**

Another role for breast MRI is in the local staging in patients with recently diagnosed breast cancer. It may also be used post-operatively after initial excision finds more extensive disease than expected i.e. positive margins. MRI may provide more accurate information of true size of the index cancer than conventional imaging as well as the presence of multifocal or multicentric disease.

Currently local recurrence due to improper patient selection or inadequate local therapy is infrequent. This is despite a number of studies demonstrating additional tumour foci found with breast MRI in 11- 31% of women with localised cancers. Clinical experience would suggest that the majority of these subclinical foci are controlled with radiotherapy as shown by ten year local recurrences of < 7 % in women treated with radiotherapy and systemic therapy. Currently there is no convincing evidence that pre-operative MRI improves local control in women undergoing breast conserving therapy (BCT). Pre-operative MRI also results in more extensive surgery and increased bilateral mastectomy rates without decreasing the rate of re-excision surgery and local recurrence. We are currently conducting a validation study of our cohort at the San. Breast MRI does however detect synchronous cancers in the contralateral breast in 3-4%.

**OCCULT CANCER DETECTION**

One of the most clinically relevant uses for MRI has been for the detection of occult breast cancers. This occurs in two settings, women presenting solely with axillary nodal disease (sensitivity of at least 60 %) or with Paget’s disease of the breast. Identification of a primary tumour allows BCT and radiotherapy for local control.

**ROLE IN NEOADJUVANT THERAPY**

The MRI evaluation of response to neo-adjuvant therapy is a growing role which may render locally advanced breast cancer operable or may convert a tumour requiring mastectomy to one where BCT may be sufficient.

In summary there is clear evidence for MRI screening of women at high genetic risk of breast cancer (with an associated Medicare item number if < 50 years of age). Recently a new study has shown screening breast MRI results in additional breast cancers detected when performed as a supplemental (not stand alone) screening examination in women with dense breasts with average lifetime risk.

It is important to realise breast MRI is a supplemental study to mammography and ultrasound and not an alternative.

The role of MRI in the setting of recent cancer diagnosis is less clear with contralateral detection rates of 3-4% and with increased detection of multicentric/multifocal ipsilateral disease but without improved local recurrence rates and often with more extensive surgery. The role of MRI in preoperative neoadjuvant therapy is growing and helps in the down staging of tumours.

References available on request.
Nipple sparing mastectomy (NSM) with implant reconstruction

**IMPLANT BASED BREAST RECONSTRUCTION**

Breast cancer is the most common cancer in women with 1 in 8 Australian women affected by the age of 85. The goals of breast cancer surgery are to remove the cancer with clear margins, with a secondary aim of maintaining or recreating the breast shape and aesthetic appearance.

In Australia, the current rate of reconstruction following a mastectomy is relatively low compared to other developed countries. Only around 10% of Australian women who have a mastectomy undergo some form of reconstruction.

A mastectomy can be recommended for medical reasons or for patient preference. Implant-based reconstruction is a common type of breast reconstruction following a mastectomy. It can be a direct-to-implant, ‘one stage’ reconstruction or an expander-implant, ‘two stage’ reconstruction. The breast skin can be preserved ‘nipple sparing’ or removed ‘skin reducing’, and the nipple can either be preserved ‘nipple sparing’ or removed ‘nipple sacrificing’.

**WHO IS SUITABLE FOR A NSM?**

Many women who undergo a mastectomy are suitable candidates for a NSM. This procedure is becoming more widely performed. Generally the nipple can be preserved if the breast cancer is more than 1cm from the nipple. This would allow a clear margin, and it has been shown that NSM is an oncologically safe procedure. In smaller breasts (A-B cup) with minimal ptosis, the nipple position usually does not need to be moved up, and these patients are very appropriate for this operation. This would apply to many premenopausal women. If the breast is larger or the breast is more ptotic, then the nipple may need to be shifted up and the remainder of the breast skin reshaped. If the nipple needs to be moved more than 1cm, then it may not be possible to keep the nipple as it may become ischaemic, and so the nipple will either need to be sacrificed, or re-implanted as a free nipple graft.

Patients who require post mastectomy radiotherapy (such as the primary cancer > 5cm, lymph node positive cancers, lymphovascular invasion) are at high risk of developing implant complications following radiotherapy. Delayed reconstruction following radiotherapy may be a better option, such as using autologous tissue. Patient factors which are contraindications for implant based reconstruction include smoking, diabetes, poor skin quality or previous radiotherapy to the breast.

**WHAT DOES THIS PROCEDURE INVOLVE?**

In smaller breasts, a single incision is used, commonly along the inframammary fold. The breast parenchyma is carefully excised while preserving the overlying skin and nipple. A pocket is created beneath the pectoralis major muscle. An appropriately sized implant is then placed beneath the muscle and the lower pole reinforced and held with mesh such as titanium coated Tiloop. In these cases, a similar sized implant to the original past is usually placed (See Figure 1a). If the patient prefers to be larger, then a two stage expander-implant reconstruction is used, where a temporary saline filled expander is gradually inflated over weeks to stretch the muscle and skin, and then replaced with the definitive implant at the second stage. In larger breasts, women, nipple sparing mastectomies may still be possible with other techniques such as a vertical scar skin reducing, or a wise pattern skin reducing nipple preserving.

**WHAT ARE SOME ADVANTAGES OF A NSM?**

- A round drain is routinely placed and removed after 2 weeks. The patient is then discharged 2-3 days following surgery.
- Being a longer procedure than a mastectomy, there can be potentially more complications. Short term complications include skin or nipple necrosis, seroma formation, infection or even implant loss in about 5%. With meticulous surgery and post operative care, in the appropriately selected patient these complications can be minimised. Longer term complications include implant migration, capsular contracture and implant damage. Minor contour deformities can be improved with lipofilling.

**WHAT ARE SOME COMPLICATIONS?**

- There is also an increasing number of women without breast cancer but at high risk of developing breast cancer due to a strong family history of breast and/or ovarian cancer; or are proven to carry the breast cancer genes (BRCA1/2). These women may choose to undergo bilateral risk reducing mastectomies with reconstruction.

**SUMMARY**

In the appropriately selected patient, NSM with implant reconstruction is an oncologically safe procedure that can achieve excellent cosmesis, fast recovery with minimal morbidity.

References available on request.
Deep Inspiration Breath Holding (DIBH) to reduce risk of cardiotoxicity in adjuvant RT in breast cancer

DR LEE NA CHONG  BHB MBCHB (AUCK) RANZCR

Dr Lee Na Chong is a Senior Radiation Oncologist at Radiation Oncology Centres (ROC), Wahroonga. She completed postgraduate specialty training at Westmead and Nepean Hospitals. In addition to breast and skin cancer, her interests include the treatment of gastrointestinal, sarcomas, CNS, lung, haematological malignancies and palliative care. Dr Chong is a clinical lecturer for The University of Sydney medical program based at the Sydney Adventist Hospital Clinical School.

Adjuvant radiation therapy (RT) for breast cancer patients reduces the risk of local recurrence and improves overall survival. However, adjuvant radiotherapy to the left breast or left chest wall can result in unwanted radiation dose to the heart and coronary arteries. Current evidence suggests the existence of a dose-response relationship linking the risk of cardiac morbidity and radiation dose to the heart. The use of cardiotoxic chemotherapy may further increase this risk.

Updated data from the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) has related mortality from heart disease after breast radiotherapy to cardiac radiation exposure in over 30 000 women followed for up to 20 years. The relative risk of death increases with larger mean cardiac doses by 3% per Gy (95% CI, 2–5%; p < 0.00001).

Threshold doses to the heart and coronary arteries have not been determined however a recent international breast cancer randomized trial (NSABP B-51/RTOG1304), has proposed that the mean heart dose should be <4 Gy during left-sided breast/chest wall irradiation. Dose limits have not been established for the left-anterior descending coronary artery (LAD), which may be the crucial target to mitigate ischemic heart disease risk from RT.

For each patient, stereotactic radiotherapy plans are made on both the FB and DIBH scans. All patients receive CT simulation with standard free breathing (FB) and DIBH, positioned supine with both arms supported above their head. The RPM system uses a perspex box placed on the midline anterior abdominal wall at the level of the diaphragm outside the treatment area. The box has neon markers which are tracked by an infrared camera situated on the end of the CT couch to analyse and monitor the patients’ respiratory cycle. A deep inspiratory breath-hold is then analysed on the RPM monitor ensuring the maximum variability in movement is within 5 mm of an upper and lower gate threshold. Patients undergo training in the respiratory techniques immediately prior to CT simulation to improve accuracy. Once sufficient reproducibility in the DIBH technique is established patients are translated through the CT with an abdominal compression device to improve stability of breath hold.

Clinical target volumes (CTV) include the breast and/or chest wall for all patients. If the regional nodes are to be treated, additional CTVs for the internal mammary chain nodes inclusive of the first to third interspaces, axillary and supraclavicular nodes are also delineated. Boost to the primary tumour bed is also included when deemed necessary. In figure 2 (a) FB (b) DIBH showing the displacement of the breast PTV (green) and boost PTV (orange) away from the heart in DIBH and the inferior movement of the heart in the DIBH image in line with diaphragmatic expansion.

CONCLUSION

DIBH reduces mean heart and LAD doses for patients receiving breast and regional nodal irradiation. Evidence suggests that limiting the dose to the heart reduces subsequent post-RT cardiac morbidity. DIBH modified radiotherapy for patients with breast cancer requires specialised radiotherapy equipment, staff able to train patients in the technique and planning staff familiar with the procedure. This advanced technique is offered at San ROC and used to limit potential treatment related complications.

References available on request.
The San Integrated Cancer Centre has been officially opened, providing a comprehensive and easily accessible range of screening, diagnostic, medical, surgical, counselling and recovery services. Highlights include the new state-of-the-art multi-disciplinary meeting room. Opening attendees included cancer doctors and health professionals, local Federal and State MP’s Paul Fletcher, Jonathon O’Dea, Matt Kean and Alister Henskens, Ku-ring-gai Mayor Jennifer Anderson, generous donors and patients.

The world’s smallest heart pacemaker has recently been implanted at the San by interventional cardiologist Dr Peter Illes. One-tenth the size of current pacemakers, it is suitable for patients requiring a single chamber pacemaker.

Highly regarded San cardiothoracic surgeon Dr Alan Farnsworth has retired after starting at the San in 1982. His life-saving 6000 surgeries included volunteer work with Open Heart International in third-world countries.

San Nutritionist Carol Zeuschner’s chapter on “Red meat and health: evidence regarding red meat, health and chronic disease risk” in the book “Impact of meat consumption on health and environmental sustainability” has been recognised with the book’s first prize in the Gourmand World Cookbook Awards 2017.

San female staff shared their professional experience in the fields of science, information technology, engineering, medicine and maths (STEMM) with 250 local year 10 students hoping to assist in their school subject choice.

Environmental workplace improvements have been recognised by the NSW Office of Environment and Heritage Sustainability with the San naming as a Bronze Partner of the Sustainability Advantage Recognition Scheme.

GP Conferences 2017 (6.15pm for 7pm start)

Wednesday 18th October GI Cancer Update

Bookings essential. P: 9487 9871 E: comrel@sah.org.au