

BREAST SURGERY

**BS01
LOCALLY ADVANCED BREAST CANCER: NEED FOR
A CO-ORDINATED, MULTIDISCIPLINARY APPROACH**

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Historically, patients presenting with large, inoperable cancers were treated with radiation therapy alone or radiation therapy followed by surgical resection. The use of systemic therapy in patients with locally advanced breast cancer (LABC) has led to improved disease outcome when compared with surgery or radiotherapy alone. In comparison with operable breast cancer, there is a relative paucity of randomised trials evaluating systemic therapy for LABC. Of the randomised trials published, a statistically significant survival benefit is only demonstrated in a few. The difficulties in performing large randomised trials in LABC relate to several issues. The classification of LABC which includes T3, T4, and N2 disease incorporates a heterogeneous group of patients. There is a variable approach taken by clinicians in terms of the type of pre-operative chemotherapy used, sequencing of locoregional therapy and whether post-operative adjuvant systemic therapy is also given. To date, the efficacy of systemic therapy in LABC has largely been established from results of non-randomised Phase II studies. These studies compare favourably to historical data with higher 5- and 10-year disease-free and overall survival. A common finding in several trials of pre-operative systemic treatment is that the rates of breast conserving surgery is increased and those patient achieving a complete pathological response have superior disease outcomes than those who do not.

An overview of trials supporting the current management of LABC will be presented. The objectives and preliminary findings of a multicentre study initiated in Perth for women with LABC will also be discussed.

**BS02
MODERN APPROACH TO PALLIATIVE CARE**

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This paper explores the modern concept of Specialist Palliative Care. This includes the gradual and ongoing development of specialist palliative care services in New Zealand, embedded within cancer services and the wider health sector: within the community and the acute care environment. No longer is it accurate to assume that a referral to palliative care indicates that the person is imminently dying or that their care will be transferred to that service as an alternative to any form of continued active treatment. Cancer can be aggressive and unremitting but is increasingly experienced as a chronic illness and patients have concerns and needs that fluctuate over time. Multi-disciplinary palliative care must be responsive, flexible and able to assist at "points of need", working together with the referring team. Collaboration across all the medical disciplines and the full health care team is essential and communication between services must be robust so that our care is consistent, unambiguous and patient-centred. Palliative care is an aspect of clinical care that we all practice, every day, sometimes without realising it. We need to continually develop our own skills in symptom control, effective communication and decision-making, as well as exploring the philosophy and ethics of end-of-life care. Accessible, meaningful education in all of these areas is vital. While it is challenging, we must also find time to reflect on our own practice, learning to acknowledge and work within our own prejudices, fears and short-comings.

This paper will draw on recent work in the area of palliative care and cancer care: The New Zealand Palliative Care Strategy (2001), the Cancer Control Strategy (2006), the proposed adoption of a model of palliative care within NZ that incorporates clear definitions of both Specialist and Generalist services and the new Ministry of Health "Palliative Care Service Specifications" that highlight the need for specialist services to be available in all locations, providing not just clinical care but also education and support.

**BS03
PATTERNS AND PROGNOSIS OF BREAST CANCER RECURRENCE**

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The data base of The Strathfield Breast Centre (TSBC) was reviewed to determine the patterns of recurrence and their prognosis after the treatment of breast cancer.

The TSBC has a prospective data base from 1989 forward with information on 2509 patients up to 2002. The follow-up on these patients is 81%. This data was interrogated.

Breast conservation was performed in 1390 (55.4%) and of these 84.7% had adjuvant radiotherapy and 62.7% had adjuvant systemic treatment. Rates of recurrence were related to grade and stage of the tumour.

Local regional or distant relapse occurred in 456 (18%). The site of first cancer recurrence was local 27.2%, bone 27.4%, lung 16% liver 12.5% and supraclavicular fossa 5.5%.

At the end of the study 527 patients had died, 323 were cancer related deaths, the majority of the recurrences occurred in the first three years (58%) and 79% occurred within 5 years.

Local recurrence in the breast occurred in 4.6% of patients and in the chest wall in 5.2%. The 5 yr disease free survival of these patients was 49.4% and 33.1% respectively.

Distant metastases occurred to bone, lung and liver in the majority of cases in which it happened. The 5 yr survival for these patients was 16%, 12% and 0%.

The recurrence data from the TSBC is comparable to that reported elsewhere. The majority of recurrences occur in the first 5 yrs, The prognosis after relapse varies with site. Local in the breast being better than in the chest wall and bone being better than visceral.

**BS04
TRASTUZUMAB (HERCEPTIN): REVIEW OF ADJUVANT TRIALS
IN EARLY BREAST CANCER**

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Trastuzumab (Herceptin) is a humanized, monoclonal antibody to the Her2 neu receptor which is over-expressed in approximately 15 to 20% of patients with breast cancer. The presence of this growth factor gene over-expression is associated with more aggressive disease. The pivotal trials in metastatic breast cancer in the late 1990s demonstrated that Herceptin combined with chemotherapy produced significantly higher response rates, improved time to progression and superior overall survival compared to chemotherapy alone. There have been five clinical trials conducted to evaluate the effectiveness of Herceptin when used in combination with chemotherapy in women with early breast cancer. For the four larger trials, more than 13,000 women were essentially randomly assigned to either standard chemotherapy alone or the same chemotherapy plus Herceptin for one or two years. A small Finnish trial of 232 women, evaluated 9 weeks of Herceptin given with chemotherapy. Each trial confirmed a statistically improved disease-free survival with a 42% to 50% reduction in the risk of relapse. In the four larger trials, a statistically significant overall survival benefit with a 33% to 41% reduction in the risk of death was seen. The only significant side effect associated with the inclusion of Herceptin was a higher incidence of cardiac dysfunction. This ranged from 1.7% to 4.1% in those patients receiving Herceptin, compared to <1% in the control group.

**BS05
NIPPLE INVERSION: AETIOLOGY AND INVESTIGATION**

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Nipple inversion is a significant heterogeneous condition with both oncological and cosmetic implications.

The clinician needs to decide:

- 1) Are the changes "normal", congenital or acquired
- 2) If changes are acquired, are they benign or malignant
- 3) What therapy is indicated

The cornerstone of assessment, in acquired change, is triple assessment. There are difficulties in imaging premenopausal or inflamed breasts. The interpretation of cytology may also be compromised.

The clinician assessment is therefore crucial to lead the process of cancer diagnosis and freehand core biopsy should be used without hesitation.

Once cancer has been excluded the clinician faces the psychological and cosmetic aspects of nipple inversion.

The anthropological origins of the display of prominent nipples will be discussed.

BS06 PATIENT-RATED OUTCOME MEASURES WERE MORE SENSITIVE THAN CLINICIAN-RATED MEASURES AT DISTINGUISHING THE EFFECTS OF SENTINEL NODE BIOPSY AND AXILLARY CLEARANCE IN THE SNAC TRIAL

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Purpose We sought to determine which outcome measures were most sensitive at detecting the benefits of Sentinel node based management (SNBM) over routine axillary clearance (RAC) in the SNAC trial.

Patients and Methods 1088 women with early breast cancer were randomised to either SNBM or RAC. The primary endpoint was the percent increase in arm volume based on clinicians' measurements of arm circumference at 10cm intervals. Secondary endpoints included patients self-ratings of arm swelling and other aspects of quality of life, assessed using the SNAC Study Specific Scales (SSSS: 15 questions asking about symptoms, dysfunction and disabilities). We report a comparison of the relative sensitivity of these endpoints in detecting differences between the treatment groups.

Results Patients' ratings on the SSSS were 3.2 times as sensitive as clinicians' ratings of arm swelling, requiring 68% fewer patients to detect a given treatment effect. The 7 questions asking patients about symptoms were most sensitive. Questions asking about dysfunctions and disabilities were less sensitive.

Conclusion Patient-rated measures were more sensitive in this trial than clinician-rated measures at distinguishing the effects of SNBM and RAC. Similar trials would require only a third as many patients if the primary endpoint was rated by patients rather than clinicians.

BS07 PATENT BLUE AND SENTINEL NODE BIOPSY – THE NEW ZEALAND EXPERIENCE

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Purpose Since adopting sentinel node biopsy at North Shore Hospital, we have become increasingly aware of cases of major reactions to patent blue dye within our unit. This study aims to assess the use of sentinel node biopsy in breast cancer patients in NZ and document the complications related to the use of patent blue.

Methodology Questionnaires were sent to all NZ surgeons registered with the Breast Section of the RACS. Hospitals with no breast section member were individually contacted and questionnaires sent to those surgeons performing breast surgery. Follow-up phone calls were used to improve completion rate.

Results Completion rate was 83%. Eighty four percent of surgeons report using sentinel node biopsy.

Indications varied widely including all grades and sizes of DCIS and invasive cancer.

Most surgeons utilized colloid plus lymphoscintigraphy and patent blue dye.

Surgeons' perceptions of the expected reaction rate to patent blue dye varied from 1 in 200 to 1 in 100 000.

In our study there were 12 minor reactions including rash, urticaria and blistering. There were 11 major reactions including hypotension and anaphylaxis. There was one myocardial infarct and one patient requiring CPR. There were no deaths.

All major reactions reported were in high volume Auckland centres.

Conclusions There is no consistency amongst NZ surgeons on the indications and technique for sentinel node biopsy.

A notable number of major reactions have occurred with the use of patent blue dye. These findings show the need for comparative studies on technique for sentinel node biopsy. There is also a need for a comprehensive system of adverse reaction reporting and consideration of skin testing.

BS08 SENTINEL NODE BIOPSY IN LARGER OR MULTIFOCAL BREAST CANCERS: TO DO OR NOT TO DO

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Background The use of sentinel node biopsy in breast cancer patients with large and/or multifocal tumours is controversial.

Methods A review of clinical records was undertaken for 213 consecutive patients undergoing sentinel node biopsy for invasive breast cancer from September 2000 to February 2006. The results of sentinel node biopsy and axillary dissection were compared for patients with unifocal or multifocal tumours less than 3 cm or greater than 3 cm. Patient outcomes were also assessed.

Results The mean number of sentinel nodes removed per patient increased from 2.33 in 2000 to 4.17 in 2006. For patients with unifocal tumours less than 3 cm, 47/147 (32.0%) were sentinel node positive compared to 15/30 (50%) for multifocal tumours less than 3 cm ($p = 0.04$), 19/28 (67.9%) for multifocal tumours greater than 3 cm ($p < 0.001$) and 7/8 (87.5%) for multifocal tumours greater than 3 cm ($p = 0.003$). Following axillary dissection, 20/48 (41.7%) patients with sentinel node macrometastases were found to have positive non-sentinel nodes, compared to 4/20 (20.0%) and 1/8 (12.5%) for patients with sentinel node micrometastases and isolated tumour cells. The mean total number of positive nodes was 1.74 compared to 4.21 for unifocal tumours less than or greater than 3 cm respectively ($p = 0.005$). No axillary recurrences were detected during the follow-up period.

Conclusions Although patients with large and/or multifocal tumours were more likely to have a positive sentinel node, the findings suggest that sentinel node biopsy is safe, accurate and reliable for staging the axilla in these patients.

BS09 WHY WOMEN IN TARANAKI CHOOSE MASTECTOMY OVER BREAST CONSERVATION

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Purpose Breast conservation treatment (BCT) rate is recognized as a marker of surgical practice. An historically low BCT rate in Taranaki, may reflect the requirement for Taranaki women, to travel for adjuvant radiotherapy. The aim of this study was to determine the reasons Taranaki women with breast cancer choose mastectomy or BCT.

Methodology Prospective information, on all women presenting with breast cancer between May 2004–Dec 2006, was collected on a standardised questionnaire. After factual advice from their surgeon, patients suitable for both BCT and mastectomy completed a questionnaire on reasons for their treatment preference. Surgeons completed a questionnaire for all patients with breast cancer on BCT/mastectomy suitability.

Results BCT was offered to 67% (139 of 209), but chosen by only 45% ($n = 62$) of suitable patients.

If radiotherapy had been available locally 23% (17 of 73) of patients who chose mastectomy, would have instead opted for BCT. Travel distance, time away from family, wait for treatment, exposure to radiation and fear of side effects were other important considerations to this group.

A quarter of each group of women thought they knew their surgeon's treatment preference and most chose this option.

Fear of local recurrence and need for further surgery were important factors.

Conclusion The rate of BCT in Taranaki is low, despite being offered by surgeons to the majority of patients. Local availability of radiotherapy and neutral patient guidance may increase the BCT rate to a level more consistent with larger centres in New Zealand.

BS10 THE PROGNOSTIC SIGNIFICANCE OF THE OVEREXPRESSION OF THE GROWTH FACTOR CRIPTO IN PATIENTS WITH BREAST CANCER

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Purpose To determine the prognostic significance and long term survival of breast cancer patients with overexpression of the epidermal growth factor Cripto.

Methodology 120 formalin fixed paraffin embedded breast cancer specimens were constructed on a tissue microarray and detection of Cripto carried out by immunohistochemical staining. Patients were treated between 1989 and 1995 and the median follow up was 125 months. We examined the association of Cripto positivity with age, menopausal status, grade and size of tumour, lymph node status, tumour type, ER/PR/HER2 status, Ki67 and Nottingham Prognostic Index (NPI).

Results 48% of patients were Cripto positive. We demonstrated a significant association between overexpression of Cripto and NPI ($p < 0.01$), grade of tumour ($p < 0.01$), progesterone receptor ($p = 0.02$), Ki 67 ($p = 0.02$), tumour type ($p = 0.04$) and most importantly overall survival ($p = 0.0003$). Cox regression analysis revealed Cripto to be an independent prognostic variable for survival – HR 2.79 (95% CI 1.20–6.50).

Conclusion Overexpression of Cripto is associated with high grade poor prognostic breast cancer and a significantly decreased patient survival. Future research is required to confirm these findings and to develop an anti-Cripto humanised antibody for clinical use.

BS11 THE ROLE OF PRE-OPERATIVE MRI IN PATIENTS WITH INVASIVE LOBULAR CARCINOMA OF BREAST

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Background Conventional breast imaging with mammography and ultrasonography have a tendency to underestimate the extent of invasive lobular carcinoma (ILC) of the breast. The aim of the study is to determine the role of routine pre-operative breast MRI in treatment of patients with ILC of breast.

Methods 33 patients with ILC and 6 patients with pleomorphic lobular cancer (PLC) of the breast had pre-operative contrast enhanced MRI of the breasts. Suspicious additional foci were evaluated with focussed ultrasound and biopsy, selectively in ipsilateral breast and routinely in contralateral breast. The histological results of additional foci were correlated with MRI findings to determine the accuracy.

Results In 1 patient (3%) index tumour was detected only by MRI. In ipsilateral breast, additional foci were found in 16 patients (41%) that led to more extensive surgery in 13 patients (33%) with a false positive rate of 15%. In the contralateral breast MRI detected suspicious foci in 7 patients (18%) and malignancy was confirmed by biopsy in 1 patient (false positive rate 86%).

Conclusions In patients with ILC or PLC routine pre-operative MRI alters management of ipsilateral breast significantly with a high accuracy. Due to high false positive rate contralateral breast surgery should not be undertaken based on MRI finding only without biopsy confirmation.

BS12 PREDICTIVE MARKERS FOR BREAST CANCER NEOADJUVANT CHEMOTHERAPY

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Purpose Although neoadjuvant chemotherapy (NACT) is routinely used in the management of breast cancer, there is no definitive way of predicting which patients are more likely to respond to a particular therapy. The aim of this study was to identify markers that can be used to predict tumor response to chemotherapy in breast cancer.

Methodology We used immunohistochemistry to evaluate blood microvessel density (MVD) (CD31), tumor cell proliferation (Ki-67), anti-apoptotic marker (Bcl-2), ER and PR expression, and HER-2/neu expression in core biopsy samples (taken before chemotherapy) from patients with locally advanced breast cancer ($n = 20$), receiving neo-adjuvant chemotherapy {anthracycline-based regimen (FEC100) ($n = 10$) vs single agent taxane regimen (docetaxel) ($n = 10$), and correlated these factors with tumor response (as assessed clinically and by tumor imaging) after 4 cycles of treatment.

Results Tumors expressing low levels of Bcl-2 showed significantly greater reduction in size to both taxane ($P < 0.05$) and anthracycline-based ($P < 0.01$) regimens, compared to tumors expressing high levels of Bcl-2. Further, HER-2/neu positive tumors showed significantly greater reduction in size to taxane regimen ($P < 0.05$), while estrogen receptor (ER) negative tumors showed a trend of greater reduction in size to anthracycline-based regimen ($P = 0.06$).

Conclusions Bcl-2 and HER-2/neu expression may be useful markers to predict response to neoadjuvant chemotherapy in breast cancer. While subject numbers are still too low to draw firm conclusions, the current data indicates that HER-2/neu may specifically predict a positive tumor response to taxane regimen, and high Bcl-2 is a marker of chemoresistance.

BS13 THE EFFECT OF ANTIBIOTIC TREATMENT OF INFLAMMATORY BREAST DISEASE ASSOCIATED WITH THE ISOLATION OF LIPOPHILIC CORYNEBACTERIA

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Granulomatous mastitis is a rare benign condition effecting women of reproductive age and is most commonly treated surgically. It is an inflammatory disease of the breast associated with the isolation of intracellular lipophilic corynebacteria and has a course of chronicity with recurrences.

Purpose Our aim was to observe the clinical response and subsequent course of women diagnosed with granulomatous mastitis and treated by a long course of lipophilic antibiotics. We also recorded the concurrent requirement for surgical intervention.

Methodology The clinical course of seventeen women with inflammatory breast disease and microbiologic and histologic evidence of infection with *Corynebacterium kroppenstedtii* were prospectively followed. 11 received treatment with doxycycline (or clindamycin if breast feeding), 5 women received alternative antibiotics, and one patient received no antibiotics.

Results Among the 11 who received doxycycline, full resolution without surgery of disease was achieved in 9 women while another woman showed improvement at follow up, further surgical management was required by 2. All the five women who received alternative antibiotics also had surgery. They each had full resolution of disease at follow up. Further admissions were required by one woman.

Conclusion Optimal treatment for granulomatous mastitis is yet to be determined. We found promising results with a small group of young women who were treated with the lipophilic antibiotic doxycycline alone. These had resolution of disease without requiring surgical intervention.

BS14 UPDATE ON IN SITU PROLIFERATIONS OF THE BREAST

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This is a pathologist's view of in situ proliferations of the breast, particularly those other than DCIS. The increasing evidence for Lobular Carcinoma In Situ (LCIS) as a non-obligate precursor, at least in some instances, and the emerging entity of pleomorphic LCIS will be discussed. Columnar cell proliferations including Flat Epithelial Atypia will also be presented with particular emphasis on clinical significance and currently recommended management strategies.

A short discussion of other "indeterminate" in situ proliferations will also be included.

BS15P FACILITATING NATIONAL CONSISTENCY IN BREAST CANCER DATA COLLECTION

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In Australia there is currently no consistent approach to collecting breast cancer specific data. The National Health Data Dictionary (NHDD) recommends a core set of generic data items for clinical cancer registration. However this list does not include the more detailed items required by specific tumour streams. The NBCC has developed a supplementary set of Breast Specific Data Items and definitions to serve as a guide for specialist breast cancer data collection in Australia.

A multidisciplinary Working Group comprising clinical and consumer representation, including three breast surgeons, identified 16 breast specific data items for collection. The items are designed to align with items collected through the RACS National Breast Cancer Audit and leading cancer centres. A range of items from patient data (menopausal status), diagnostic data (HER2 status, sentinel lymph node), treatment (surgical margin clearance and involvement), and breast reconstruction are included.

The data items are recommended as best practice for breast cancer specific data collection and aim to facilitate national consistency in defining, recording, and monitoring information about patients with breast cancer. This national approach will contribute to improved patient outcomes by informing planning, quality improvement and evaluation strategies for cancer services. The items are currently being piloted in two sites in NSW and will be available nationally in late 2007.

BS16P MULTIFOCAL BREAST CANCER: WHICH DIMENSIONS CORRELATE WITH NODAL SPREAD AND OUTCOME?

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Purpose In the presence of multifocal breast cancer, debate continues as to which dimension (the diameter of the largest lesion or combined total diameter of all synchronous lesions) correlates best with the likelihood of nodal spread, local and systemic recurrence and hence death. Pathological assessment and reporting on such tumours is a mandatory part of Breast Audit. What is the value of this?

Methodology Data from all women with multifocal breast cancer (as defined by more than one focus of invasive cancer in an ipsilateral breast on pathological examination) presenting during the period between 1997 and March 2003 was reviewed. Lymph node status, local recurrence, systemic recurrence and death were correlated with the diameter of the largest focus and aggregate diameter of all lesions.

Results 63 patients with multifocal breast cancer (from 534 primary breast cancers treated) were reviewed, with a median follow-up of 4.98 years. There were 10 cancer-related deaths during this time. 34 tumours (54%) were upstaged using the aggregate diameter. "Aggregate diameter" correlated more strongly than the "largest diameter" with regards to survival however only nodal status and number of foci statistically significantly correlated with survival. "Aggregate diameter" and "largest diameter" were both similarly highly correlated with nodal status.

Conclusions The results obtained from this study suggest assessment and inclusion of all foci appears to be an important part of pathological breast cancer assessment. Our current work involves comparison to similarly staged unifocal tumours to determine whether multifocality per se can be used as a surrogate prognostic factor independent of the diameter of the largest focus.

BS17P UTILISATION OF CYTOLOGICAL AND HISTOLOGICAL DIAGNOSIS IN THE MANAGEMENT OF BREAST CANCER BY NEW ZEALAND SURGEONS

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The purpose of the study was to determine the practice of breast surgeons working in New Zealand with regard to utilisation of fine needle aspiration and core biopsy in the diagnosis of breast cancer. Surveys were distributed to surgeons in New Zealand involved in breast cancer surgery. Two cases examples were given and their subsequent management questioned. There were 68 respondents (87% response rate).

For a palpable breast abnormality which is clinically, radiologically and cytologically (C5) consistent with breast cancer but without pre-operative histology: 81.5% of respondents would be comfortable to proceed with wide excision 46.2% mastectomy 44.6% with axillary clearance.

For a non-palpable breast abnormality which is radiologically and cytologically (C5) consistent with breast cancer but without pre-operative histology: 66.2% of respondents would be comfortable to proceed with wide excision 27.7% mastectomy 26.1% with axillary clearance.

This survey shows a wide variation in New Zealand in the management of breast cancer with respect to the use of cytology and/or histology to establish diagnosis. There was no statistically significant difference between those who were members of Aotearoa Breast Screening New Zealand, number of years as a surgeon or number of years working in New Zealand.

The concern is that patients with non-invasive disease will undergo an axillary clearance or procedure unnecessarily. Axillary clearance/procedure is not recommended for non-invasive malignancy. FNA cannot distinguish between non-invasive and invasive malignancy as can a core biopsy.

BS18 DCIS AND TREATMENT

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Ductal carcinoma in situ now represents 30% of all screen detected breast cancers. Breast conserving surgery for ductal carcinoma in situ is now established although the extent of margin clearance necessary to prevent recurrence after breast conserving surgery remains controversial. None of the previous trials which compared radiotherapy with breast conserving surgery alone have achieved clear margin status in all patients and analysis of their data suggests that the recurrence rate when clear margins around the ductal carcinoma in situ are achieved is low (approximately 10% at six years). Data from randomised trials indicates that a margin of greater than 1 mm clearance is sufficient to minimise recurrence in the breast. Several centres have published that clear margins are essential in the management of ductal carcinoma in situ whether radiotherapy is used or not.

Tamoxifen has been studied after wide local excision and radiotherapy in the NSABP24 trial and in the UK DCIS trial. In the former trial a 40% reduction in recurrence in the breast using tamoxifen was seen but the majority of this effect was in women under 50 years of age and only a marginal effect was seen in older patients. In the UK DCIS trial a 20% non-significant reduction in recurrence was seen in women who were not given radiotherapy. Studies show that younger women (less than 50 years of age) have a significantly higher risk of recurrence after ductal carcinoma in situ treatment and tamoxifen is therefore recommended in women under 50 years of age who are undergoing wide local excision for ductal carcinoma in situ. Oestrogen receptor status was retrospectively assessed in the NSABP B24 trial and ER positive DCIS had a 60% reduction in recurrence whilst ER negative DCIS had no benefit. The BASO DCIS II trial assesses the benefit of adding radiotherapy in ER positive DCIS treated with 5 years Tamoxifen on local recurrence. Aromatase inhibitors are more effective in the presence of CerbB2 oncogene, which is frequently expressed in ductal carcinoma in situ and studies comparing aromatase inhibition with Tamoxifen in ductal carcinoma in situ are already underway (IBIS II). These studies should take account of oestrogen receptor status in the ductal carcinoma in situ to allow us to more adequately define the role of oestrogen receptor status in predicting response to therapy in patients with ductal carcinoma in situ.

**BS19
BRCA 1 & BRCA2 GENE TESTING FOR BREAST AND
OVARIAN CANCER IN AUSTRALIA AND NEW ZEALAND –
THE GTG EXPERIENCE**

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Over the past three years, Genetic Technologies Ltd (GTG) has been providing a fee for service (commercial) BRCA 1 & 2 genetic pathology testing service. Full gene screening is performed within 8 weeks and fast tracking of testing for clinical management purposes can be performed in 2–4 weeks.

We present a schema for testing that utilizes robotics, LIMS, automated DNA sequencing, computer aided analysis and ISO15189 / NATA / RCPA accredited test protocols.

Despite the active testing that has been carried out of the BRCA1 & 2 genes worldwide over the past decade, it is interesting to note that significant numbers of new (not previously reported) BRCA mutational events and gene variants have been identified in our testing service – the GTG experience.

**BS20
FAMILIAL GYNAECOLOGICAL CANCER – ASPECTS OF
CLINICAL MANAGEMENT**

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There are significant familial associations between surgical and gynaecological cancers. hereditary non polyposis coli cancer was first described as a family with an increased risk of gynaecological cancer and BRCA mutations have a well known association with ovarian as well as breast cancer. To complicate issues colorectal and breast cancer share similar etiologic factors to colorectal and breast cancers and treatments may influence the incidence and treatment of these cancers. This talk will discuss issues related to; the identification of familial cancer syndromes, screening and prophylactic treatment in women with familial cancer syndromes, quality of life and hormone replacement therapy.

The following issues are considered relevant:

Women with breast cancer and people under 50 with colorectal cancer or should have family histories taken and genetic counseling referrals made where appropriate.

Women with HNPCC related or BRCA mutations should be counseled by a gynaecologist with expertise in familial cancer.

Women with BRCA mutations probably do not benefit from screening.

Prophylactic surgery is normally indicated.

Women with HNPCC should be counseled regarding their risk of gynecological cancer risk reducing surgery is sometimes indicated.

Menopause caused by oophorectomy, radiotherapy or chemotherapy is associated with a significant reduction in quality of life. Hormone replacement therapy should be considered.

**BS21
SCREENING FOR BREAST CANCER – THE UK APPROACH**

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In the United Kingdom the Forest Report in 1985 recommended the setting up of breast screening with women aged 50–64 years screened every 3 years

by single view mammography. Since 2000 the screening process has been increased to women aged 50–70 years and the screening every 3 years is now with two view mammography, producing a 40% expansion in workload.

Screening for breast cancer was funded centrally with allocation to each region and regional and national quality assurance centres were set up for both surgery, pathology and radiology. The programme is dependant on a high compliance rate with a low recall rate and a high cancer detection rate. It is carried out by a combination of mobile vans and static site for screening. Around 5% of women are recalled to the assessment clinics and 16% of these will have cancer (CF symptomatic practice where 6% have cancer).

Survival rates in screening programmes of those patients who attend is 90.2% at 10 years whereas for non-attendees it is 52% survival from diagnosed breast cancer. The cancer detection rate per 1,000 women has gone up regularly from inception such that last year it was 8 cancers detected per 1,000 women screened, with a total of 14,040 cancers detected in the screening programme in the UK.

The development of breast screening centres led to the development of breast specialisation in pathology surgery and radiology across the UK and has had a major impact in the multidisciplinary management of breast cancer and the improvement in overall survival.

**BS22
PROGNOSTIC INDEX IN SCREEN-DETECTED BREAST CANCER**

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A meta-analysis of symptomatic breast cancer trials advises chemotherapy to women less than 70 years of age at high risk of death (i.e. benefit of >1% survival from treatment). UK screen detected breast cancers (SDBC) (aged 50–65 years) have an overall 95.5%, 5 year relative survival, a figure similar to the Two Counties Swedish Trial survival. NIH Guidelines (2001) recommend chemotherapy for all cancers greater than 10 mm in size (i.e. 35% of screen detected breast cancers) yet the overall benefit for chemotherapy is based on mortality data from symptomatic cancer trials and in postmenopausal women aged greater than 50 years of age the average benefit is a 10% reduction in mortality (EBCTG Overview).

We have compared screen detected breast cancer SDBC with symptomatic breast cancer in the same age group (50–65 years) with regard to clinicopathological features, recurrence and survival in one unit from 1990–1998 and validated a new index on 4,195 operable screen detected breast cancer SDBC treated by NHSBSP surgeons from 1996–1997 in the United Kingdom. Median follow-up on 1,607 breast cancers was 70 months (range 21–103) and indicated that breast cancer diagnosis by screening (as opposed to symptomatic presentation) had a reduced risk of recurrence RR = 0.37, 95% CI 0.23–0.53 and fatality RR = 0.28, (0.19–0.42), which was independent of grade, node status and tumour size. Smaller tumours and higher node negativity occurred in SDBC's but tumour grade and oestrogen receptor status did not differ from symptomatic cancers. A screening prognostic index (MSI) based on combining scores for grade (1; 2 or 3), size less than 15 mm = 1, 1.5–2.5 = 2, greater than 2.5 = 3) and nodal status (negative = 1, less than 4 nodes = 2, greater than 4 nodes = 3) was defined in the initial series and demonstrated that those with scores 3–5 had a 99.5% survival at 5 years in the screening group with a 98.6% survival for score 6. For SDBC scores 7–9 overall survival at 5 years dropped to 80%. In a larger screen detected breast cancer from the BASO Audit overall survival is shown below:

| Manchester SI | All Cases 1996–97 | | 1996/97 Cases Only | | | Chemotherapy Use in 2001/2 |
|------------------|----------------------|------|--------------------|---------------|--|-------------------------------|
| | N | % | Grade III | Node Positive | 5 Year Relative Survival ($\pm 95\%$ CIs) | |
| 3 | 833 | (20) | 0% | 0% | 100% | 1% |
| 4 | 1111 | (26) | 0% | 9% | 98.5% (97.1–100.0) | 6% |
| 5 | 1090 | (26) | 20% | 25% | 96.3% (94.7–98) | 22% |
| 6 | 630 | (15) | 42% | 55% | 93.6% (91–96.1) | 49% |
| 7 | 363 | (9) | 49% | 80% | 81.1% (78.5–85.7) | 63% |
| 8 | 143 | (3) | 66% | 100% | 71.6% (63.4–79.8) | 83% |
| 9 | 26 | (1) | 100% | 100% | 57.1% (38–78–3) [†] | 85% |

[†] Chi-Squared test for trend ($\dagger p < 0.001$) Index scores identified women at high risk of mortality (score 7–9).

Patients in the original series in Manchester with SDBC received significantly less adjuvant radiotherapy and chemotherapy than symptomatic cancers yet had a better overall survival. Only 1.9% of screen detected breast cancer scores 3–5 received chemotherapy compared to 7% of symptomatic cancers whilst in scores 7–9, 81% in both groups received chemotherapy. This data indicates that despite the NIH Guidelines screen detected breast cancer needs less chemotherapy than symptomatic cancer and has a good overall survival. The better survival of mammographically detected breast cancer (age 50–70 years) suggests that women whose cancer is diagnosed by mammography will receive unnecessary adjuvant chemotherapy if symptomatic guidelines are applied. The new Manchester Screening Index identifies only 13% of post-menopausal SDBC women with a 5 year survival below 93.6% who would benefit from chemotherapy (scores 7–9).

BS23 TARGETED THERAPY

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Breast cancer has led the way in developing drugs for targets (e.g. oestrogen receptor) since the initial excitement over the benefit of Tamoxifen and more latterly, Aromatase Inhibitors (AI's) research has focussed on finding novel agents to other targets. The HER2 oncoprotein is targeted extracellularly by Herceptin with an appropriate 50% reduction in breast cancer recurrence in 4 major trials. Newer agents, such as the HER1/HER2 inhibitor, Lapatinib, are currently entering clinical trials.

Problems arise when the target (e.g. HER1) does not reflect the growth drive of a tumour. Thus, targeted therapy to the HER1 receptor has largely been unsuccessful in breast cancer.

Biological subtypes will help to improve trial development and identify which patients need which therapies. Importantly, it will allow rational development of combination therapies within subgroups. Newer agents becoming available include progesterone receptor antagonists and Src inhibitors which may only be effective in tumours expressing the receptor (i.e. luminal A or triple negative cancers respectively). Potential benefits of targeted therapy on breast cancer treatment will be discussed.

BS24 APOPTOSIS: WHY SURGEONS NEED TO UNDERSTAND IT

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Apoptosis (programmed cell death) is a mechanism which enables regulation of cell number in tissues and elimination of unneeded, ageing or damaged cells. Imbalances between epithelial proliferation and apoptosis contributes tumour genesis and tumour progression. Apoptosis is morphologically characterised by nuclear condensation and cytoplasmic shrinkage. The process of proliferation and apoptosis within tumours is closely linked with higher proliferative accounts being associated with higher apoptotic rates. Initial therapeutic advances involved agents that block proliferation but evidence is mounting that it is blocks to apoptosis which need to be overcome to enhance

treatments for breast cancer. A newer group of novel biological agents such as the HER2 inhibitors trigger apoptosis to achieve responses.

Apoptosis occurs via two predominant pathways, which act via a Caspase effector mechanism. An extrinsic pathway activated by ligands to the TRAIL, FAS/TNF family of cell membrane bound death receptors which recruits intracellular adaptor proteins including pro-Caspases to induce apoptosis in the cells. Recent studies suggest Caspase 8 alterations influence breast cancer development via the extrinsic pathway.

The intrinsic pathway starts from the mitochondria and can be activated by a large number of signals including irradiation, DNA damage and alteration of the ratio of BCL2, BAX family members. This leads to release of Cytochrome C and activation of Caspase 9 leading to apoptosis. Apoptosis and activation of Caspase 9 can be prevented by the Inhibitor of Apoptosis Protein (IAP) family. Breast cancers often express mutated p53 which makes them resistant to apoptosis induced by alkylating agent chemotherapy. Pro-apoptotic agents will potentially improve the effectiveness of chemotherapy. Breast cancer expresses the BCL2 family proteins which are induced by oestrogen and thus anti-oestrogens such as Tamoxifen and Fulvestrant can induce apoptosis by increasing BAX expression and decreasing BCL2 activity.

Newer agents such as Herceptin, Lapatinib (dual molecular HER1/HER2 inhibitor) and the RAS farnesylation transferase inhibitors induce apoptosis by activating the pro-apoptotic protein BAD another member of the BCL2 family. Combinations of drugs which induce apoptosis can potentially be used to cause tumour regression. For instance, a one per cent increase in apoptosis is likely to have the same effect as a 50% reduction in cell proliferation on tumour growth. Current targets for drug discovery includes targets against endogenous antagonists of Caspase activation and IAP antagonists. Therapies for inducing apoptosis will be discussed.

BS25 BREAST RECONSTRUCTION WITH TRANSVERSE RECTUS ABDOMINUS MYOCUTANEOUS FLAP

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Introduction In the absence of contraindications, autologous tissue reconstruction is an attractive method of breast reconstruction. The TRAM flap has become the cornerstone of autologous tissue only breast reconstruction. In most women, there is sufficient abdominal adipose tissue and skin for bilateral breast reconstruction without the need for prosthetic devices. This flap can be employed for both immediate and delayed reconstruction. It provides soft pliable tissue for post-mastectomy reconstruction and in general has fewer radiation therapy associated complications than implant based methods of breast reconstruction.

Methods Pedicled TRAM flaps are employed for breast reconstruction. Each hemi-TRAM is based on a single pedicle. In cases of immediate breast reconstruction the flap is raised at the same time the mastectomy is being performed. In cases of DM, tobacco history, or moderate obesity, a vascular delay is performed by ligating the DIEP vessels 2 weeks prior to elevating the flap and a bipedicle flap is used to maximize blood supply. The rectus sheath fascia is repaired primarily, and the abdominal wall is reinforced with onlay marlex mesh. The TRAM flap is inset and shaped to form a youthful but mildly ptotic breast. Drains are used in both the donor site and recipient site. Long term catheter delivery of local anesthetic is employed at the donor site.

Results Over the past years 10 years, 78 TRAM breast reconstructions have been performed with satisfactory to excellent results. 90% were performed for immediate reconstruction and 10% for delayed reconstructions. 10% underwent surgical vascular delay of the flap for the indications discussed above and in order to avoid a free flap. There were 2 cases of total flap loss. The percentage of fat necrosis was 15%. Other complications included mastectomy skin loss (8%), hematoma/seroma (5%), and infection (5%). Revision surgery to improve the aesthetic outcome was performed in (20%). NAC reconstruction using the purse-string method was performed in 95% of the patients.

Conclusions TRAM flap breast reconstruction is a very favorable method for assisting in the overall care of a patient with breast cancer. Satisfaction is very high and major complications are acceptable. The disadvantages include longer operative time and prolonged recovery compared to tissue expander reconstruction. I feel the advantages of autologous tissue reconstruction outweigh these risks in addition to the risks of complications associated with tissue expander, implant reconstruction. A staged approach to TRAM flap reconstruction should be considered for patients who may require postoperative radiation for local control in order to avoid the deleterious effects of radiation on the TRAM flap.