Breast Cancer Research Review™

Making Education Easy

Issue 14 – 2013

In this issue:

Abbreviations used in this issue

AI = aromatase inhibitor
BC = breast cancer
ER = oestrogen receptor
FN = febrile neutropenia
G-CSF = granulocyte-colony stimulating factor
IHD = ischaemic heart disease
mBC = metastatic breast cancer
PFS = progression-free survival
SN = sentinel node
US = ultrasound

Welcome to the fourteenth issue of Breast Cancer Research Review.

The first paper that we discuss quantifies the potential risks of developing ischaemic heart disease (IHD) in a case control series from Scandinavia. While the absolute increase in IHD risk appears to be small, it persists over time, indicating such potential morbidities need to be considered when radiotherapy is offered, particularly in cases with a lower risk of locoregional relapse.

Another paper in this issue suggests that selective sentinel node excision may be sufficient to control locoregional and distant disease in early breast cancer patients with micrometastatic sentinel lymph nodes. Over a median 5-year follow-up, there were no statistically significant differences in disease-free survival between patients assigned to the completion axillary lymph node dissection group versus those assigned to clinical follow-up only. In addition, there were no cancer-related deaths.

I hope you find the papers in this issue useful in your practice and I welcome your comments and feedback.

Kind regards,

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Risk of ischemic heart disease in women after radiotherapy for breast cancer

Authors: Darby SC et al

Summary: Radiotherapy for breast cancer may incidentally expose the heart to ionising radiation. The effect of this exposure on the subsequent risk of ischemic heart disease (IHD) is uncertain. This population-based, case-control study determined the number of major coronary events (myocardial infarction, coronary revascularisation, or death from IHD) in 2168 women who underwent radiotherapy for breast cancer between 1958 and 2001 in Sweden and Denmark; including 963 women with major coronary events and 1205 controls. For each woman, data from radiotherapy charts and medical records were used to estimate the mean radiation doses to the whole heart and to the left anterior descending coronary artery. The overall average of the mean doses to the whole heart was 4.9 Gy (range, 0.03 to 27.72) during this period. Rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per Gy (95% CI, 2.9 to 14.5; p<0.001), with no apparent threshold. The increase started within the first 5 years after radiotherapy and continued into the third decade after radiotherapy. The proportional increase in the rate of major coronary events per Gy was similar in women with and without cardiac risk factors at the time of radiotherapy.

Comment (RI): This study confirms that exposure of the heart to ionising radiation during radiotherapy for breast cancer does increase the subsequent rate of IHD, in a dose-dependent manner. Rates of IHD increase within a few years after exposure, and continue for at least 20 years. Women with pre-existing cardiac risk factors have greater absolute increases in risk from radiotherapy than other women. While modern techniques have reduced exposure, such longer-term risks still need to be considered, especially in women post-mastectomy for left-sided breast cancers with relatively low risks of disease recurrence.

Reference: N Engl J Med 2013;368(11):987-98

http://www.nejm.org/doi/full/10.1056/NEJMoa1209825

Analysis of circulating tumor DNA to monitor metastatic breast cancer

Authors: Dawson SJ et al

Summary: The radiographic imaging of tumours with the assay of circulating cell-free DNA carrying tumour-specific alterations (circulating tumour DNA) was compared with cancer antigen 15-3 (CA 15-3) and circulating tumour cells in 30 women with metastatic breast cancer who had somatic genomic mutations and were receiving systemic therapy. CA 15-3 levels and numbers of circulating tumour cells were measured at identical time points. Circulating tumour DNA was found in 29 women (97%), whereas CA 15-3 and circulating tumour cells were detected in 21 of 27 women (78%) and 26 of 30 women (87%), respectively. Circulating tumour DNA levels showed a greater dynamic range and greater correlation with changes in tumour burden, than did CA 15-3 or circulating tumour cells. Also, in 10 of 19 women (53%), circulating tumour DNA provided the earliest measure of treatment response – increases at one or more consecutive points occurred on average 5 months before imaging established there was disease progression.

Comment (RI): This was a proof-of-concept study and showed that, when detected, circulating tumour DNA was apparently a highly specific and sensitive biomarker of metastatic breast cancer. However, there is marked heterogeneity in the mutations that occur in different breast cancers, making the technique difficult to standardise. In the reported group of patients, where a variety of sophisticated techniques were used, including whole-genome sequencing, only 60% of tumours had specific mutations that could then be screened for circulating tumour DNA. The future potential of this approach is great, however, with possible roles in identifying early relapse to prevent unnecessary therapy and defining those who might benefit from targeted therapies. Its role as a prognostic factor requires further research.

Reference: N Engl J Med 2013;368(13):1199-209

http://www.nejm.org/doi/full/10.1056/NEJMoa1213261

Risk of asynchronous contralateral breast cancer in noncarriers of *BRCA1* and *BRCA2* mutations with a family history of breast cancer: a report from the Women's Environmental Cancer and Radiation Epidemiology Study

Authors: Reiner AS et al

Summary: This was a population-based case-control study comparing 594 women with contralateral breast cancer (CBC) to 1119 women with unilateral breast cancer (UBC; controls), who had tested negative for *BRCA1* and *BRCA2* mutations. The association between family history of breast cancer and risk of asynchronous CBC was explored, with estimation of age- and family history-specific 10-year cumulative absolute risks of CBC. Family history of breast cancer was associated with increased CBC risk; risk was highest among young women (<45 years) with first-degree relatives affected at young ages (<45 years; RR, 2.5; 95% CI, 1.1 to 5.3) or women with first-degree relatives with bilateral disease (RR, 3.6; 95% CI, 2.0 to 6.4). Women diagnosed with UBC before age 55 years with a first-degree family history of CBC had a 10-year risk of CBC of 15.6%.

Comment (RI): Young women with breast cancer who have a family history of breast cancer, but test negative for mutations in *BRCA1* and *BRCA2,* are at significantly greater risk of CBC than other breast cancer survivors. Absolute risks vary with diagnosis age, family history of CBC, and degree of relationship to an affected relative. The extent of these risks of CBC has not been previously quantified, but in this study some groups had risks of CBC similar to those for *BRCA* mutation carriers. This data should be considered with women at higher risk of CBC when discussing screening or intervention such as surgery or hormonal therapy to reduce risks.

Reference: J Clin Oncol 2013;31(4):433-9

http://jco.ascopubs.org/content/31/4/433.abstract

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Randomized phase III placebo-controlled trial of letrozole plus oral temsirolimus as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic breast cancer

Authors: Wolff AC et al

Summary: The phase III HORIZON study examined the effect of adding an mTOR inhibitor, temsirolimus (30 mg), to a nonsteroidal aromatase inhibitor (AI), letrozole (2.5 mg), as daily first-line therapy for 5 days every 2 weeks in 1112 patients with AI-naive, hormone receptor-positive advanced disease. An independent data monitoring committee recommended early study termination for futility. Compared with letrozole alone, the addition of temsirolimus did not result in an overall improvement in the primary end point of progression-free survival (PFS; median, 9 months; HR, 0.90; 95% CI, 0.76 to 1.07; p=0.25) or in the 40% patient subset with prior adjuvant endocrine therapy. An exploratory analysis suggested improved PFS favouring letrozole/temsirolimus in patients aged ≤65 years (9.0 vs 5.6 months; HR, 0.75; 95% CI, 0.60 to 0.93; p=0.009).

Comment (RI): In contrast to the BOLERO-2 study, where adding everolimus to exemestane in AI-resistant disease showed major benefits in PFS, this study failed to show any clear advantage from adding another mTOR inhibitor, temsirolimus to letrozole, when used as first-line therapy in patients with AI-naïve advanced breast cancer. It would appear from these results that mTOR inhibition has a predominant role in those with AI-resistant disease, while such inhibition does little to enhance the activity of the AIs in those not previously exposed to these agents.

Reference: J Clin Oncol 2013;31(2):195-202

http://jco.ascopubs.org/content/31/2/195.abstract

Colony-stimulating factors for febrile neutropenia during cancer therapy

Authors: Bennett CL et al

Summary: This is a review of the use of granulocyte-colony stimulating factor (G-CSF) in preventing febrile neutropenia (FN) in patients treated with chemotherapy for malignancy. National Cancer Institute (NCI) data show that approximately 8/1000 patients receiving cancer chemotherapy develop FN, which causes major morbidity, particularly if severe neutropenia persists for longer than 10 to 14 days. Various US analyses demonstrate in-hospital rates of death from FN of 6.8 to 9.5% (and 15.3% for patients with documented infection). The mean costs per hospitalisation in two of the NCI studies were US$13,372 and $19,110 respectively. G-CSF supports the survival and stimulates the proliferation of neutrophil progenitors, promotes differentiation of these cells into mature neutrophils, causes premature release of neutrophils from the marrow and enhances phagocytic capacity, the generation of superoxide anions, and the killing of bacteria by these cells. A number of meta-analyses have shown that the rates of FN in solid tumours can be reduced by >50% by the use of primary G-CSF prophylaxis. Many adjuvant therapies used for breast cancer have rates of FN of >20%, where morbidity may be reduced by the use of primary G-CSF.

Comment (RI): International guidelines now recommend the use of G-CSF for patients receiving chemotherapy regimens with FN rates of >20%. In the MidCentral Regional Cancer Treatment Service we have recently audited the incidence of FN in our patients receiving docetaxel-containing adjuvant breast cancer chemotherapy regimens and found that these regimens generated FN rates >20%. The recent funding of filgrastim by PHARMAC has enabled us to introduce primary G-CSF as primary prophylaxis in such high-risk regimens and we hope to see significant reductions in FN rates, consistent with overseas findings. This paper provides a good summary of the current data and indicates that not only the treatment regimen, but also patient-related risk factors, need to be considered in treatment decisions.

Reference: N Engl J Med 2013;368(13):1131-9

http://www.nejm.org/doi/full/10.1056/NEJMct1210890

Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01)

Authors: Galimberti V et al

Summary: The IBCSG 23-01 trial recruited patients with clinically non-palpable axillary lymph node(s) and a primary tumour of ≤5 cm and minimal sentinel node (SN) involvement, defined as one or more micrometastatic (≤2 mm) SNs with no extracapsular extension. Outcomes are reported for 464 patients who underwent axillary dissection and for 467 who did not. At a median 5-year follow-up, 69 disease-free survival events were noted in the axillary dissection group and 55 in the no axillary dissection group. Breast cancer events were recorded in 48 patients in the axillary dissection group and 47 in the no axillary dissection group (10 local recurrences in the axillary dissection group and 8 in the no axillary dissection group; 3 and 9 contralateral breast cancers; 1 and 5 regional recurrences; and 34 and 25 distant relapses, respectively). Other non-breast cancer events were recorded in 21 patients in the axillary dissection group and 8 in the no axillary dissection group (20 and 6 second non-breast malignancies; and 1 and 2 deaths not due to a cancer event, respectively). Five-year disease-free survival was 84.4% in the group with axillary dissection and 87.8% in the group without axillary dissection (log-rank p=0.16; HR for no axillary dissection vs axillary dissection was 0.78; non-inferiority p=0.0042). Long-term surgical events (grade 3–4) included sensory neuropathy (grade 3), lymphoedema and motor neuropathy (grade 3), all in the group that underwent axillary dissection, and one grade 3 motor neuropathy in the group without axillary dissection. One serious adverse event was reported, a postoperative infection in the axilla in the group with axillary dissection.

Comment (IC): See right

Reference: Lancet Oncol 2013;14(4):297-305

http://tinyurl.com/dx6me7h

Complete axillary lymph node dissection versus clinical follow-up in breast cancer patients with sentinel node micrometastasis: final results from the multicenter clinical trial AATRM 048/13/2000

Authors: Solá M et al

Summary: This study recruited patients with newly diagnosed breast cancer at an early stage (*T* <3.5 cm, clinical N0, M0) who had undergone surgical excision (mastectomy or breast-conserving surgery) as the primary treatment. All had sentinel node (SN) micrometastasis. The patients were randomised to undergo either complete axillary lymph node dissection (ALND; controls; n=112) or clinical follow-up (experimental arm; n=121). Median follow-up was 5 years. In 15 controls (13%), completion ALND was positive, with a low tumour burden. Disease recurred in 1 of 108 controls (1%) and in 3 of 119 patients (2.5%) on the experimental arm. Rates of disease-free survival did not differ between the arms and there were no cancer-related deaths.

Comment (IC): Both these recently published randomised trials test the need for axillary dissection after the finding of a micrometastasis or metastases in sentinel node or nodes. They therefore address a similar question to the American College of Surgeons Z0011 Trial but in a population that excludes macrometastatic disease. Both studies failed to meet planned accrual after prolonged accrual intervals (9 and 8 years, respectively). The second study from Solá et al. was particularly underpowered with only 233 of a planned 352 cases accrued and analysed, but may in the long term contribute to meta-analysis of this issue. The small sample size was reflected in the significant imbalance in baseline characteristics, with 26.2% of tumours palpable in the observation arm versus 39.9% in the axillary dissection arm. We know screen-detected breast cancers have on average better outlook, advantaging the experimental arm. Extraordinarily, the size of sentinel node metastasis was missing in about one-quarter of cases in this study and hormone receptor status in 10–15%. Baseline characteristics were well matched in 23-01. Although any primary breast surgery could be utilised, only 9% of women underwent mastectomy in 23-01, and 5% and 7.7% of women underwent mastectomy in the Spanish study. So most women had breast-conserving surgery and whole breast radiotherapy, which we know usually includes some of the lower axilla in tangential fields.

The slow accrual, I think, reflects the uneasiness of surgeons and/or patients on this question at the time. As a result, only predominantly small and good biology breast cancers were entered in the studies with 97.5% 5-year overall survival in 23-01 and no breast cancer deaths in the Spanish study. There were only 4 recurrences in the Spanish study at this stage of follow-up, 2 axillary recurrences (1.7%) in the observation group compared with one cutaneous axillary recurrence (0.9%) in the ALND group. Five regional recurrences were noted in the observation group for 23-01, and 1 in the ALND group. Of the 5, one patient received no radiotherapy, and 2 intraoperative partial breast radiotherapy, after breast-conserving surgery.

Both studies demonstrated a low residual burden of axillary disease on ALND. In both studies, only 13% of patients had a further node involved on ALND. For the Spanish study, the majority had one node only, and half of these were micrometastases only. Young women, especially, were more likely to have involved nodes on AND and there was also a tendency for larger, palpable tumours with LVI to be high-grade and hormone receptor-negative. For 23-01, 96% of women had systemic therapy (31% chemotherapy) and all women on the Spanish Trial, including 92.1% receiving chemotherapy.

Taking the above factors into consideration, these studies have produced remarkably similar results to Z0011, and indicate that surgeons may not need to perform completion axillary dissection for women with good biology breast cancers and micrometastasis to a sentinel node, where the residual burden of nodal disease is likely to be low. These women should have adjuvant radiotherapy and systemic therapy. These results need longer follow-up to be more certain that late recurrences will not change these outcomes and should not be extrapolated to women with poor biology breast cancer, nor to younger women at this stage.

Reference: Ann Surg Oncol 2013;20(1):120-7

http://link.springer.com/article/10.1245%2Fs10434-012-2569-y

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Independent commentary by Dr Richard Isaacs, a Medical Oncologist at Palmerston North Hospital and member of the ANZ Breast Cancer Trials Group, current Chair of the NZ Association of Cancer Specialists Breast Cancer Special Interest Group and an invited member on the New Zealand Breast Cancer Guideline Implementation Group. He is also Chair of the Mid-Central RCTS Research and Protocol Committee and Vice President of the Palmerston North Medical Research Foundation.

Independent commentary by Associate Professor Ian Campbell, ONZM, a Breast Oncoplastic and General Surgeon at Waikato Hospital and Associate Professor of Surgery with the Waikato Clinical School, University of Auckland. Ian is the Clinical Director of the Breast Care Centre at Waikato Hospital, Chairman of the Waikato Breast Cancer Trust, and the NZ Representative on the Breast Section of the Royal Australasian College of Surgeons. He is the NZ Representative, elected to the Board of Directors of the ANZ Breast Cancer Trials Group, a member of the ANZ BCTG Scientific Advisory Committee and he is a member of the NZ Association of Cancer Specialists Breast Cancer Special Interest Group.

Effect of ASCO/CAP guidelines for determining ER status on molecular subtype

Authors: Deyarmin B et al

Summary: The current American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) guidelines recommend that tumours with ≥1% positively staining cells should be considered oestrogen receptor (ER)-positive. These researchers examined how this cut-off relates to molecular subtype, by comparing clinicopathological characteristics between ER-negative, ER-positive, and low-ER-staining (1–10%) tumours. Low-ER-staining tumours were clinicopathologically more similar to ER-negative than to ER-positive tumours; 88% of low-staining tumours were basal-like or human epidermal growth factor receptor 2 (HER2)-enriched. Only those tumours expressing 10% ER-positive cells were classified as luminal A subtype.

Comment (IC): This is an important piece of work that raises doubt about current thresholds for decision making around adjuvant therapy for breast cancer. The majority of clinical trials have used a cut-off of 10% staining on immunohistochemistry (or equivalent in older studies using ligand binding assays) to define hormone receptor positivity. The applicability of the results of these studies for women with <10% staining can therefore already be questioned. The results of this study highlight the need to take particular care over adjuvant therapy decision making in women with low levels of hormone receptor positivity. These tumours are more likely to be basal type or Her2-enriched not only on the basis of gene expression, but also in terms of their behaviour and prognosis. The authors recommend that in the absence of molecular subtyping, tumours with <10% expression on IHC should be considered ER-negative.

Reference: Ann Surg Oncol 2013;20(1):87-93

http://link.springer.com/article/10.1245%2Fs10434-012-2588-8

Pain in long-term breast cancer survivors: the role of body mass index, physical activity, and sedentary behavior

Authors: Forsythe LP et al

Summary: This analysis of pain in long-term breast cancer survivors assessed associations of body mass index (BMI), physical activity and sedentary behaviour with mean pain severity and above-average pain, using data from survivors who completed pain assessments 40 months post-diagnosis (n=801), 10 years post-diagnosis (n=563), or both (n=522). Above-average pain was defined by SF-36 bodily pain scores ≥1/2 standard deviation worse than age-specific population norms. A greater proportion of survivors reported above-average pain at 10 years than at 40 months (32.3% vs 27.8%; p<0.05). Approximately one-quarter of survivors reported improved pain, 9.0% maintained above-average pain and 33.1% reported worsened pain. At 10 years, overweight and obese survivors reported higher pain than normal-weight survivors and women meeting physical activity guidelines were less likely to report above-average pain than survivors not meeting these guidelines (p<0.05). Weight gain (>5%) was positively associated with above-average pain (OR 1.76; 95% CI, 1.03 to 3.01), whereas women meeting physical activity guidelines were less likely to report above-average pain (OR 0.40; 95% CI, 0.20 to 0.84) (both p<0.05).

Comment (IC): This study shows just how common long-term pain is in breast cancer survivors and provides yet more grist to the mill, in terms of the benefits of maintaining healthy weight and adequate levels of activity for breast cancer survivorship.

It is a cohort study, and suffers a potential bias, given that about a quarter of the baseline population did not complete the 40-month follow-up assessments, increasing to over one-half of the population by 10 years. Pain severity was similar at the 40-month assessment in women who did and did not complete the 10-year assessment, however. Outcomes were also self-reported. On a positive note, it was a large, comprehensive and prospective design.

The effect of adequate activity (defined as 150 minutes per week of moderate activity or 75 minutes per week of vigorous activity) was dramatic – halving the likelihood of having above average pain. Being overweight and gaining weight were both associated with increased pain at 10 years.

The study suggests we should take a more active approach to finding successful interventions for maintenance of healthy weight and adequate physical activity amongst survivors.

Reference: Breast Cancer Res Treat 2013;137(2):617-30

http://link.springer.com/article/10.1007%2Fs10549-012-2335-7

Intraoperative ultrasound guidance for palpable breast cancer excision (COBALT trial)

Authors: Krekel NM et al

Summary: In this study, 134 patients with palpable T1–T2 invasive breast cancer were randomly assigned to undergo either ultrasound (US)-guided surgery (n=65) or palpation-guided surgery (n=69). Primary outcomes were surgical margin involvement, need for additional treatment, and excess healthy tissue resection (defined with a calculated resection ratio derived from excision volume and tumour diameter). The proportion of tumour-involved resection margins was significantly lower with US-guided surgery compared with palpitation-guided surgery (3% vs 17%; p=0.0093). US-guided surgery also resulted in fewer patients requiring additional treatment (7 vs 19; p=0.015), smaller excision volumes (38 vs 57 cm^3; p=0.002) and a reduced calculated resection ratio (1.0 vs 1.7; p=0.0001) compared with palpation-guided surgery.

Comment (IC): Although a number of papers have been published demonstrating the benefits of intraoperative ultrasound for nonpalpable breast cancers, this is one of the first for palpable breast cancer.

The volume of tissue removed at the time of breast-conserving surgery is the key factor in determining poor cosmetic outcome. Not only did ultrasound guidance reduce this, but the frequency of margin involvement and further intervention were both significantly reduced. There were no subsequent mastectomies in the USS group compared with 5 in the palpation-guided group. There was much less work for the pathologists, because none of the USS group required additional excision after specimen imaging and cavity shaves were virtually not used in this group.

Major benefits were seen and at the expense of only some 5 minutes additional theatre time to take a sterile ultrasound probe on board and plan the surgery.

The study suffers one major flaw – there was unfortunately an imbalance in baseline characteristics between the two groups, with 70% of tumours in the upper outer quadrant for the palpation group, compared with only 49% in the USS group. Because this is the quadrant with the greatest volume and thickness of breast tissue, if surgeons performed subcutaneous to fascia excision in most cases, this would automatically bias the palpation group to greater volumes of excision. These findings may therefore be exaggerated.

The study excluded DCIS and women with an obviously extensive DCIS preoperatively. It included cases where DCIS in addition to invasive cancer was found on pathology after study entry. The findings were just as applicable to this group in spite of the fact that DCIS is often not visible on USS.

Avoiding re-excision, radiotherapy boosts, and/or mastectomy have major benefits for our patients in terms of psychological distress and cosmesis, as well as for health costs. For women with nonpalpable lesions, using USS guidance additionally enables many women to avoid having to have a hookwire placed – an unpleasant and timeconsuming process.

We breast surgeons need to become competent with USS-guided surgery.

Reference: Lancet Oncol 2013;14(1):48-54

http://tinyurl.com/bt7yvq6