Diagnosis and local management of breast cancer: part II

John R Benson
Cambridge Breast Unit, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK ■ Tel.: +44 122 358 6577 ■ Fax: +44 122 358 6932 ■ john.benson@addenbrookes.nhs.uk

Second Kyoto Breast Cancer Consensus Conference (KBCCC)

Kyoto, Japan, 14–16 April 2011

This is the second of a two-part conference report and covers the other main themes of the Second Kyoto Breast Cancer Consensus Conference (KBCCC) including ductal carcinoma *in situ*, sentinel lymph node biopsy and therapeutic algorithms for local management of breast cancer. Once again, this report emphasizes conclusions from the consensus sessions that were a key feature of the KBCCC.

John Forbes from the University of Newcastle, Australia, provided an insightful overview of the biology and management of ductal carcinoma *in situ* (DCIS) and emphasized the need for more information from reliable clinical trials containing randomized prospective data. Although DCIS generally has a good prognosis, there is an increased risk for subsequent invasive breast cancer dependent on tumor extent, grade, HER2 expression and probable mammographic density. Local recurrence of DCIS is influenced by margin status, which is a modifiable risk factor – the most important component of treatment for DCIS is excision with clear surgical margins. It should be noted that MRI does not accurately predict the extent of DCIS. When the size of DCIS on MRI is less than 2 cm, MRI can assist in surgical planning. Otherwise, it can potentially overestimate the extent of disease in up to 50% of cases and may increase mastectomy rates. MRI may play a role in the evaluation of patients with a strong family history of breast cancer and those with a documented mutation in the breast cancer susceptibility genes *BRCA-1* and *BRCA-2*.

Forbes presented results of the recently published UK/Australia and New Zealand Ductal Carcinoma *In Situ* (UK/ANZ DCIS) trial [1]. No differences in rates of ipsilateral breast tumor recurrence (IBTR) were found between low and intermediate nuclear grade DCIS, suggesting that distinction between these categories may be unnecessary and grading should be reclassified as low/intermediate, high and very high. Cytonuclear grade should be accepted as the basic method for assessing intrinsic biological aggressiveness. Surgical excision should aim for a minimum tumor-free radial margin of 2 mm. Interestingly, in the UK/ANZ DCIS trial, the relative risk of IBTR for margins of 0–1 mm was 1.0 compared with 0.47 for margins of 1–2 mm. There was no additional improvement in local control beyond a margin of 1 mm. Randomized trials have confirmed that both radiotherapy and tamoxifen reduce the risk of IBTR and the chance of any subsequent invasive breast cancer. In the UK Coordinating Committee on Cancer Research (UKCCCR) trial, patients in both the radiotherapy and no radiotherapy arms were randomized to receive tamoxifen or no systemic therapy. Tamoxifen yielded a 29% reduction in risk of recurrence, but for those patients receiving radiotherapy, much of the benefit of tamoxifen disappeared. Similarly, radiotherapy produced a 60% risk reduction for both noninvasive and invasive cancer, with little additional benefit from concomitant tamoxifen. Nonetheless, tamoxifen had a longer-term preventative effect on disease in the contralateral breast. These findings may limit the ability of the International Breast Cancer Interventional Study (IBIS) II trial to detect any advantage of anastrozole over tamoxifen for post-menopausal women with hormone-sensitive DCIS treated with breast-conserving surgery (BCS; not mastectomy). For patients not receiving radiotherapy, local recurrence risk for high- and low-density breasts was 40 and 0%, respectively, suggesting that benefits in risk reduction were confined to the group for whom tamoxifen decreased breast density.

Mehra Golshen, of the Dana Farber/Brigham and Women's Cancer Center, MA, USA, briefly discussed sentinel lymph node (SLN) biopsy in the context of DCIS and adamantly maintained that there was no indication for axillary staging except for cases of DCIS mandating mastectomy (both intermediate and high nuclear

Keywords
■ breast cancer ■ DCIS ■ MRI ■ neoadjuvant therapy ■ PET ■ sentinel node

future medicine part of fsg

grade) where the chance of finding invasive disease was approximately 10%. He cited an incidence of only 0.8% for lymph node metastases in DCIS and often only isolated tumor cells are found in nodes. No groups of patients undergoing BCS for DCIS only on core biopsy (no micro-/overt invasion) were considered appropriate for simultaneous SLN biopsy, which is associated with some morbidity, including allergic reactions to lymphazuran (the most commonly employed blue dye tracer agent in the USA), lymphedema (1–7%), seroma formation (13%) and infection (3%). SLN biopsy can be performed as a delayed procedure when invasive cancer is found in a wide-excision specimen.

An exciting and topical area of discussion and interest came from results of the Z0011 trial evaluating omission of completion axillary lymph node dissection (cALND) in SLN biopsy-positive patients [2]. This trial examined disease-free survival and overall survival in a group of almost 900 patients undergoing BCS for relatively favorable T1 and T2 tumors (80% estrogen receptor positive) with macro- and micro-metastases in one or two SLN nodes. Patients were randomized to cALND or observation only and all received whole-breast irradiation and systemic therapy (chemotherapy/hormonal therapy). At a median follow-up of 6.3 years, there was no difference in either 5-year rates of locoregional recurrence (SLN biopsy alone = 1.6% [95% CI: 0.7–3.3%] vs ALND = 3.1% [95% CI: 1.7–5.2%]; p = 0.11) nor overall survival (SLN biopsy alone = 92.5% [95% CI: 90.0–95.1%] vs ALND = 91.8% [95% CI: 89.1–94.5%]) between the two arms. The unadjusted hazard ratio for treatment-related overall survival was 0.79 (90% CI: 0.56–1.11), and when adjusted for age and adjuvant therapy was 0.87 (90% CI: 0.62–1.93). It has been commented by Golshen (and others) that this trial was seriously underpowered and failed to accrue its target goal of 1900 patients. However, the trial was terminated early due to a lower mortality rate than expected. Furthermore, patients in the SLN biopsy-only arm had slightly better prognostic factors overall, with a higher proportion of micrometastases in the SLN biopsy arm (45%) compared with the ALND arm (35%). The group of patients within this trial had a low burden of axillary disease, with minimal likelihood of having more than two positive nodes; thus, the therapeutic value of SLN biopsy was similar to axillary clearance. Moreover, adjuvant treatments may have partly compensated for undertreating the axilla surgically. Due to the limited follow-up, some consider it premature to assume that the results from Z0011 will dramatically change surgical practice [3]. However, this has happened in some centers in the USA for patients fulfilling relevant criteria, including receipt of radiotherapy after BCS. On the basis of results to date, Forbes considered it highly unlikely that any equivalence of outcomes would be overturned by additional cases of locoregional recurrences to reveal any clinically meaningful survival benefit in the dissection group with longer follow-up. Consensus opinion supported omission of cALND in breast-conservation therapy patients with T1/T2 tumors and micrometastases only in the SLN and perhaps macrometastases when the metastatic ratio is low – say one out of two or two out of four nodes, rather than one out of one or two out of two nodes. Nomograms devised for the estimation of non-SLN involvement are difficult to reliably apply in practice and in particular may not be transferable to data sets generated from other institutions [4,5].

Kazuhiko Yamagami from Shinko Hospital, Japan, discussed the application of indocyanine green (ICG) fluorescence to breast cancer patients in Japan, where blue dye is currently the most common tracer agent used. He emphasized the problems of radioisotopes, including mandatory licencing and availability. SLN biopsy using blue dye alone can be problematic, especially with a fat-rich axilla. It is necessary to dissect through fatty tissue to reach a node and the blue color is readily obscured by a thin covering of fat. Pinpointing the SLN can be difficult in a fatty axilla and extensive dissection (with consequent damage to lymphatics) may be necessary. An illuminated or fluorescent node can direct dissection, permitting a more direct approach to the SLN. A combination of blue dye and ICG are injected into the subareolar region and fluorescent lymphatics are visualized immediately. These delve deep into the axillary tissues at the 'fluorescent line', which can help guide the site of the skin incision. A plastic sphere can be used to visualize approximately 50% of nodes through the skin and thus mark their location. This is difficult in obese patients with a BMI >30 in whom the axillary skin must be first incised. Identification rates for the SLN are reported to be 97.8% and the staining characteristics showed that almost 90% of nodes were blue and fluorescent.

In an interesting study using triple localization, 86 out of a total of 145 nodes were blue, hot and fluorescent, with all nodes containing metastases being visualized with all three tracer

agents. This approach is being investigated in the author's unit in the UK where nodal tracer characteristics are being evaluated using a combination of blue dye, ICG and radioisotope. This feasibility study is a prelude to a larger trial comparing the dual localization techniques with either a combination of blue dye and isotope (conventional) or blue dye and ICG. Results of this trial will determine standard practices for SLN localization in the future.

A central theme of the conference was the use of treatment algorithms and alternating decision tree development for the management of patients with primary breast cancer. These are often based on probabilities, and various decision-making tools can be used to guide treatment recommendations that depend on the risk of a particular factor being present. In the future, it is likely that molecular profiling of tumors will assist in predicting treatment responses to neoadjuvant therapies and absolute benefits from both adjuvant and neoadjuvant chemotherapy in terms of disease-free and overall survival. These technologies also offer the potential to assess the risk of local relapse when BCS is undertaken after primary chemotherapy; such information could be incorporated into a nomogram and indicate whether mastectomy might be more appropriate than BCS (whatever the final imaging appearances).

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Bibliography

1. Cuzick J, Sestak I, Pinder SE *et al*. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma *in situ*: long-term results from the UK/ANZ DCIS trial. *Lancet Oncol.* 12(1), 21–29 (2011).
2. Giuliano AE, Hunt K, Ballman K *et al.* Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastases: a randomized clinical trial. *JAMA* 305, 569–575 (2011).
3. Jatoi I. Axillary vs sentinel lymph node dissection for invasive breast cancer. *JAMA* 305(22), 2288 (2011).
4. Van Zee KJ, Manasseh DM, Bevilacqua JL *et al.* A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. *Ann. Surg. Oncol.* 10, 1140–1151 (2002).
5. Pal A, Provenzano E, Duffy SW *et al.* A model for predicting non-sentinel lymph node metastatic disease when the sentinel lymph node is positive. *Br. J. Surg.* 95, 302–309 (2008).