

Diagnosis and local management of breast cancer: part I

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This is the first of a two-part conference report and focuses primarily on newer technologies (e.g., molecular methods for intraoperative nodal assessment and MRI/PET imaging) and surgical management in the context of neoadjuvant chemotherapy. A notable feature of the Second Kyoto Breast Cancer Consensus Conference was a consensus session for which a series of key clinical questions in the aforementioned areas formed the basis for discussion. Preconference questionnaires had been issued to all delegates and the final consensus sessions focused on more controversial and problematic areas where there is divergence of opinion and clinical management.

The opening session of the second Kyoto Breast Cancer Consensus Conference (KBCCC) addressed some of the leading-edge technologies that are being employed in the diagnosis and management of breast cancer. Seigo Nakamura from the Breast Center of Showa University Hospital, Tokyo, Japan, pointed out problems of a lack of consistency, limited sampling of nodal tissue and the time-consuming nature of conventional histopathological methods for intraoperative node assessment. Nakamura reported sensitivity and specificity for the one-step nucleic acid amplification (OSNA) system of 95.0% (95% CI: 75.1–99.9%) and 97.1% (95% CI: 91.8–99.4%), respectively, and validation of the assay against routine histopathological examination revealed a concordance rate of 92.9% (95% CI: 90.1–95.1%), with only four false-positive cases reported. Unlike the breast lymph node assay (Genesearch™ Breast Lymph Node Assay [Veridex], Warren, NJ, USA), which is binary, OSNA is semiquantitative and can differentiate between macrometastases, micrometastases and isolated tumor cells. This raises the intriguing possibility that OSNA values may have independent prognostic significance and may ultimately permit molecular diagnostics to supersede histopathology.

Nonetheless, there are lingering concerns regarding potential false positivity, and even the fundamental need for intraoperative node assessment has been questioned in a recent editorial by Benson and Wishart, which formed the basis for a conference presentation [1]. Following this, a significant proportion of delegates (almost a third) conceded that intraoperative nodal assessment may not be essential in a modern

breast practice that incorporates sentinel lymph node (SLN) biopsy prior to both immediate breast reconstruction and primary chemotherapy (PC), preoperative axillary ultrasound (with or without nodal biopsy) and selective omission of completion axillary lymph node dissection (cALND) in SLN biopsy-positive cases. These factors collectively reduce the absolute numbers of isolated cALNDs, particularly when up to half of patients have cALND performed alongside definitive or additional breast surgery. Intraoperative node assessment may further reduce these low recall rates for isolated cALND (~10%), but may not be cost-effective nor logistically feasible within many healthcare systems [2].

The role of PET in breast cancer continues to evolve, but dedicated breast PET scanners have much improved sensitivity and resolution compared with conventional whole-body PET cameras. It is unlikely that PET will ever replace surgery for axillary staging due to innate limitations in resolution at the microscopic level, but for selective cases of a positive SLN biopsy, a negative PET scan could increase confidence in any decision to omit cALND.

Mitsuhiro Tozaki from the Kameda Medical Center, Kamogawa, Japan, reviewed the current status and value of preoperative breast MRI among Japanese women. MRI has enhanced sensitivity for the detection of invasive cancer compared with mammography and is useful for imaging the denser breasts of younger women and those with a strong family history of breast cancer. MRI can generate false-positive results and a degree of 'overcall' may have inadvertently increased rates of

Keywords

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

mastectomy in recent years [3,4]. Tozaki cautioned against interpretation of results from the Comparative Effectiveness of MRI in Breast Cancer (COMICE) trial that involved a very large number of centers and, consequently, limited individual experience and no MRI-guided biopsies [5]. Technological advances have improved the specificity of MRI and facilitated more widespread use of MRI biopsies, but there are concerns regarding the costs of MRI, and MRI-guided biopsies take approximately 1 h to perform. MRI has an established role in evaluating the extent of disease and assessing suitability for breast-conserving surgery (BCS). However, routine preoperative use of MRI has not been shown to reduce rates of ipsilateral breast tumor recurrence following BCS [6]. When nipple-sparing mastectomy is being considered, the absence of any enhancement patterns immediately beneath the nipple is reassuring and has a high false-negative predictive value. It was agreed that MRI is generally poor at predicting residual cancer after PC, and it can be difficult to ascertain from the MRI images whether a tumor has shrunk concentrically (and hence may be amenable to BCS) or in a 'dendritic' (or honeycomb) fashion, whereby resection of the original tumor bed volume is indicated (and hence mastectomy is more likely to be the appropriate surgical option depending on the initial tumor:breast size ratio). The sensitivity and specificity of MRI for the assessment of pathological complete response is 63.1 and 98.5%, respectively. It was concluded that the overall cost:benefit ratio of MRI in monitoring patients during neoadjuvant therapy and improving outcomes remains to be established.

John Robertson from Nottingham University, UK, discussed PC from a surgical perspective, which prompted more questions than answers. This treatment strategy was originally devised on the premise that upfront chemotherapy might improve disease-free and overall survival. However, clinical trials (including the National Surgical Adjuvant Breast and Bowel Project [NSABP] B-18) have shown equivalence of outcomes for adjuvant and neoadjuvant regimens. There is evidence for a survival benefit for those patients who receive a complete pathological tumor response after chemotherapy. Although neoadjuvant trials of chemotherapy have shown increased rates of BCS, this was not the main purpose of these trials and indeed BCS was adopted post-induction chemotherapy without adequate justification from clinical trials. Within the B-18 trial, 60% of patients receiving

postoperative (adjuvant) chemotherapy underwent BCS compared with 68% of those having a preoperative schedule of chemotherapy. Despite an increase of 8% in the BCS rate, the local recurrence rate (ipsilateral breast tumor recurrence) actually doubled ($p < 0.001$). Thus, rates of local relapse are higher for PC, and many patients in these studies were considered suitable for BCS even before PC. Robertson pointed out that few if any neoadjuvant trials were specifically designed to assess local control as an end point. Any apparent lack of detriment in terms of long-term survival might be attributable to effective rescue treatments, but could also be due to a 'type II error' due to limited numbers of patients and length of follow-up. It can take up to 15 years for local recurrence to impact on overall survival, and studies of PC and BCS have only 6.5 years of follow-up. An overview of 11 randomized controlled trials found that only 18% of patients who were initially deemed unsuitable became amenable to BCS following PC. Moreover, BCS following neoadjuvant treatment was associated with a 50% increase in risk of local recurrence, which was invariably higher in premenopausal women who often request BCS. This risk of local recurrence continues to increase for up to 10 years, with estrogen receptor-positive tumors and lobular cancers having much lower response rates to PC compared with estrogen receptor-negative tumors (5 vs 20%, respectively). For patients undergoing BCS after PC, it is often unclear how much tissue should be resected. Should a volume corresponding to the original tumor size be removed? Basically, we do not know the answer to this crucial question, for which there are no data from randomized trials. If a tumor shrinks concentrically and appears small (<3 cm) and unifocal on follow-up MRI, then the volume of resected tissue should correspond to the final tumor size on imaging. The tumor bed should be localized with a clip irrespective of surgical intent, and when a complete response has occurred clinically and radiologically, tissue around the clip (~2 cm radius) should be resected. Ultimately, only pathological examination can determine whether the whole tumor is likely to have been resected after BCS.

Robertson cautioned against overinterpretation of the current data and recommended that issues such as the chance of BCS and local recurrence risk should be discussed with patients embarking on neoadjuvant therapy. Randomized controlled trials are needed in order to elucidate factors that are predictive of local recurrence,

pathological complete response and BCS to facilitate a better understanding of the relationship between local recurrence and overall survival.

Sentinel lymph node biopsies can be carried out either before or after PC. The former provides potentially valuable information on staging, which may guide subsequent treatment decisions (e.g., for radiotherapy). Current trends favor SLN biopsy following PC, for which false-negative rates are approximately 11% (comparable to routine SLN biopsy). Mehra Golshen from Harvard Medical School, MA, USA, further explored the timing of SLN biopsy in relation to PC, citing 100% identification rates when performed before chemotherapy compared with 81% post-chemotherapy. Image-guided node biopsy can be carried out with either core biopsy or fine needle aspiration cytology and preferably at the time of breast core biopsy in order to avoid the possibility of enlarged reactive nodes being found. Secondary nodal changes can occur in response to recent breast core needle biopsy. Nonetheless, concomitant nodal

assessment is only appropriate when the index of suspicion for breast malignancy is relatively high. Patients who are initially node positive (based on either needle core biopsy/fine needle aspiration cytology or SLN biopsy) should have an ALND after PC. The Z1071 trial is evaluating either SLN biopsy or ALND after chemotherapy at the time of definitive surgery and will incorporate lymphedema and quality of life measurements. A clip can be deployed in a lymph node at the time of biopsy and hence the response to chemotherapy can be assessed.

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