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Personalization of loco-regional care for primary breast cancer patients (part 1)

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The loco-regional management of breast cancer is increasingly complex with application of primary systemic therapies, oncoplastic techniques and genetic testing for breast cancer susceptibility. Personalization of loco-regional treatment is integral to optimization of breast cancer care. Clinical and pathological tumor stage, biological features and host factors influence loco-regional treatment strategies and extent of surgical procedures. Key issues including axillary staging, axillary treatment, radiation therapy, primary systemic therapy (PST), preoperative hormonal therapy and genetic predisposition were identified and discussed at the Kyoto Breast Cancer Consensus Conference (KBCCC2014). In the first of a two part conference scene, consensus recommendations for axillary management are presented and focus on the following topics: indications for completion axillary lymph node dissection in primary surgical patients with ≤ 2 macrometastases or any sentinel nodal deposits after PST; the timing of sentinel lymph node biopsy in the context of PST; use of axillary irradiation as a component of primary treatment plans and the role of intraoperative node assessment in the post-Z0011 era.

The American Society of Clinical Oncology clinical practice guideline recommends that women without sentinel lymph node metastases should not receive axillary lymph node dissection (ALND) [1]. Recent randomized trials have examined noninferiority of sentinel lymph node (SLN) biopsy alone in comparison to SLN biopsy followed by either completion ALND or axillary radiotherapy (ART) in clinically node-negative patients with one or two nodes positive for micro/macrometastases and receiving standard schedules of adjuvant treatments. It seems likely that completion ALND can be safely omitted in selected patients, although longer term follow-up data are essential [2,3]. The concept of SLN biopsy being therapeutic is gaining widespread acceptance within the breast cancer community and influencing routine practice [4]. Patient selection criteria used within the Z0011 trial are being applied with variable degrees of stringency – recent surveys suggest that up to one-quarter of breast units are still undertaking completion ALND for micrometastases only [5]. Amongst those patients with limited node involvement who are treated with breast conserving

KEYWORDS

• axillary conserving therapy
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surgery (BCS) and systemic therapy, SLN biopsy alone does not lead to inferior survival outcomes in terms of regional control, disease-free nor overall survival compared with SLN biopsy and completion ALND. The latest American Society of Clinical Oncology guidelines state that women with one or two metastatic sentinel nodes following BCS with whole breast irradiation and systemic therapy can avoid completion ALND [1]. There remains uncertainty about precise details of radiation fields to the lower axilla and further information is awaited. There was consensus agreement at Kyoto Breast Cancer Consensus Conference that completion ALND should not be recommended for patients with SLN micrometastases only. The panel acknowledged that approximately 50% of breast surgeons have embraced results of the ACOSOG Z0011 trial and modified axillary surgery for BCS patients with a low axillary tumor burden (≤ 2 sentinel lymph node macrometastases). It remains unclear whether primary mastectomy patients can safely avoid ALND for ≤ 2 sentinel nodes containing macrometastases. Neither the Z0011 nor IBCSG 23-01 trials specifically addressed this issue although the AMAROS trial randomized patients with both partial and total mastectomy to ALND or radiation therapy [2–3,6–7]. By contrast, the POSNOC trial randomizes mastectomy and BCS patients with one or two macrometastatic nodes to either no further surgery or completion ALND [8]. In the AMAROS trial, the sentinel node was positive in 51% of patients with multifocal tumors and in 28% of patients with unifocal lesions; additional nonsentinel lymph node metastases were found in 40% of the multifocal group and in 39% of the unifocal disease group [6]. Both completion ALND (to level III) and ART following SLN biopsy provided equivalent regional disease control, but ART was associated with much lower rates of lymphedema. Therefore both axillary dissection and radiotherapy provide good loco-regional control for node-positive patients, but radiotherapy is associated with lower rates of lymphedema (21.7 vs 40%; $p < 0.001$) in short-term follow-up. KBCCC2014 highlighted a hybrid procedure termed “conservative axillary regional excision” (CARE) which has been described by Japanese surgeons and involves removal of tracer sentinel and other palpably suspicious lymph nodes. Neither intraoperative frozen section nor reoperation for node-positive cases was undertaken as part of CARE and the

regional recurrence rate among a group of pN1 patients was relatively low (3.4%) [7]. Those patients with limited metastatic tumor burden (1 or 2 sentinel nodes with macrometastases; metastatic ratio ≤ 0.5) would be suitable for ACT as part of contemporaneous practice. The presence of extra-nodal spread or extensive infiltration of 3 or more sentinel nodes would warrant more intensive regional therapy with completion ALND and supraclavicular nodal irradiation/internal mammary nodal irradiation.

An important question is whether or not ACT (be this SLN biopsy alone or combined with ART) is appropriate for patients who have undergone mastectomy and for whom post-mastectomy radiotherapy (PMRT) is planned. In the AMAROS trial, both partial and total mastectomy cases with a positive SLN biopsy were randomized to ALND or radiation therapy to the axillary and supraclavicular nodal basins. There was no significant difference for either regional disease control or overall survival suggesting that radiation therapy can effectively suppress loco-regional disease recurrence in selected patients with low volume nodal disease [6]. Since PMRT is indicated for some node-positive patients, ACT could be evaluated among (total) mastectomy patients to reduce rates of lymphedema. Contemporary analyses have demonstrated how axillary recurrence has decreased dramatically consequent to advances in systemic treatment and radiation therapy, suggesting that ACT might be applicable to patients responding well to PST [4].

Pathological nodal status and breast tumor response following PST predicts for locoregional recurrence and guides use of adjuvant radiotherapy [8,9]. Patient selection and timing of SLN biopsy in the context of PST remains controversial; SLN biopsy undertaken prior to PST minimizes risk of a false negative result and may allow more accurate pathological staging [10,11]. Knowledge of nodal response to PST provides prognostic information, although it is uncertain whether PMRT should be based upon pathological nodal status after PST as well as clinical stage at presentation. Whether response to PST can select those patients most likely to benefit from PMRT is unknown [12]. The National Surgical Adjuvant Breast and Bowel Project B-32 trial confirmed high rates of identification for SLN biopsy in clinically node-negative disease (92.6%) with an overall false-negative rate (FNR) of 9.8% [11]. However,

the ACOSOG Z1071 (Alliance) trial reported FNR of 12.6% among women with clinically N1 disease receiving PST who had two or more sentinel nodes examined [12]. In the German SENTINA study, patients who converted after PST from cN+ to ycN0, had detection rates of 80.1% while the FNR was 14.2%, similar to Z1071 for this category of patients. However, the FNR was much higher (24.3%) when only a single node was removed and 51.6% in patients who had a second SLN biopsy procedure after PST [13]. In clinically node-positive patients who had SLN biopsy after PST, the false negative rate decreased to 8.6% with dual tracer methodology (blue dye and radioisotope) and at least three nodes dissected. When nodal involvement is proven by core biopsy/fine needle aspiration cytology or strongly suspected by sonographic features, SLN biopsy should be considered after PST if a favorable tumor response is anticipated (pCR or near pCR). Removal of more than two sentinel nodes improves accuracy of SLN biopsy in clinically N1 patients following PST. Several ongoing clinical trials are assessing the role of post-PST SLN biopsy (details are not shown). There was discussion at Kyoto Breast Cancer Consensus Conference of whether fluorescence imaging with indocyanine green can offer advantages for detection of SLNs after PST [14–16]. For clinically and sonographically node-negative patients, SLN biopsy before PST should be considered for staging purposes and can influence decision-making for systemic therapies and radiation therapy. However, it is acceptable practice to undertake SLN biopsy either before or after PC and should involve dual localization techniques (blue dye and isotope) when core biopsy positive at presentation [13].

A positive SLN after PC (isolated tumor cells, micro-/macrometastases) should always prompt completion ALND which is also preferable in those patients who are SLN negative after PC but node positive initially. Intraoperative node assessment may become less relevant in the post-Z0011 era when increasing numbers of SLN positive patients receive no further axillary treatment (surgery or radiotherapy). There was general agreement that molecular thresholds for distinguishing between micro- and macro-metastases may have limited accuracy [17].

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