

## Identifying Gaps in the Locoregional Management of Early Breast Cancer: Highlights from the Kyoto Consensus Conference

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**ABSTRACT** A consensus conference was held to investigate issues related to the local management of early breast cancer. Here, we highlight the major topics discussed at the conference and propose ideas for future studies. Regarding axillary management, we examined three major issues. First, we discussed whether the use of axillary reverse mapping could clarify the lymphatic system of breast and whether the ipsilateral arm might help avoid lymphedema. Second, the use of an indocyanine green fluorescent navigation system was discussed for intraoperative lymphatic mapping. These new issues should be examined further in practice. Finally, some agreement was reached on the importance of “four-node diagnosis” to aid in the diagnostic accuracy of sentinel nodes. Regarding breast treatment, there was general agreement that the clinical value of surgical margins in predicting local failure was dependent on the tumor's intrinsic biology and subtypes. For patients treated with preoperative chemotherapy, less

extensive excision may be feasible in those who respond to systemic therapy in an acceptable manner. Most trials of preoperative chemotherapy lack outcome data on local recurrence. Therefore, there is a need for such data for overview analysis. We also agreed that radiation after mastectomy may be beneficial in node-positive cases where more than four nodes are involved. Throughout the discussions for both invasive and noninvasive disease, the investigation of nomograms was justified for major issues in the decision-making process, such as the presence or absence of microinvasion and the involvement of nonsentinel nodes in sentinel node-positive patients.

When the paradigm for breast cancer treatment shifted from the localized Halstedian view to Fisher's systemic vision, the role of surgery in the local management of breast cancer changed simultaneously. Appropriate local management is critical for the effective treatment of early breast cancer, because local recurrence might be a marker for the development of distant disease. In addition, reducing the failure of local treatment might result in the reduction of systemic treatment failure. Understanding the biological and pathological phenotype of breast cancer helps in constructing systemic therapeutic plans as well as in achieving successful individualized local management strategies.

Among the aspects of breast cancer treatment that have recently drawn attention, we have focused on the local

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management of primary noninvasive and invasive breast cancer, including: breast conservation in conjunction with preoperative systemic treatments; axillary management; radiation therapy for the breast, chest wall, and regional lymph nodes; and the pathological assessment of excised tissues. At the Kyoto Breast Cancer Consensus Conference, held in 2009, we clarified these issues for purposes of discussion and sought to reach a consensus.

## **PATHOLOGICAL ANALYSIS**

Tumor extension to the surgical margins of the resected specimen should be examined meticulously using appropriate inking protocols. Ductal carcinoma in situ (DCIS) found at an inked margin should be considered as a positive margin. The best method of manipulating the specimen to reveal the status of the margin (e.g., the use of a perpendicular cut versus Carter's orange peel technique) is controversial. Furthermore, no consensus was attained on the definition of negative margin. The definitions of a negative margin ranged from no tumor at the inked margin to an invasive tumor at a minimum of 5 mm from the edge. In addition, even greater margins have been proposed for DCIS when postoperative radiation therapy was not performed.

There was a lack of agreement about the number of levels of a frozen section required to adequately examine the sentinel lymph nodes. Other points of discussion included the appropriate use of cytokeratins and the type of methodology used (e.g., molecular or immunohistochemical analysis) (Table 1). Despite the differences in the definition of isolated tumor cells (ITC) and micrometastasis (MIC), there was general agreement that the presence of ITC should be considered node negative, whereas the presence of MIC (0.2–2 mm) should be considered node positive for staging purposes.<sup>1</sup>

In addition to histological grading according to the Nottingham criteria, the analysis of the status of cell proliferation using biomarkers such as the MIB1/Ki67 index provides important prognostic information.<sup>2</sup> To collect the data necessary to reach a consensus regarding controversial issues such as the definition of positive margins, it is recommended that each institution maintain precise records.

## **AXILLARY SURGERY**

Sentinel lymph node biopsy (SLNB) partially reduces the complications related to axillary staging by avoiding level I axillary lymph node dissection (ALND), level II ALND, and full ALND in the case of sentinel node-negative patients based on the reports of the ALMANAC experience.<sup>3</sup>

**TABLE 1** Pathological factors to be recorded while analyzing breast cancer specimens

|                             |  |
|-----------------------------|--|
| Tumor size                  | Measured microscopically in orthogonal directions including the largest size of invasion   |
| Margin                      | Method used to assess (orange peel or perpendicular cut)<br>Definition of positive margin<br>Distance of margin from cut edge (mm)<br>Additional treatment in positive cases (re-excision or boost RT)   |
| Biological markers          | ER (%)<br>PR (%)<br>HER-2 (IHC or FISH)<br>MIB1/Ki67 index (%)   |
| Other conventional factors  | Nuclear grade<br>Vessel invasion   |
| Fixation                    | Time to fixation<br>Time for fixation  |
| Sentinel lymph nodes (SLNs) | Techniques to identify SLNs (RI, dye, fluorescent or others)<br>Method of diagnosis (HE, IHC, molecular analysis or others)<br>Definition of metastasis<br>Number of excised SLNs<br>Number of positive SLNs<br>Number of frozen sections<br>Was ALND performed? |

*PR* progesterone receptor, *IHC* immunohistochemistry, *FISH* fluorescent in situ hybridization, *HE* hematoxylin and eosin

### *Lymphatic Mapping*

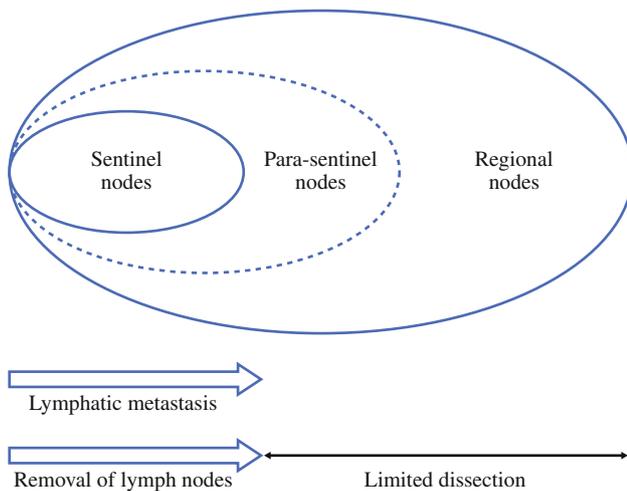
SLNB causes arm lymphedema in approximately 5–8% of patients, even when they are assessed at 6 months postoperatively. The axillary reverse mapping (ARM) procedure, which can clarify the anatomical relationship between the lymphatic system of the breast and the ipsilateral arm, may provide a method to avoid this complication.<sup>4</sup> In nearly 98% of primary breast cancer cases, the lymphatics from the arm, which were identified with a subcutaneous injection of blue dye in the volar surface of the upper arm, did not drain into the sentinel lymph node of the breast. This method should be standardized for common practice.

Another novel and highly sensitive method for visualizing the lymphatic system and the sentinel lymph nodes involved indocyanine green fluorescent (ICGf) navigation.<sup>5</sup> A photodynamic eye that recognizes fluorescence emission from protein-binding ICG enables real-time mapping of the lymphatic network. It was generally agreed that further

studies, such as clinical trials and long-term outcome studies, are needed to elucidate the issue of lymphatic mapping and determine the ultimate impact of these modalities on the incidence of lymphedema. It is necessary to determine more precisely the value of combination of ICGf with radioisotope (RI) in prospective studies.

*Number of Nodes Required for Diagnosis*

Non-SLN metastases have been reported in 4–7% of SLN-negative cases.<sup>6</sup> It is crucial to consider the number of nodes that should be excised for diagnosis and staging and from the perspective of the therapeutic benefit of local control.<sup>7–11</sup> We agreed that examination of four SLN-containing nodes was sufficient to determine the status of metastases in the axilla. There were indications that four-node diagnosis would help to avoid unnecessary ALND and may enable less extensive axillary surgery (Fig. 1). Another important issue discussed was lymph node dissection for SLN-positive patients. Several studies have indicated that it may be possible to avoid subsequent axillary dissection in certain subgroups of node-positive patients.<sup>12–14</sup> Table 2 summarizes these options.



**FIG. 1** Limited axillary lymph node dissection

**TABLE 2** Impact of four-node diagnosis for sentinel nodes on subsequent ALND

| No. of involved nodes | Requirement for completion of ALND |
|-----------------------|------------------------------------|
| 0 (ITC included)      | Avoidable                          |
| 1–3                   | Avoidable (individually)           |
| More than 3           | Inevitable                         |

ITC isolated tumor cells

*SLNB Prior to Systemic Therapy*

Although SLNB before preoperative systemic therapy (PST) under local anesthesia is difficult, we concluded at the meeting that it is useful for the purpose of confirming the nodal status, especially in clinically node-negative cases. In clinically node-positive cases, SLNB before PST is controversial. The nodal information is important for designing and individualizing therapeutic plans for local and systemic treatment, because the nodal status can be altered by the treatment.

SLNB after PST is also controversial.<sup>15</sup> The major concerns are the relatively high false-negative rate and the uncertainty in the conversion of the positive nodes to negative. Future studies are warranted to clarify the accuracy of lymphatic mapping after PST, including anti-human epidermal growth factor receptor 2 (HER2) therapies, and to develop nomograms to facilitate the decision-making process (Table 3).

*SLNB in DCIS*

SLN metastases were identified by RI lymphatic mapping in approximately 1.4% of 854 patients with pure DCIS.<sup>16</sup> Most of these patients underwent complete ALND, and only one of these patients exhibited additional positive axillary lymph nodes. Several studies investigating the long-term outcomes of local control in proven DCIS cases determined that local failures were rare.<sup>17</sup> During the conference, there was general agreement that SLNB can be recommended for patients with DCIS who undergo mastectomy and for those diagnosed with invasive carcinoma upon final pathology. In addition, there was agreement that SLNB should be avoided in patients with needle biopsy-proven DCIS and without high risk factors for invasive cancer who undergo breast-conserving surgery (BCS). Therefore, the development of an algorithm to predict potential invasion and thus avoid SLNB for needle biopsy-proven DCIS (Table 3) is warranted.<sup>18</sup>

**BREAST SURGERY**

*Ipsilateral Breast Tumor Recurrence (IBTR)*

It is difficult to decide upon one margin width that is appropriate for all patients.<sup>19</sup> Opinions about the minimal acceptable margin in local breast cancer resection varied from less than 5 mm to more than 20 mm. The recommendations were divided into three major categories based on tumor location: within 5 mm, tumor within 2 mm, and tumor at the margin. With respect to the re-excision criteria in the case of BCS, the consensus was that a 2 mm radial margin was satisfactory and should not prompt

**TABLE 3** Nomogram for breast cancer

| Decision factors | Decision goal  |
|------------------|--|
| DCIS             | To determine whether SLNB is required by examining possible microinvasion <sup>46</sup>    |
| PST              | To determine the type of surgery required by examining possible pCR <sup>47</sup>          |
| IBTR             | To determine whether RT or re-excision is necessary <sup>48</sup>                          |
| SLNB             | To determine whether ALND is required by predicting non-SLN metastasis <sup>18,49–52</sup> |

re-excision.<sup>20</sup> For a close margin (i.e., 2–5 mm), boost irradiation can be considered.

The 20-year follow-up data from the National Surgical Breast and Bowel Project (NSABP) B-06 trial showed that 39.2% of the patients who received wide local excision without radiotherapy developed ipsilateral breast tumor recurrence (IBTR), as compared with 14.3% of those who received postoperative radiotherapy. Some believe that IBTR does not influence overall survival and that it can be considered a marker of distant metastases rather than a cause; its presence therefore cannot change the intrinsic risk of distant disease.<sup>21</sup> However, according to a meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), the impact of local radiation therapy (RT) to prevent local recurrence, either to the breast following BCT or to the chest wall after mastectomy, exhibited overall survival benefit in patients with greater than 10% risk of local recurrence, but it did not show any benefit in patients with less than 10% risk of local recurrence.<sup>22</sup> An analysis of hazard ratios for distant metastases in patients who had undergone breast-conservation surgery with or without postoperative radiotherapy indicated that local recurrence might be a cause of distant metastases.<sup>23</sup> These results suggested that the group with a high risk for locoregional recurrence gained a survival benefit from local radiotherapy. In addition, local relapse could be a crucial psychological stressor for a patient even if her long-term survival was unaffected.

### PST

In the case of sequential chemotherapeutic regimens such as doxorubicin and cyclophosphamide (AC) followed by a taxane, the pathological complete remission (pCR) rates are higher in patients who responded to the preceding regimen than in nonresponders. Furthermore, combining chemotherapy with an anti-HER2 treatment such as trastuzumab resulted in even higher pCR rates in HER2-positive cases.<sup>24</sup> A multidisciplinary team, which included an attending surgeon, a radiologist, a medical oncologist, and a pathologist, was indispensable in making appropriate decisions regarding

BCS after PST. The findings also led to the recommendation that long-term outcome data, particularly data related to local recurrence rates, and methodologies for assessing the response and success of treatment should be collected, analyzed, and clarified at each institution.<sup>25</sup>

The large majority of the attendees agreed that neoadjuvant endocrine treatment (NAET) is an acceptable approach for certain patients, including those with low-grade, estrogen receptor (ER)-positive breast cancers and postmenopausal patients. Recent studies have suggested that NAET provides higher breast-conservation rates. Nevertheless, because of a lack of randomized clinical trial data, especially on local recurrence, this issue remains to be studied with respect to the tailoring of treatment using biomarkers.<sup>26</sup> Future studies are required to investigate the factors that are predictive of a shrinkage pattern in tumors that have responded to NAET and to determine their postoperative prognosis.

### Hereditary Breast Cancer

There was some consensus that patients at higher risk for local recurrence or development of breast cancer in the contralateral breast due to genetic mutations (e.g., *BRCA1* or *BRCA2*) require a more aggressive surgery than BCS. Although this is a controversial topic, the risks of IBTR and of developing contralateral breast cancer may be higher in patients with *BRCA* abnormalities. Therefore, performing a bilateral mastectomy may be preferable to BCS. In addition, performing a bilateral mastectomy would avoid use of RT in a majority of patients. Fifteen years of follow-up data from postoperative radiotherapy in *BRCA* patients suggested that there is a higher risk of radiation toxicity in these patients. Taking these data together, bilateral mastectomy for this specific subgroup could result in reducing cancer recurrence in the affected breast, decreasing new breast cancer development in the unaffected breast, and avoiding the late toxicity of radiotherapy.<sup>27–29</sup>

### BCS for DCIS

The Van Nuys Prognostic Index (VNPI), originally proposed and validated by Silverstein et al., is a scoring system for predicting the risk of IBTR in DCIS patients undergoing BCS. Three major factors—margin status, high histological grade, and young age—were recognized as significant risk factors for IBTR after resection of DCIS. The distribution of the opinions as to the proper margin needed for DCIS was similar to that for invasive ductal carcinoma (IDC).

Several retrospective studies have suggested that RT after BCS is useful in avoiding IBTR, especially in patients with high-risk DCIS.<sup>30,31</sup> Tamoxifen in combination with RT has

also been reported to decrease IBTR in DCIS.<sup>32</sup> Prospective trials of neoadjuvant therapies for DCIS using trastuzumab or lapatinib have recently been initiated. These trials may elucidate the effect of anti-HER2 treatments on the local management of HER-2-neu-overexpressing DCIS.

Dunne et al. performed a meta-analysis of 4,660 cases identified from Medline with regard to the margins required for DCIS and RT. They found that a negative margin significantly reduced the risk of IBTR compared with a close margin, and a 2-mm margin was superior to a margin less than 2 mm. However, they observed no significant differences in the IBTR rates with margins over 2 mm.<sup>33</sup> Fisher et al. demonstrated the benefit of tamoxifen in the treatment of DCIS in NSABP B-24, a randomized controlled trial.<sup>34</sup> Because these data suggest that BCS alone is insufficient to prevent IBTR after surgery for DCIS, there was consensus at the meeting that RT and/or endocrine therapy is necessary after BCS.

## RADIATION THERAPY

### *RT as a Component of the Local Management of Breast Cancer*

Postoperative RT reduces the risk of locoregional recurrence to approximately one-third of that without RT. Although the baseline risks have varied among existing reports, depending on the method of surgery and the pathological evaluation, the relative risk reduction related to RT was consistent.<sup>22</sup>

For each group of patients who received BCS, there have been continual efforts to find a subgroup of patients who do not require RT.<sup>32,35–38</sup> Unfortunately, such a subgroup had not yet been identified in a prospective trial. However, the eligibility criteria and systemic treatment used in early clinical trials were suboptimal in comparison with today's standards.<sup>32</sup> A clinical trial in a selected group of patients, which included individuals over 70 years old with hormone-responsive tumors treated with a suitable resection margin and appropriate hormonal therapy, demonstrated that the absolute reduction in the risk of local recurrence due to RT, although significant, was small enough that omission of RT could be considered.<sup>32</sup> It is suggested that the intrinsic subtype of breast cancer might be an independent predictive factor related to the benefit of postoperative RT.<sup>39,40</sup> At the meeting it was indicated that these findings should be verified in prospective trials.

### *Trends in Postoperative Irradiation for the Conserved Breast*

Both hypofractionated whole-breast RT and accelerated partial-breast irradiation (APBI) were increasingly used

after BCT. Hypofractionated whole-breast RT demonstrated equivalent tumor control and cosmetic results compared with conventional fractionation.<sup>41,42</sup> In the consensus conference, we discussed hypofractionation as an option for certain patients, such as those who are margin free. However, APBI is still considered an experimental treatment.

### *Indication for Boost to the Tumor Bed after BCT*

Although a large randomized clinical trial demonstrated a significant reduction of IBTR in patients with a negative margin, we were unable to reach a consensus on the indications for an RT boost. The most important issue to be resolved was the definition of a "positive" margin after BCS. This definition varied by country and region.<sup>43</sup> Therefore, it should be further examined whether patients with positive margins benefit from routine administration of boost irradiation after whole-breast radiation therapy. At the consensus conference, approximately half of the participants responded that boost irradiation is not necessary if the margin is greater than 5 mm.

In addition to the dose dependency of the ipsilateral tumor control, the European Organisation for Research and Treatment of Cancer (EORTC) 22881-10882 trial clearly demonstrated that younger patients receive a greater benefit from boost irradiation secondary to their greater baseline risk of IBTR. However, in this consensus conference, approximately half of the participants answered that young age alone is not a sufficient criterion for providing a boost, if the margin is widely clear. To resolve this issue, we must standardize the definition of a positive margin, clarify the relationship between the distances required for a clear margin, and understand the magnitude of the effect of boost irradiation.

### *Survival Benefit of Postoperative RT for Breast Cancer*

Meta-analyses performed by EBCTCG demonstrated that a reduction in the risk of locoregional recurrence at 5-year postoperative follow-up could eventually lead to a reduction in death from all causes at 15-year postoperative follow-up.<sup>30</sup> This survival benefit was attributed to prevention of secondary dissemination from local recurrence. However, the benefit was substantial only if the absolute risk reduction of the locoregional recurrence at 5 years exceeded 10%.

Currently, patients with four or more positive lymph nodes are regarded as being at high risk for local recurrence. Postoperative RT to the supraclavicular lymph nodes and the chest wall and breast are recommended in this group after both breast-conserving surgery and mastectomy. Furthermore, meta-analyses of existing trials have

suggested that patients with one to three positive lymph nodes might also receive a survival benefit from postoperative RT, although a randomized clinical trial investigating this hypothesis is ongoing. Patients with negative axillary lymph nodes generally exhibit a low risk of local recurrence. These patients do not benefit from such RT and may have increased risks of radiation side-effects if RT is given. Of note, the number of positive axillary lymph nodes in this context is only a surrogate for the risk of isolated locoregional recurrence. The indication for postoperative RT should ultimately be based on the absolute risk of local recurrence.

### *Postoperative Radiation Therapy in Patients Receiving PST*

Recently, PST has been offered not only to patients with advanced disease but also to patients with early-stage breast cancer. The expansion of this practice has unveiled a new clinical question: What is the optimal RT dose for patients who respond favorably to PST? Randomized trials are needed to answer this question. However, the general consensus was that, for all patients who receive PST and BCS, postoperative RT is recommended. Retrospective studies of patients who received a mastectomy after PST showed that RT significantly improved local control even in patients with pCR after PST.<sup>44</sup> These investigators also found that RT improved survival in patients at higher risk of locoregional recurrence after PST and mastectomy.<sup>45</sup> These results provide insight that the decision to offer RT should be based on both the pretreatment assessment and the final pathologic findings. Postoperative RT is recommended for patients initially diagnosed as having a high risk of locoregional recurrence, regardless of their response to PST.

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