Identifying gaps in the local-regional 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 that 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 the overview analysis. We also agreed that radiation after mastectomy may be beneficial in node-positive cases where more than 4 nodes are involved.

Throughout the discussions for both invasive and non-invasive 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 non-sentinel nodes in sentinel node-positive patients.

Running title: Local management of early breast cancer

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Introduction:

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 management of primary non-invasive and invasive breast cancer, focusing on 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 in 2009, we clarified these issues for purposes of discussion and sought to reach a consensus.

I. 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 post-operative 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) [1], there was a general agreement that the presence of ITC should be considered node-negative, whereas the presence of MIC (0.2 mm - 2 mm) should be considered node-positive for staging purposes.

In addition to histological grading according to the Nottingham criteria, the analysis of the status of cell proliferation using biomarkers such as MIB1/Ki67 index provides important prognostic information [2]. 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.

II. Axillary surgery

Sentinel lymph node biopsy (SLNB) partially reduces the complications related to axillary staging by avoiding Level I axillary lympho 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 [3].

1. Lymphatic mapping

SLNB causes arm lymphedema in approximately five to eight percent of patients, even when they are assessed at six 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 [4], may provide a method to avoid this complication. In nearly 98 percent of primay 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 ICGf navigation [5]. A photodynamic eye that recognized 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 RI in prospective studies.

2. Number of nodes required for diagnosis

Non-SLN metastases have been reported in four to seven percent of SLN-negative cases [6]. 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 [7-11]. We agreed that the examination of four SLN-containing nodes was sufficient to determine the status of metastases in the axilla. There were indications that the 4-node diagnosis would help to avoid unnecessary ALND and may enable less extensive axillary surgery (Figure 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 [12-14]. Table 2 summarizes these options.

3. 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 confirm 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 [15]. 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-HER2 therapies, and to develop nomograms to facilitate the decision-making process (Table 3).

4. SLNB in DCIS

SLN metastases were identified by RI lymphatic mapping in approximately 1.4% of 854 patients with pure DCIS [16]. 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 DCIS proven cases determined that local failures were rare [17]. During the conference, there was general agreement that SLNB can be recommended for patients with DCIS who undergo mastectomy and for those who 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 [18].

III. Breast surgery

1. Ipsilateral breast tumor recurrence (IBTR)

It is difficult to decide one margin width that is appropriate for all patients [19]. 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 re-excision [20]. 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 [21]. However, according to a meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group, 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 [22]. An analysis of hazard ratios for distant metastases in patients who had undergone breast conservation surgery with or without post-operative radiotherapy indicated that local recurrence might be a cause of distant metastases [23]. These results suggested that the group with a high risk for loco-regional 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.

2. PST

In the case of sequential chemotherapeutic regimens such as AC followed by a taxane, the pathological complete remission (pCR) rates are higher in patients who responded to the preceding regimen than in non-responders. Furthermore, combining chemotherapy with an anti-HER2 treatment such as trastuzumab resulted in even higher pCR rates in HER2-positive cases [24]. 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 [25].

The large majority of the attendees agreed that neoadjuvant endocrine treatment (NAET) is an acceptable approach for certain patients, including those with low-grade, 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 [26]. 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.

3. Hereditary Breast Cancer

There was some consensus that the patients at higher risk for the 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 the use of RT in a majority of patients. Fifteen years of follow-up data from post-operative 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 [27-29].

4. 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 the resection of DCIS. The distribution of the opinions as to the proper margin needed for DCIS was similar to that for

IDC.

Several retrospective studies have suggested that RT after BCS is useful in avoiding IBTR, especially in patients with high-risk DCIS [30,31]. Tamoxifen in combination with RT has also been reported to decrease IBTR in DCIS [38]. 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 4660 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 [32]. Fisher et al. demonstrated the benefit of tamoxifen in the treatment of DCIS in NSABP B-24, a randomized controlled trial [33]. 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.

IV. Radiation Therapy

1. RT as a component of the local management of breast cancer

Post-operative RT reduces the risk of loco-regional recurrence to approximately 1/3 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 [34].

For each group of patients who received BCS, there have been continual efforts to find a subgroup of patients who do not require RT [35-39]. 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 to today’s standards [38]. 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 the omission of RT could be considered [38]. It is suggested that the intrinsic subtype of breast cancer might be an independent predictive factor related to the benefit of postoperative RT [40,41]. At the meeting it was indicated that these findings should be verified in prospective trials.

2. 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 to conventional fractionation [42,43]. 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.

3. 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 [44]. Therefore, it should be further examined whether the patients with positive margins benefited 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 larger than 5 mm.

In addition to the dose dependency of the ipsilateral tumor control, the 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 in 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.

4. Survival benefit of post-operative RT for breast cancer

Meta-analyses performed by EBCTCG demonstrated that a reduction in the risk of loco-regional recurrence at the 5-year postoperative follow-up could eventually lead to a reduction in death from all causes at the 15-year postoperative follow-up [30]. This survival benefit was attributed to the prevention of secondary dissemination from local recurrence.

However, the benefit was substantial only if the absolute risk reduction of the local-regional recurrence at 5 years exceeded 10%.

Currently, patients with 4 or more positive lymph nodes are regarded as being at high risk for local recurrence. Post-operative 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 1 to 3 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 loco-regional recurrence. The indication for post-operative RT should ultimately be based on the absolute risk of local recurrence.

5. Post-operative 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 [45]. These investigators also found that RT improved survival in patients at higher risk of loco-regional recurrence after PST and mastectomy [46]. These results provide insight sthat the decision to offer RT should be based on both the pre-treatment assessment and the final pathologic findings. Postoperative RT is recommended for patients initially diagnosed as having a high risk of loco-regional recurrence, regardless of their response to PST.

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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)
	Definition of positive margin
	Distance of margin from cut edge (mm)
	Additional treatment in positive cases (re-excision or boost RT)
Biological Markers	
	ER (%)
	PR (%)
	HER-2 (IHC or FISH)
	MIB1/Ki67 index (%)
Other conventional factors	
	Nuclear grade
	Vessel invasion
Fixation	
	Time to fixation
	Time for fixation
Sentinel lymph nodes (SLNs)	
	Techniques to identify SLNs (RI, Dye, Fluorescent or others)
	Method of diagnosis (HE, IHC, Molecular analysis or others)
	Definition of metastasis
	Number of excised SLNs
	Number of positive SLNs
	Number of frozen sections
	Was ALND performed?

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

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

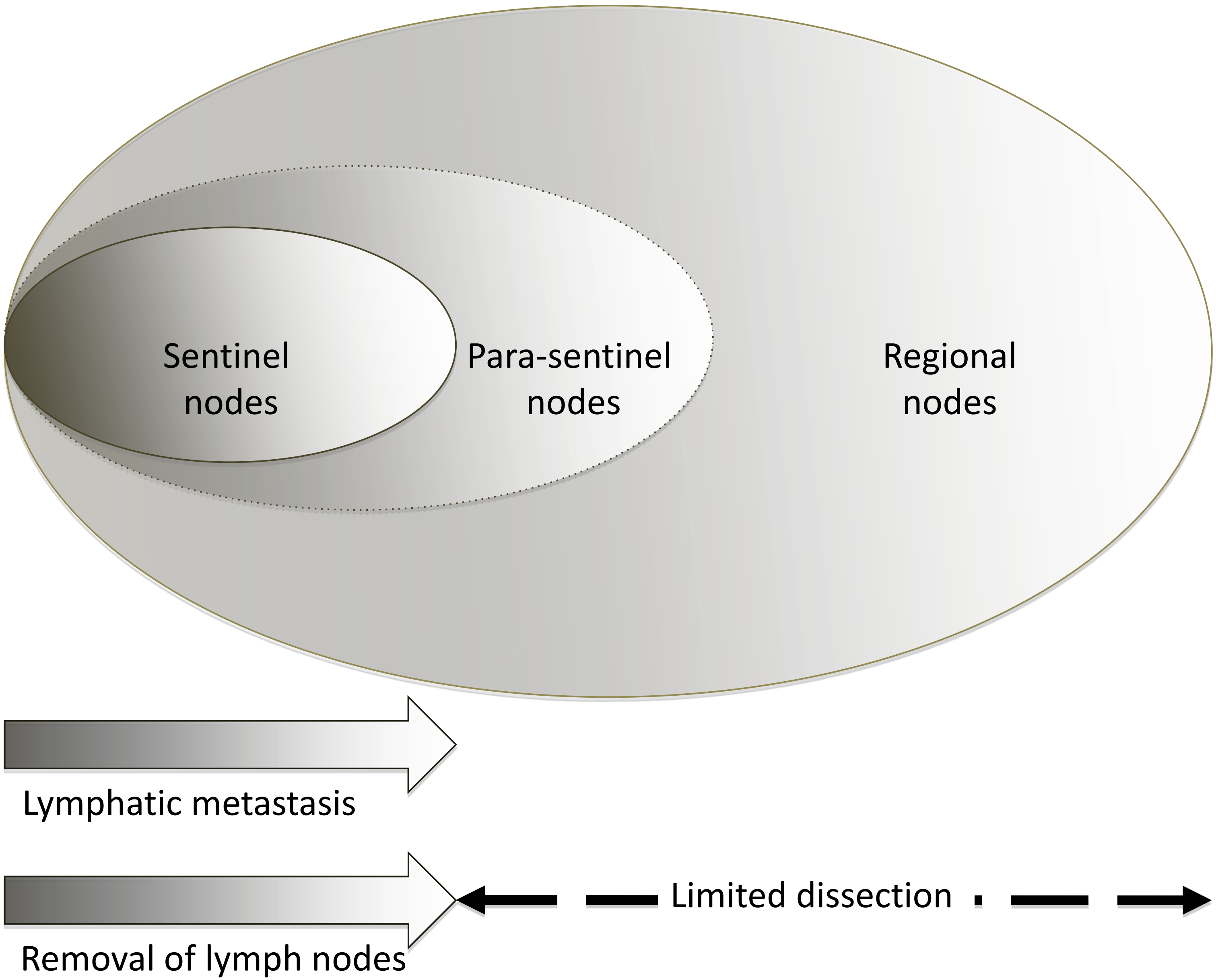
ITC: isolated tumor cells

TABLE 3. Nomogram for breast cancer

Decision factors	Decision goal
DCIS	To determine whether SLNB is required by examining possible micro-invasion [47]
PST	To determine on the type of surgery required by examining possible pCR [48]
IBTR	To determine whether RT or re-excision is necessary [49]
SLNB	To determine whether ALND is required by predicting non-SLN metastasis [50-54]

Figure 1. Limited axillary lymph node dissection

Figure 1


Sentinel nodes
Para-sentinel nodes
Regional nodes
Lymphatic metastasis
Removal of lymph nodes
Limited dissection