Kinoshita et al., 2009; Nanjo et al., 2011), thereby providing clues to effective nursing interventions. We identified 'half fusiform shape over the dressing' as a key morphological characteristic of MAD. This shape was observed at the edge of the breast, possibly sug gesting exudate leakage along this edge. We also consider 'radial shape matching the dressing' to be a morphological characteristic of MAD and suggest that this is caused by the skin coming in contact with excess wound exudates absorbed by the dressing. Other non MAD types of morphological characteristics were also identified in the peri wound skin. Dermatitis with 'line shape matching the tape' may be caused by repeated tape stripping (Mohammed et al., 2011), contact dermatitis related to the adhesive tape (Russell and Thorne, 1955) or sweat or wound exudates pre sent at the taping site. The 'erythema' of the dermatitis that appeared in 'shape matching the subcutaneous tumour' in 'elevated portion of the subcutaneous tumour' or 'irregular shape spreading over the trunk' in 'body trunk' may be considered as a morpho logical characteristic of cancer (Manning, 1998; Thiers, 1986). These findings may make it possible to distinguish between MAD and other skin changes. This distinction is clinically very important because nurses have many options for wound care in cases of MAD (leakage check, selection of dressing, method for attaching the dressing or assessment of daily self care activities). In this context, our morphoqualitative analyses of MAD are quite important for evaluating the possible causes of MAD as well as for selecting effective interventions.

Necrotic tissue type and wound exudate leakage were identified as factors related to MAD surrounding MBWs. Debridement of necrotic tissues is usually encouraged to prevent bacterial infection or colonisation [European Wound Management Association (EMWA), 2004]. However, debridement is not recommended for MBWs because of bleeding risk. It is thus reasonable to consider that the thick necrotic tissue associated with MBWs may be a focus of infection (Anazawa, 2005). Cameron et al. (Cameron and Powell, 1996) reported that exudates from some types of ulcers may contain a component that irritates the skin, leading to eczema or even loss of epithelium. Notably, they found that exudates from infected wounds may be even more irritating. We consider that MAD in our patients could have been caused by irritant exudates produced by bacteria. Further study is required before this point can be addressed in detail.

Our findings have several implications for nursing care of MBWs. Frequent dressing changes or the use of a more absorbent dressing are strongly recommended for patients with MBW, particularly those with massive exudates or thick necrotic tissues. All patient behaviours in everyday life, such as changing clothes, should be carefully assessed to ensure that the dressing remains attached without exudate leakage. With respect to thick necrotic tissues, antimicrobial drugs or a silver dressing should be used to control the bacterial load. New wound care products should also be developed, such as an ointment or a dressing that will directly inactivate irritant exudates. It should be stressed that the contri bution of nurses is indispensable in this type of study because of the morphoqualitative analysis method used and because meticulous wound care cannot be achieved unless the nurses build an intimate rapport with their patients.

There are some limitations of this study. First, careful consid eration is required before our data related to the prevalence of MAD are extrapolated to the general population because the sample size of this study was small and a possible bias cannot be ruled out. In addition, we could not show a precise causal relationship between MAD and related factors because this was a cross sectional study. Histopathological observation is required for a more precise diag nosis of MAD, although biopsy was practically difficult in cases such as ours.

## Conclusion

This study revealed the prevalence and morphoqualitative characteristics of MAD surrounding MBWs.

It is important for nurses to understand the findings of MAD related to wound exudates ('radial shape matching the dressing' or 'half fusiform shape over the dressing') for appropriate skin care of patients with MBWs. Our study is important for evaluating the possible causes of MAD as well as selecting effective nursing in terventions by nurses. In brief, nurses could provide necessary care for patients with necrotic tissue type (thick and yellow or black necrotic tissue) and wound exudate leakage.

## Conflict of interest

None declared.

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REVIEW

# Axillary lymph node dissection in sentinel node positive breast cancer: is it necessary?

*Seigo Nakamura*

**Purpose of review**
Sentinel lymph node biopsy (SLNB) has become a gold standard procedure for axillary lymph node evaluation in clinically node negative patients. In those patients with positive SLNB, completion axillary lymph node dissection (ALND) has been routely performed. Recent clinical trials suggest that ALND is not necessary in some cases, even when the sentinel lymph node (SLN) is positive. The appropriate conditions under which ALND may be eliminated are defined in this review.

**Recent findings**
The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial studied the impact of SLNB alone versus completion axillary node dissection (AND) on survival in clinically node negative breast cancer patients undergoing partial mastectomy and whole breast irradiation who were found to have a positive SLN on pathological evaluation. Results of this study showed no survival advantage for complete AND in patients with one or two positive SLNs. In other words, those patients appeared to be treated safely without completion AND.

**Summary**
Despite the small sample size and limited stastical power and the relatively short median follow up for ACOSOG Z0011, many breast cancer teams no longer believe it mandatory to perform axillary dissection for patients with one or two positive SLNs. The results of other prospective randomized trials called After Mapping of the Axilla: Radiotherapy Or Surgery study and International Breast Cancer Study Group trial 23 01 study will be available soon, and may further change the confidence with which ALND is performed or eliminated.

**Keywords**
*After Mapping of the Axilla: Radiotherapy Or Surgery study, American College of Surgeons Oncology Group Z0011, axillary dissection, sentinel lymph node biopsy*

## INTRODUCTION

Sentinel lymph node biopsy has become a gold standard procedure for women with breast cancer who present with clinically negative axillary lymph nodes [1–4]. Lymphedema and paresthesias occur in approximately 5–8% of patients after sentinel node biopsy (SNB) and 10–20% of patients after axillary lymph node dissection (ALND) [5▪▪,6–9]. SNB is, thus, the optimum approach in terms of morbidity for the assessment of axillary metastasis in clinically node-negative breast cancer.

The results of American College of Surgeons Oncology Group (ACOSOG) Z0010 and National Surgical Adjuvant Breast and Bowel Project (NSABP) B32 trials help estimate the prevalence and prognostic significance of positive sentinel lymph nodes (SLNs) found only by immunohistochemistry [10–12]. Among patients with negative intraoperative frozen section who are found to be SLN positive on final pathologic examination, the risk of non-SLN metastases is low [13–15]. A growing number of patients are electing not to undergo completion ALND; a decision that may in part be due to the adoption of a predictive nomogram based on pathologic variables for the risk of non-SLN metastasis [16,17].

Retrospective studies have indicated that in up to 40–60% of cases with a positive sentinel node the sentinel node is the only positive node [13–15,18].

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## KEY POINTS

- From the result of ACOSOG Z0011, AND may safely be omitted in breast conservation patients whose tumor size is 5 cm or less with clinically node negative and who will have whole breast radiation and appropriate systemic adjuvant therapy.
- Because there are several critiques to ACOSOG Z0011, we should carefully follow up such patients who have not received axillary dissection and pay attention to the result of other similar studies (AMAROS study and International Breast Cancer Study Group 23 01.)

A positive SLN will prompt a recommendation for systemic therapy in the vast majority of women. Whether surgical excision of any positive nonsentinel nodes would improve long-term outcome has been an issue of uncertainty.

ACOSOG Z0011 is a prospective randomized trial to determine the effects of complete axillary node dissection (AND) on survival of patients with SLN metastasis of breast cancer [19,20▪▪]. Women who were eligible for the trial had tumors less than 5 cm, clinically negative axillary lymph nodes, lumpectomy to negative margins, no neoadjuvant chemotherapy, planned whole breast irradiation, and 1 or 2 positive SLNs. Almost all received systemic adjuvant chemotherapy and/or endocrine therapy. The results show that ALND is not associated with 5-year overall survival and 5-year disease-free survival. Cases of lymphedema were significantly higher in the ALND group. Therefore, this study does not support the routine use of ALND in breast cancer with 1–2 involved SLNs and undergoing breast conserving therapy including whole breast irradiation. This requires that the role of ALND be reconsidered [21▪].

## THE MANAGEMENT OF ISOLATED TUMOR CELLS OR MICROMETASTASIS IN SENTINEL NODES

It has been a standard practice to perform ALND in breast cancer patients with positive SLN, and this is done in the majority of patients. However, controversy exists over the management of patients found to have positive SLN by immunohistochemical (IHC) staining alone. Tan *et al.* [22] reported worse survival for patients with occult metastasis detected by serial sectioning and immunohistochemistry. The results of the ACOSOG Z0010 and NSABP B32 trials will help estimate the prevalence and prognostic significance of positive SLN found only by immunohistochemistry [23,24]. A systematic review by Bear *et al.* also concluded occult axillary node metastases detected by serial sections and/or IHC staining of SLN are prognostically significant [24]. However, NSABP B-32 showed the magnitude of the difference in outcome at 5 years was quite small (1.2 percentage points) [25]. Therefore, there appears to be little clinical benefit of including IHC analysis of hematoxylin and eosin stained negative sentinel nodes in patients with breast cancer [26].

## THE MANAGEMENT OF AXILLARY MACROMETASTASIS: RETROSPECTIVE STUDY

Veronesi *et al.* [26] from the European Institute of Oncology presented 10-year follow up of their single-institution trial designed to compare outcomes in patients who received no axillary dissection if the sentinel node was negative, with patients who received complete axillary dissection. From March 1998 to December 1999, 516 patients with primary breast cancer under 2 cm were randomized either to SNB and complete axillary dissection (axillary dissection arm) or to SNB with axillary dissection only if the sentinel node contained metastases (sentinel node arm). Eight patients in the axillary dissection arm had false-negative sentinel nodes on histologic analysis: a similar number [8, 95% confidence interval (CI) 3–15] of patients with axillary involvement was expected in sentinel node arm patients who did not receive axillary dissection; but only two cases of overt axillary metastasis occurred. There were 23 breast cancer-related events in the sentinel node arm and 26 in the axillary dissection arm (log-rank, $P = 0.52$), whereas overall survival was greater in the sentinel node arm (log-rank, $P = 0.15$). They concluded that preservation of healthy lymph nodes may have beneficial consequences. Even though there might be around 5% false-negative rate in the sentinel node arm, axillary dissection should not be performed in clinically node-negative patients without performing SNB.

Spiguel *et al.* [27▪] retrospectively reviewed their institution's 12-year experience with SNB alone for a tumor-positive sentinel node. Among 3 806 patients who underwent SNB, 2 139 underwent SNB alone, of which 1 997 were tumor negative and 123 were tumor positive. Sentinel nodes were staged node-positive (N1mic or N1) according to American Joint Committee on Cancer criteria.

Mean age was 57 years (range 32–92 years) and mean tumor size was 1.9 cm (range 0.1–9 cm). Eighty-nine (72%) underwent lumpectomy and 34 (28%) underwent mastectomy. Ninety-three percent of patients underwent some form of adjuvant

therapy. Forty-two patients (34%) did not undergo radiation and there were no axillary recurrences in this group. At median follow-up of 95 months, there has been only one axillary recurrence (0.8%) and 13 deaths, four of which were attributed to metastatic breast cancer and the rest to nonbreast-related causes.

They also concluded that axillary recurrence is rare after SNB alone especially in case of favorable patient or tumor characteristics (older age, ER positive and Her2 negative etc.) and standard use of adjuvant therapy.

The German Clinical Interdisciplinary Sentinel study was a large prospective randomized phase III trial performed in 33 German centers [28▪]. One thousand one hundred and eighty two patients with operable, clinically node negative and invasive breast cancer were equally randomized to either a strategy of standard axillary dissection (SAD) independent of the SNB finding (SAD arm, $n = 594$), or to a strategy of performing SAD only in case of a positive SNB finding or failure of sentinel node detection (control arm, $n = 588$), but observation only in patients with negative SNB. The trial was designed to exclude an absolute difference in relapse-free survival (RFS) of 5% after 5 years with sufficient confidence. After a maximum follow-up time of 115 months, a total of 93 RFS events (40/53) and a total of 53 death events (23/30) were observed. Comparisons of RFS yielded a hormone receptor of 1.44 (95% CI 0.95–2.18; $P = 0.084$), and of overall survival yielded a hormone receptor of 1.53 (0.88–2.66; $P = 0.13$). Paresthesia, lymphedema and pain were significantly less common in the SNB-negative group. It means that this trial also showed that the false-negative rate of SNB was negligible in terms of RFS and overall survival.

## THE MANAGEMENT OF AXILLARY MACROMETASTASIS: PROSPECTIVE STUDY AND ANOTHER APPROACH

ACOSOG Z0011 is a prospective randomized trial to determine the effects of complete AND on survival of patients with SLN metastasis of breast cancer. Eight hundred and ninety one clinically node-negative patients, T1N0 and T2N0, with one or two H&E positive SLNs (Fig. 1) were randomized to no further axillary surgery or to axillary dissection.

The trial was conducted among 115 centers in the United States between 1999 and 2004. The sample size was not reached to the targeted enrollment (1900 women with final analysis after 500 deaths), but the trial was closed early because mortality rate was lower than expected, and final follow up for data analysis was completed in 2010. [The result was presented at ASCO2010 (Fig. 2) and published in JAMA 2011 [19,20▪▪]].

Type of operation was not associated with outcome in 5-year overall survival (92.5% in the sentinel group, versus 91.8% in the axillary group, Fig. 3) and 5-year disease-free survival (83.9% of the sentinel node group, versus 82.2% of the ALND group (Fig. 4). About 70% of participants in the axillary lymph node group had side effects such as shoulder pain, weakness, infection and tingling, versus 25%

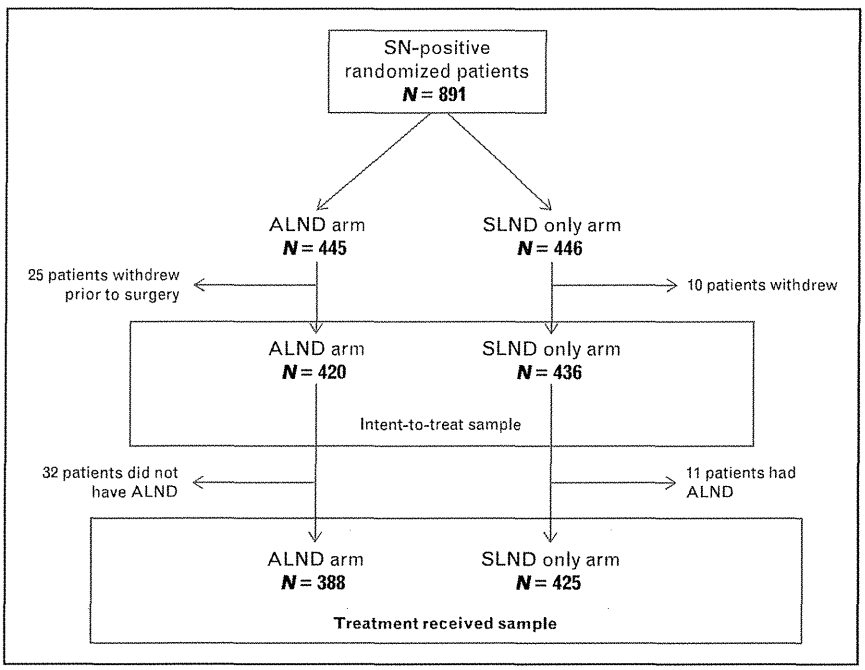


**FIGURE 1.** ACOSOSG Z0011 patient accrual. Adapted from [20▪▪].

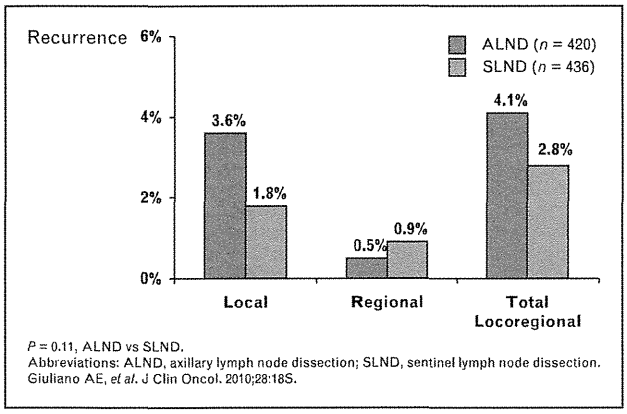


**FIGURE 2.** ACOSOG Z0011: 5 year recurrence rates. Adapted from [32].

in the sentinel group. Cases of lymphedema were significantly higher in the axillary group. Therefore, this study does not support the routine use of ALND in early nodal metastatic breast cancer in women undergoing breast conservation including whole breast irradiation.

Although additional axillary involvement was observed 27% in the ALND group, axillary recurrence rate was extremely low at 0.5% in the SLND group. There are several speculations. One is that systemic adjuvant treatment with hormonal therapy and/or chemotherapy has some effect in preventing locoregional recurrence. And the other is that tangent radiation fields used to the breast also covered the low axillary area and brought a therapeutic effect to the low axillary lymph nodes. Supporting this are the results of NSABP B-04, a trial comparing radical mastectomy (including ALND), total mastectomy without ALND, and total mastectomy with radiation therapy to the regional lymph nodes [27▪]. An update of this study with a median follow-up of 180 months (range 12–221 months) showed that long-term survival did not differ after axillary radiotherapy and axillary dissection. The only difference was better axillary disease control in the group with axillary dissection. In the Z0011 study, all the cases had the radiation to the residual breast, however, the radiation fields were not fully prescribed by the protocol, and the radiotherapy delivered is not fully specified.

There are several critiques for this study. First, the sample size is small because axillary recurrence was observed in two cases in the ALND group and four in the SLND group. Second, median follow up is 6.3 years and too short because most women (83%) had ER-positive cancers and would, thus, be expected to recur late.

From this study, AND may safely be omitted in breast conservation patients whose tumor size is 5 cm or less clinically node negative and who will have whole breast radiation and appropriate systemic adjuvant therapy.

There is another approach for sentinel node positive cases. Kim *et al.* [29] reported the significance of FDG-PET/CT to determine the indication of AND or SNB in breast cancer patients. They performed FDG-PET/CT scans in 137 biopsy-proven breast cancer patients planning to have an SNB to select patients for either AND (PET/CT N+) or SNB (PET/CT N0). In performing SNB, they also

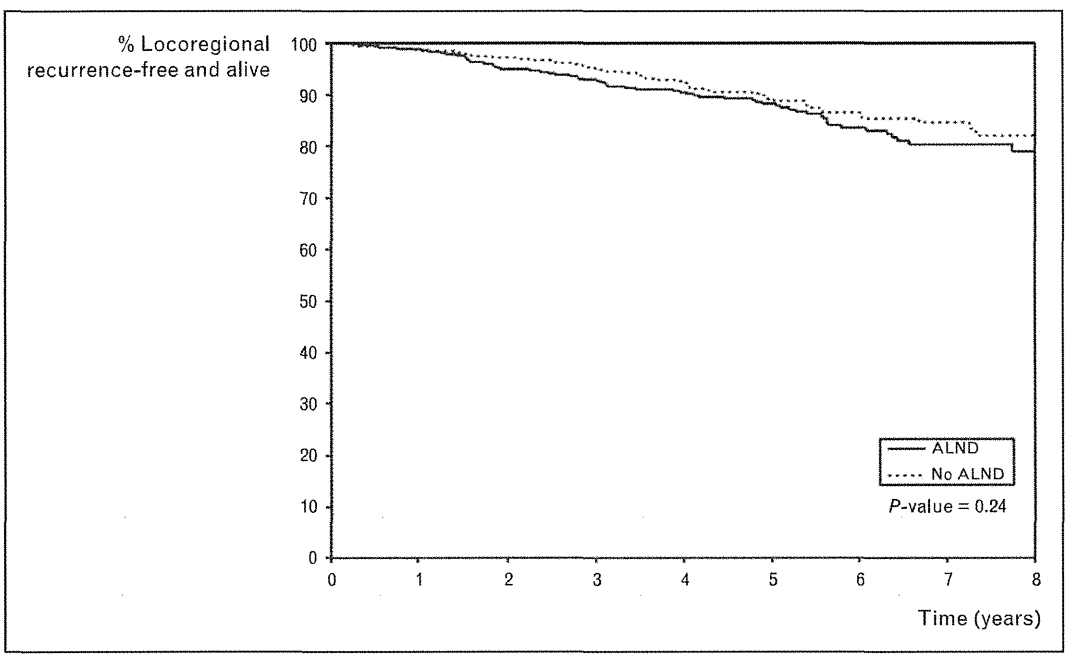


**FIGURE 3.** ACOSOG Z0011: recurrence free survival. Adapted from [20▪▪].

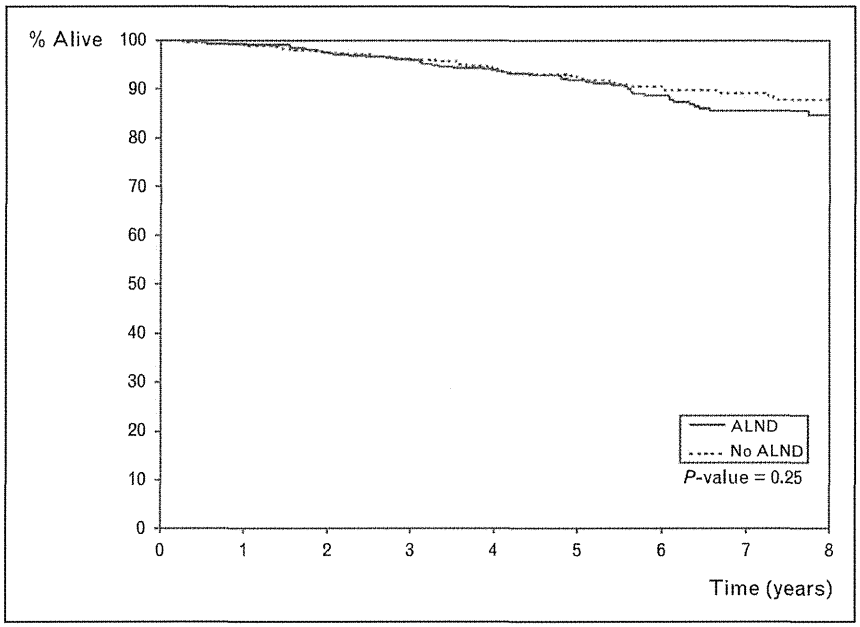


**FIGURE 4.** ACOSOG Z0011: overall survival. Adapted from [33].

performed additional non-SNB (ADD), which was enlarged at the lower axilla. Twenty-seven patients with positive scans underwent complete AND as a primary procedure, and 110 patients with negative scans underwent SNB and ADD. There were eight cases of false-negative scans, and no case of false-positive scan. Among 110 SNB and ADD cases, there were only eight cases (7.3%) of positive axillary basins in permanent biopsy, including two cases of late positives that had micrometastases in the sentinel node only. On the basis of an FDG-PET/CT, 27 unnecessary SNBs (true positive scans) have been eliminated. They concluded that an FDG-PET/CT reduced both unnecessary SNBs and positive axillary basins, enhancing the identification rates of sentinel node and the accuracy of SNB.

The After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) study has been conducted in The European Organisation for Research and Treatment of Cancer. The main endpoint of this study is axillary recurrence rate (Fig. 5) [30] and secondary endpoints are axillary recurrence free survival, disease-free survival, overall survival, quality of life, shoulder function analysis, and economic evaluation. Four thousand seven hundred and sixty seven patients had already been recruited (Feb 2001~2010). This study is comparing ALND to axillary radiation and will be available in a couple of years.

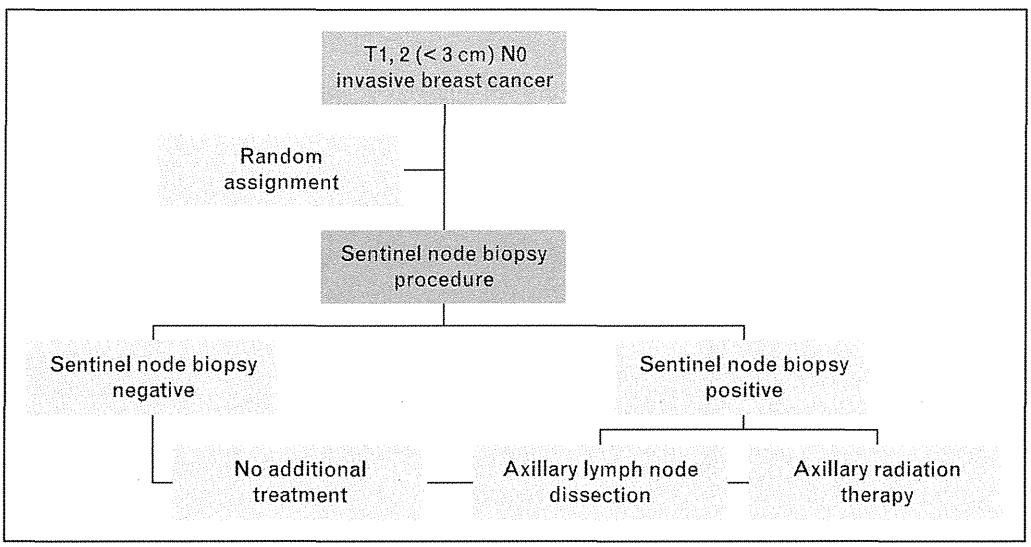


**FIGURE 5.** AMAROS study design. American Society of Clinical Oncology.

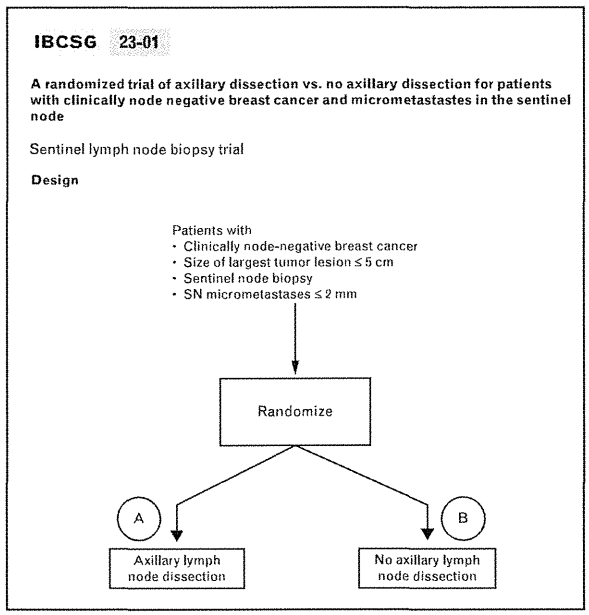


**FIGURE 6.** IBCSG23 01 study design. http://www.ibcsg.org/Public/Health Professionals/Closed Trials/IBCSG%2023 01/Pages/IBCSG23 01.aspx.

The International Breast Cancer Study Group trial 23–01 study was conducted at the European institute of Oncology in Milan (Fig. 6) [31]. The study included patients with disease limited to a relatively small primary tumor treated with initial SNB. Those who have micrometastasis (≤2 mm) are randomized to axillary dissection or no further treatment. The result of this study is also awaited.

## CONCLUSION

This result of ACOSOG Z0011 has profoundly impacted our understanding of axillary management in women with clinically node-negative breast cancer. The results of this study suggest that AND may safely be omitted in breast conservation patients whose tumor size is 5 cm or less with clinically node negative and who will have whole breast radiation and appropriate systemic adjuvant therapy [32,33]. But there are several critiques of the study, and further study is required. In patients for whom axillary dissection is eliminated, careful follow of their axillary is required, and we must also await the results of other similar studies (AMAROS study and International Breast Cancer Study Group 23–01.)

### Acknowledgements

*None.*

### Conflicts of interest

*There are no conflicts of interest.*

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000 000).

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ORIGINAL ARTICLE

# A multicenter, phase II study of epirubicin/cyclophosphamide followed by docetaxel and concurrent trastuzumab as primary systemic therapy for HER-2 positive advanced breast cancer (the HER2NAT study)

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**Abstract**
*Background* The outcome in patients with human epidermal growth factor receptor-2 (HER-2)-positive locally advanced breast cancer may be improved by integrating trastuzumab with primary systemic therapy (PST).
*Methods* The efficacy and safety of PST comprising EC (epirubicin 90 mg/m$^2$ and cyclophosphamide 600 mg/m$^2$, four cycles every 3 weeks) followed by docetaxel (75 mg/m$^2$, four cycles every 3 weeks) and concurrent trastuzumab (loading dose 4 mg/kg followed by 2 mg/kg, 12 cycles every week) was investigated in a multicenter, prospective, phase II study in patients with HER-2-positive stage IIIB/IIIC/IV breast cancer. The primary endpoint was pathologic complete response (pCR) including the tumor intraductal component confirmed by central pathologic review.
*Results* In total, 38 patients were enrolled (stage IIIB, 63.2 %; IIIC, 23.7 %; IV, 13.2 %; estrogen receptor- and/or progesterone receptor-positive, 47.4 %). The pCR rate was 16.2 % in the primary tumor (six of 37 patients in the Full Analysis Set) and 56.8 % (21/37) in the ipsilateral

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axillary lymph nodes. Treatment was given according to protocol in 28 of 37 patients; six of 28 in the Per-Protocol Set achieved pCR (21.4 %). The clinical response rate was 67.6 % (25/37 patients; complete response, 13.5 %; partial response, 54.1 %). No patients developed congestive heart failure; however, three patients had a non-symptomatic decrease of >10 % of left ventricular ejection fraction.
*Conclusions* PST including concurrent use of trastuzumab combined with docetaxel is effective and well-tolerated in HER-2-positive advanced breast cancer patients, including those patients requiring mastectomy for local control.

**Keywords** Primary systemic therapy · HER-2 · Trastuzumab · Advanced breast cancer

## Introduction

The clinical outcome for patients with locally advanced or metastatic breast cancer (stages IIIB, IIIC, IV) is poor compared with those presenting with operable disease [1]. Anthracycline taxane-based chemotherapy is the mainstay of treatment, but the therapeutic strategy needs to be tailored to individual patient characteristics. Neoadjuvant or primary systemic therapy (PST) is accepted treatment for patients with locally advanced breast cancer, but there is no standard regimen [2]. The advantages of PST in this setting include earlier treatment of subclinical distant micrometastases, downstaging of the primary tumor to facilitate surgery, and providing an opportunity to assess response to treatment in vivo [1]. Highly active PST can result in the disappearance of all invasive and non-invasive tumors [pathologic complete response (pCR)]. Since achievement of pCR correlates with improved survival in patients with operable breast cancer, pCR is accepted as a valid endpoint for trials of PST [3, 4].

The human epidermal growth factor receptor-2 (HER-2), which is amplified or overexpressed in approximately 25 % of breast cancers, is associated with aggressive disease and a poor prognosis [5]. Although it is an adverse prognostic factor, HER-2 has also emerged as a favorable predictive factor following the development of a specific treatment targeting this molecular abnormality [6]. Trastuzumab (Herceptin®, Roche, Basel, Switzerland) is a recombinant humanized monoclonal antibody targeting HER-2 that has demonstrated clinical efficacy as monotherapy [7 10] and in combination with chemotherapy in patients with HER-2-positive metastatic [10 12] and early breast cancer [13, 14]. Pivotal trials have shown that trastuzumab is well tolerated, although the potential for cardiotoxicity means that caution is required when considering concurrent or sequential use in patients receiving anthracycline-based regimens [15].

Early clinical studies in patients with HER-2-positive locally advanced breast cancer have shown that the combination of trastuzumab with taxane-based PST achieves a high pCR rate [16]. However, since anthracycline taxane regimens are the most frequently prescribed treatments in patients with operable breast cancer [2] and it is not known whether the efficacy of non-anthracycline regimens is equivalent, there is a compelling argument to investigate the addition of trastuzumab to anthracycline taxane PST. Although concurrent use is not recommended, it is feasible to administer trastuzumab sequentially after epirubicin, which is less cardiotoxic than doxorubicin, provided that a sub-cardiotoxic cumulative dose of anthracycline has been received [17].

A multicenter, prospective phase II study was therefore conducted in Japan to evaluate the efficacy of trastuzumab added to standard anthracycline taxane-based PST for patients with locally advanced or metastatic HER-2-positive breast cancer. The regimen was designed to achieve a high pCR rate.

## Patients and methods

The primary objective of this phase II study was to determine the pCR rate of trastuzumab-containing PST in patients with HER-2-positive locally advanced or metastatic breast cancer. Secondary objectives of the study included clinical response rate (cRR), pCR in ipsilateral axillary nodes, and safety and toxicity of the PST regimen.

### Patient selection

Patients eligible for the study had a histologically confirmed diagnosis of primary breast cancer and locally advanced disease according to tumor node metastasis staging (T4 or N3 or M1, clinical stages IIIB, IIIC, or IV). Patients with inflammatory breast cancer were excluded. Only patients with HER-2-positive tumors determined by immunohistochemistry (IHC 3+) and/or fluorescence in-situ hybridization (FISH+) were eligible for inclusion. HER-2 testing was performed locally according to the protocol used at the participating center. Other key eligibility criteria included age $\geq$20 years and $\leq$65 years, performance status 0 1, left ventricular ejection fraction (LVEF) measured by echocardiography or multi-gated acquisition (MUGA) scan $\geq$55 %, white blood count $\leq$10,000/mm$^3$, absolute neutrophil count $\geq$2,000/mm$^3$, platelet count $\geq$100,000/mm$^3$, hemoglobin $\geq$9.5 g/dl, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq$60 IU/l, bilirubin $\leq$1.5 mg/dl, and creatinine $\leq$1.5 mg/dl. The protocol was reviewed and approved by the institutional review board of each participating center. All patients provided written informed consent.

## Treatment

Eligible patients were scheduled to receive PST comprising four cycles of EC (intravenous epirubicin 90 mg/m$^2$ and intravenous cyclophosphamide 600 mg/m$^2$, administered on day 1 every 3 weeks) followed by four cycles of docetaxel (75 mg/m$^2$ intravenously, on day 1 every 3 weeks) and 12 cycles of concurrent trastuzumab (loading dose 4 mg/kg intravenously followed by 2 mg/kg, on day 1 every week).

Trastuzumab doses were modified in patients developing a decline in LVEF or congestive heart failure (CHF) according to the protocol used in the Herceptin Adjuvant (HERA) trial [18]. Trastuzumab was discontinued if the patient experienced symptomatic CHF and an LVEF of $\leq$45 or <50 % with an absolute reduction of $\geq$10 % from baseline. Trastuzumab was also discontinued in asymptomatic patients if LVEF did not return to a level above the criteria for withholding treatment after therapy was stopped for 3 weeks.

After completion of PST, patients were scheduled to receive surgery. Patients with stage IV disease could elect to receive salvage mastectomy for local control. Adjuvant trastuzumab therapy was administered after surgery. Patients could receive one of two trastuzumab regimens at the physician's discretion: loading dose 4 mg/kg followed by 2 mg/kg every week for 40 cycles or loading dose 8 mg/kg followed by 6 mg/kg every 3 weeks for 14 cycles. Patients with hormone-receptor positive disease also received adjuvant endocrine therapy for 5 years: premenopausal women received tamoxifen for 5 years, while postmenopausal women received tamoxifen, letrozole or anastrozole. The treatment protocol is summarized in Fig. 1.

## Assessment of endpoints

The primary endpoint of the study was pCR, defined as the absence of invasive components of ductal or lobular carcinoma in the breast with pathologic review confirming necrosis and/or disappearance of all tumor cells, and/or the replacement of cancer cells by granulation and/or fibrosis [19]. A central pathology review board confirmed all pCRs. Near pCR was defined as grade 2b, the absence of invasive component of ductal or lobular carcinoma in the breast with pathologic findings showing extremely high-grade tumor and marked changes approaching a complete response with only a few cancer cells remaining [19]. Near pCR was determined by pathologists at the local institutions.

The secondary endpoints of the study were cRR, pN0 in the ipsilateral axillary lymph nodes, and safety and toxicity. Clinical responses in the primary tumor were assessed by computed tomography (CT), ultrasonography (US) and/or by palpation. CT, US, or magnetic resonance imaging (MRI) were used to assess clinical responses in axillary lymph node tumors. Clinical responses were defined according to Response Evaluation Criteria In Solid Tumors [20].

Adverse events were reported and graded according to Common Terminology Criteria for Adverse Events v3.0 [21]. Cardiac function was monitored regularly using echocardiography or MUGA scans. Cardiac scans and electrocardiograms were performed at baseline, and after 12 weeks (four courses) and 25 weeks (completion of therapy) in the neoadjuvant setting, or at 3 months, 6 months and at the end of therapy (40 weeks) in the adjuvant setting. CHF and LVEF dysfunction were defined as described in the HERA trial [18].

## Statistics

The planned study sample size was 40 patients based on achieving a pCR of 3 % in the null hypothesis or 18 % in the alternative hypothesis ($\alpha = 0.05$; $\beta = 0.1$), assuming a rate of about 30 % of patients excluded from the analysis set [16, 22, 23].

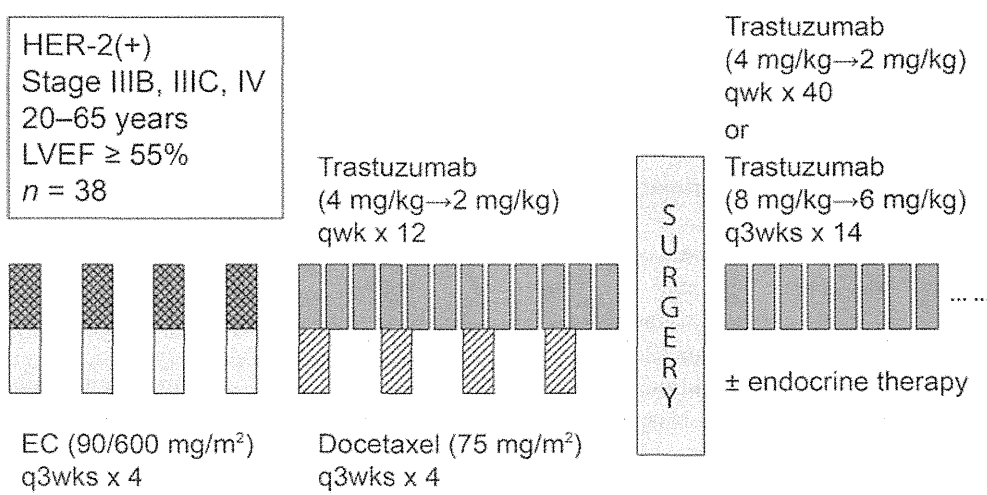


**Fig. 1** Study design and treatment protocol

All registered patients were included in the analysis for safety and toxicity. The Full Analysis Set (FAS) comprised subjects meeting the inclusion criteria specified in the protocol at the data center and treated with at least one dose of protocol-specified therapy. Subjects from the FAS who underwent protocol-specified surgical procedures and did not have any serious deviations from the treatment protocol were included in the Per-Protocol Set (PPS). Protocol deviations resulting in exclusion from the PPS included failure to undergo surgery and administration of <80 % of the total dose of treatment. The data adjusted for FAS and PPS were used for the analyses of efficacy.

Subgroup analyses were performed using Fisher's exact test to determine associations between pCR rate and hormone receptor status [estrogen receptor/progesterone receptor (ER/PgR) positive or negative] or tumor size (T4 vs. T1, 2, or 3). Fisher's exact test was also used to determine whether CT, US, or MRI were more effective than palpation in predicting pCR based on clinical complete response (cCR).

## Results

The study was performed in 11 centers in Japan between January 2006 and December 2008. In total, 38 patients entered the study and were included in the safety analysis. The characteristics of all registered patients are shown in Table 1. One patient with HER-2-negative breast cancer was ineligible and therefore the FAS comprised 37 patients. Surgery was not performed in three patients and a further six patients received <80 % of the total planned treatment dose. Consequently, 28 patients were included in the PPS.

### Dose delivery

The median dose delivered was equivalent to the planned total dose for all agents in the PST regimen (Table 2). The mean doses of chemotherapy delivered were >90 % for all regimens and the mean dose of trastuzumab delivered was 88 % of the planned total dose (Table 2).

### Efficacy of PST in the primary tumor

The pCRs and cRRs achieved in the primary tumor are shown in Table 3. The pCR rate was six of 37 patients [16.2 %; 95 % confidence interval (CI) 6.2 32.0] in the FAS and six of 28 patients (21.4 %; 95 % CI 8.3 41.0) in the PPS (Fig. 2a). In addition, 10 patients in the FAS and nine in the PPS achieved Near pCR; therefore, the rates of pCR plus Near pCR were 43.2 and 53.6 %, respectively (Fig. 2a). The overall cRR was 25 of 37 patients (67.6 %) in the FAS and 24 of 28 patients (85.7 %) in the PPS. The cCR rates were 13.5 and 17.9 %, respectively. All patients achieving pCR in the primary tumor were shown to have pN0 status in the axillary lymph nodes.

**Table 1** Patient characteristics

| Patient characteristic | *n* 38 |
|---|---|
| Median age (range) | 49.5 years (39 64) |
| Menopausal status (*n*) | |
| Pre | 22 |
| Post | 16 |
| Tumor size (*n*) | |
| T1 | 1 |
| T2 | 6 |
| T3 | 4 |
| T4 | 27 |
| Axillary lymph node status (*n*) | |
| N0 | 1 |
| N1 | 14 |
| N2 | 7 |
| N3 | 16 |
| Clinical stage (*n*) | |
| IIIB | 24 |
| IIIC | 9 |
| IV | 5 |
| ER/PgR status (*n*) | |
| ER and/or PgR positive | 18 |
| ER and PgR negative | 20 |
| HER 2 status (IHC3+ and/or FISH+; *n*) | |
| Positive | 37 |
| Negative | 1[a] |

*ER* estrogen receptor, *FISH* fluorescence in situ hybridization, *IHC* immunohistochemistry, *PgR* progesterone receptor

[a] Ineligible

[b] All patients were node positive

The rate of pCR plus Near pCR was higher in patients with ER/PgR-negative disease than in those with ER/PgR-positive disease (55.0 vs. 29.4 %, respectively); however, there was no significant association between pCR rate and hormone-receptor status ($P = 0.1886$; Fig. 2b). The rates of pCR plus Near pCR were similar in patients with T1, 2, or 3 and those with T4 tumors (45.5 vs. 42.3 %, respectively), but the pCR rate was low in patients with T4 tumors (36.4 vs. 7.7 %, respectively; $P = 0.0515$; Fig. 2c).

### Efficacy of PST in axillary lymph nodes

All patients were pathologically axillary lymph node positive prior to treatment even though one patient was clinically negative. Following PST, 21 of 37 patients (56.8 %) in the FAS had no lymph-node involvement

**Table 2** Actual dose delivery

| | Treatment | | | |
|---|---|---|---|---|
| | Epirubicin (dose in mg/m$^2$) | Cyclophosphamide (dose in mg/m$^2$) | Docetaxel (dose in mg/m$^2$) | Trastuzumab (dose in mg/kg) |
| Number of patients | 38 | 38 | 36 | 37 |
| Mean dose (range) | 347 (90 377) | 2,346 (600 2516) | 273 (75 318) | 23 (4 28) |
| Standard deviation | 47 | 309 | 63 | 7 |
| Median dose | 360 | 2,408 | 300 | 26 |
| Planned dose | 360 | 2,400 | 300 | 26 |

**Table 3** Efficacy of primary systemic therapy assessed in the primary tumor

| Efficacy endpoint | Clinical outcome | FAS, *n* 37 (%) | PPS, *n* 28 (%) |
|---|---|---|---|
| Pathologic response rate (pCR) | pCR | 6 (16.2) | 6 (21.4) |
| | Near pCR | 10 (27.0) | 9 (32.1) |
| | pCR + Near pCR | 16 (43.2) | 15 (53.6) |
| Clinical response rate | Complete response | 5 (13.5) | 5 (17.9) |
| | Partial response | 20 (54.1) | 19 (67.9) |
| | Stable disease | 3 (8.1) | 2 (7.1) |
| | Progressive disease | 2 (5.4) | 1 (3.6) |
| | Not evaluable | 7 (18.9) | 1 (3.6) |
| | cRR | 25 (67.6) | 24 (85.7) |

*cRR* clinical response rate (complete response and partial response), *FAS* Full Analysis Set, *PPS* Per Protocol Set

(pN0). Of these 21 patients, lymph-node positivity prior to PST was initially confirmed by biopsy in three, confirmed without biopsy in 14, and unclear in four patients. In the PPS, 20 of 28 patients (71.4 %) were pN0 following PST (lymph-node positivity confirmed by biopsy prior to PST in three patients, confirmed without biopsy in 13, and unclear in four).

### Association between cCR and pCR

There was a significant association between cCR and pCR in the primary tumour when clinical response was assessed by palpation ($P = 0.0015$), but not by CT or US (Table 4a, b). Table 4c shows a significant association between cCR and pN0 when clinical response in axillary lymph-node tumors was assessed by CT, US, or MRI ($P = 0.0090$).

### Safety

The trastuzumab-containing PST regimen used in this study was feasible and well tolerated. The predominant serious adverse events (grade 3/4) toxicity were hematologic (Table 5). More than 60 % of patients experienced grade 3 or 4 neutropenia, but the rate of febrile neutropenia was only 5.3 % (grade 3). The only other serious adverse event occurring at a frequency greater than 5 % (Table 5) was allergic reaction (grade 4 in 7.9 %: infusion reaction with trastuzumab in 2.6 % and allergic reaction with docetaxel in 5.3 %). No grade 3 edema associated with docetaxel was reported.

No cases of CHF were observed in the overall study population and no patients experienced a decrease in LVEF to <50 %. A decrease of >10 % in LVEF was reported in three patients (8.1 %). The decrease in LVEF prior to surgery was 10 % in one patient and 13 % in two patients. Trastuzumab was continued and all three patients underwent surgery.

## Discussion

This study was designed to investigate whether addition of trastuzumab to a standard anthracycline taxane-based PST regimen could achieve a high pCR rate in patients with HER-2-positive locally advanced or metastatic breast cancer. The pCR rate was 16.2 % in the FAS and 21.4 % in the PPS. The findings of this study add to the weight of evidence supporting the addition of trastuzumab to anthracycline taxane-based PST for patients with HER-2-positive breast cancer [4, 18, 22, 24, 25], including those patients being treated in Japan.

In a pioneering study reported by Buzdar and colleagues [22], the addition of trastuzumab to paclitaxel-containing PST resulted in a significant improvement in the pCR rate from 25 to 66.7 % ($P = 0.02$). This study included patients with mainly T2 disease, and so focused on rather early stage tumors. In the large GeparQuattro study, which also

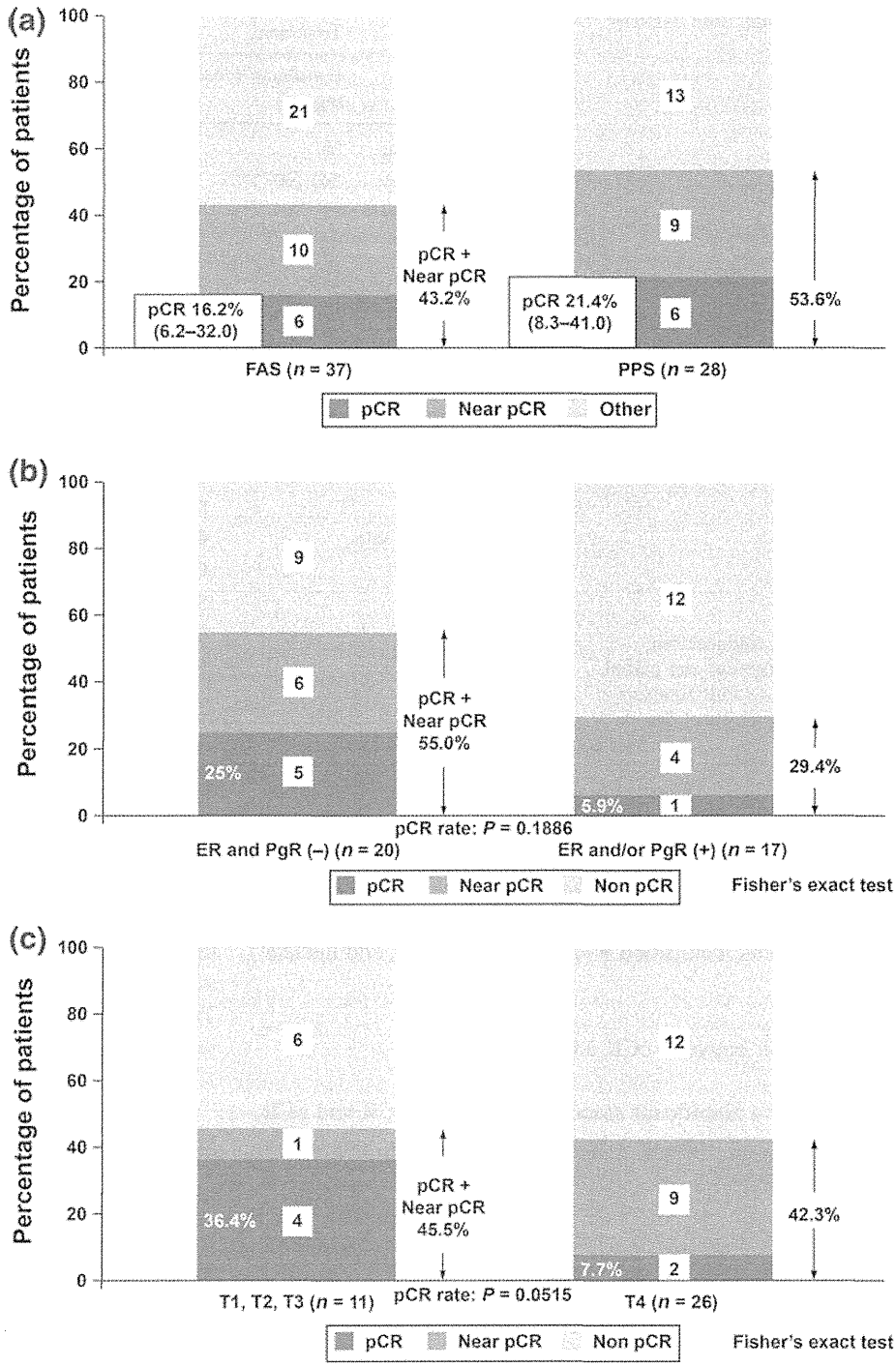


**Fig. 2** Pathologic response rate (*pCR*) according to **a** FAS or PPS data set, **b** hormone receptor status (*n* 37), and **c** tumor size (T1 T3 vs. T4; *n* 37). *ER* estrogen receptor, *FAS* Full Analysis Set, *LVEF* left ventricular ejection fraction, *PPS* Per Protocol Set, *PgR* progesterone receptor

included mainly T2 patients, the docetaxel-containing PST led to a pCR rate of 31.7 % in the HER-2-positive group [17]. In the randomized NOAH trial, which included patients with later stage disease, similar to our study, 235 patients with HER-2-positive locally advanced breast cancer (100 T4 non-inflammatory, 63 inflammatory, and 72 N2 or ipsilateral node positive) were allocated to paclitaxel and doxorubicin-containing PST with or without trastuzumab [24]. Addition of trastuzumab significantly improved the rate of pCR from 22 to 43 % ($P = 0.0007$).

Comparing pCR rates between trials is difficult because of heterogeneous patient populations, different chemotherapy regimens, and variations in the assessment and definition of pCR. Nevertheless, it is instructive to use the published data as a benchmark to assess pCR rates reported in our study. Analysis of efficacy according to tumor size

**Table 4** Association between achievement of pathologic complete response (pCR) and complete clinical response (cCR) according to the method of assessment of the primary tumor or axillary lymph node tumor

| | cCR | Non cCR | Total |
|---|---|---|---|
| (a) Primary tumor assessment by CT, US, or MRI[a] (*n* 34); *P* 0.2053 | | | |
| pCR | 2 | 4 | 6 |
| Non pCR | 3 | 25 | 28 |
| Total | 5 | 29 | 34 |
| (b) Primary tumor assessment by palpation (*n* 33); *P* 0.0015 | | | |
| pCR | 6 | 0 | 6 |
| Non pCR | 7 | 20 | 27 |
| Total | 13 | 20 | 33 |
| (c) Axillary lymph node assessment by CT, US, or MRI (*n* 33); *P* 0.009 | | | |
| pN0 | 11 | 9 | 20 |
| Non pN0 | 1 | 12 | 13 |
| Total | 12 | 21 | 33 |

Probability of significant association determined using Fisher's exact test

*CT* computed tomography, *MRI* magnetic resonance imaging, *US* ultrasonography

[a] There was no case assessed by MRI

**Table 5** Serious adverse events (CTCAE v3.0) reported in the overall study population (*n* 38)

| Adverse event | Grade 3, *n* (%) | Grade 4, *n* (%) |
|---|---|---|
| Neutropenia | 1 (2.6) | 23 (60.5) |
| Leukopenia | 9 (23.7) | 14 (36.8) |
| Febrile neutropenia | 2 (5.3) | |
| Anemia | 1 (2.6) | |
| Allergic reaction | | 3 (7.9) |
| Rash/desquamation | 1 (2.6) | |
| Rash/hand foot syndrome | 1 (2.6) | |
| Anorexia | 1 (2.6) | |
| Taste alteration | 1 (2.6) | |
| AST elevation | 1 (2.6) | |
| ALT elevation | 1 (2.6) | |
| Dizziness | 1 (2.6) | |
| Sensory neuropathy | 1 (2.6) | |
| Joint pain | 1 (2.6) | |
| Muscle pain | 1 (2.6) | |

*ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CTCAE* Common Terminology Criteria for Adverse Events

showed that the pCR rate among patients with T1 3 tumors was 36.4 %, which is similar to previous reports. Achievement of pCR is an important goal in neo-adjuvant treatment since it is a surrogate marker for better prognosis. In the NOAH trial, trastuzumab added to PST resulted in a significant improvement in event-free survival (hazard ratio 0.59; 95 % CI 0.38 0.90; $P = 0.013$) [24]. In addition, long-term follow-up of the study by Buzdar and colleagues [4] showed significantly improved disease-free survival among patients randomized to PST plus trastuzumab compared with chemotherapy alone. The pCR correlated with longer survival based on reports from the TECNO trial [25].

Differences in the pCR rate were evident when the efficacy data were analyzed according to patient characteristics. Consistent with data from the GeparQuattro study [17, 26], the probability of achieving pCR was higher in patients with hormone-receptor-negative disease. Although the pCR rate was highest in patients with T1 3 tumors, it was interesting to note that some patients with bulky tumors, including those with T4 or stage IV disease, did respond to the PST regimen used in this study. Better prognosis is expected in stage IV patients achieving pCR and surgery [27, 28]. Data have shown that pN0 is an excellent prognostic factor, even in patients with residual breast disease [29]. In the present study, the pathologic response rate in the axillary lymph nodes was 56.8 % in the FAS and 71.4 % in the PPS.

Achievement of pCR in the primary tumor and of pN0 in the axillary lymph nodes is a more relevant prognostic factor than clinical response in the setting of PST [30]. However, cCR may be predictive of pCR. In this study there was a significant association between cCR in the primary tumor and pCR when clinical assessment was done by palpation rather than CT or US. Furthermore, there was a significant association between cCR in the axillary lymph nodes and pN0 when clinical response was assessed by CT, US, or MRI.

Cardiotoxicity was identified as the major clinical problem in the upfront use of trastuzumab in combination with anthracycline-based regimens [11, 31]. In this study, the risk of cardiac toxicity was minimized by using epirubicin rather than doxorubicin and by sequential rather than concurrent administration of trastuzumab. Three patients experienced an asymptomatic decrease of >10 % in LVEF; however, no patient was unable to receive surgery because of cardiotoxicity and there were no cases of CHF reported. This observation supports the hypothesis that trastuzumab is associated with type II reversible cardiac dysfunction distinct from cardiotoxicity associated with anthracyclines [32]. Other investigators have used non-anthracycline-based regimens, including taxanes with or without platinum agents, as the foundation for trastuzumab-containing PST in patients with HER-2-positive breast cancer [17, 33 35]. It is not clear, however, if the omission of anthracycline from PST will adversely affect long-term outcome.

Our findings are in line with data from larger studies in patients with HER-2-positive operable or locally advanced breast cancer treated with trastuzumab in combination with anthracycline taxane PST [17, 24]. Although HER-2-positive T4 tumors showed a lower pCR rate than T1 T3 tumors, there was no difference in pathologic response rate including Near pCR between T4 and T1 T3 tumors. Strong PST is one of the treatment options for T4 tumors; it could improve the pCR rate of HER2-positive T4 tumors, especially in ER/PgR-negative and M0 patients. Strong PST is defined as high-dose, prolonged, dose-dense or combination of trastuzumab with anthracyclines.

## Conclusion

For patients with HER-2-positive locally advanced and metastatic breast cancer, combining trastuzumab with an anthracycline taxane-based PST might achieve high pCR without significant toxicity.

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**Conflict of interest** The authors declare no conflicts of interest.

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# Preoperative CT evaluation of intraductal spread of breast cancer and surgical treatment

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**Abstract** It is always a challenge to accurately determine the appropriate extent of resection in breast-conserving surgery (BCS), in order to reduce the need for re-excision, prevent local recurrence, and optimize cosmetic results. Detecting intraductal spread alone with high sensitivity may not be enough to realize safe BCS. Computed tomography carried out with the patient in the supine position accompanied by adequate marking is effective for preoperative determination of the optimum extent of BCS.

**Keywords** Breast cancer · CT · Breast-conserving surgery · Extent of surgery · Extensive intraductal component

**Abbreviations**

| | |
|---|---|
| BCS | Breast-conserving surgery |
| CT | Computed tomography |
| EIC | Extensive intraductal component |
| HU | Hounsfield units |
| MD-CT | Multidetector-row computed tomography |
| MIP | Maximum intensity projection |
| MMG | Mammography |
| US | Ultrasonography |

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## Breast cancer diagnosis

Although computed tomography (CT) is not a primary modality for screening the breast or differentiating between malignant and benign breast lesions, some studies have reported that CT was able to reveal the primary tumor with high sensitivity [1]. Diagnostic criteria for breast cancer using CT include an irregular margin, irregular shape, and rim enhancement [2]. Spiculation was strongly suggestive of malignancy when detected incidentally by use of CT [3 5]. Irregular shape and axillary lymphadenopathy are also morphological predictors. The CT values of malignant lesions were higher than those of benign lesions. The cut-off value ranged from 60 Hounsfield units (HU) at 30 s [6, 7] to 90 HU on the 1-min images [8]. Optimum timing of the early phase scan was 80 s after injection of contrast media [9].

Multidetector-row computed tomography (MD-CT) detected contralateral breast cancer in 2.6% of newly diagnosed breast cancer cases [10].

## Preoperative MD-CT evaluation of the extent of cancer in the breast

Extensive intraductal spread is often accompanied by invasive ductal carcinoma and becomes a major cause of positive margins after breast-conserving surgery (BCS). It is always a challenge to accurately determine the appropriate extent of resection in order to prevent local recurrence, reduce the need for re-excision, and optimize cosmetic results. Diagnostic criteria for intraductal spread using CT (axial image) are non-mass-like enhancement which is contiguous with and enhanced to the same extent as the index tumor, and the presence of linear or segmental enhancement around the main tumor [11]. The maximum

intensity projection (MIP) image is also useful in diagnosing the extent of breast cancer [12]. The morphological type of intraductal spread using the MIP image is continuous extension from the index tumor (Fig. 1) [13]. Linear enhancement at the edge of the mammary gland, detected using either axial or coronal sections, or diffuse punctate enhancement with smooth margin, are associated with fibrocystic change [13]. They are sometimes seen bilaterally.

Sensitivity and specificity in the detection of the intraductal spread have varied from 71.8 to 88.0% and from 67.8 to 81.9%, respectively (Table 1) [11 15]. CT evaluation of the maximum diameter of the extent of breast cancer has been shown to be substantially better correlated with histopathological diameter than that determined by mammography (MMG) [13, 16]. The median deviation of the tumor extension revealed by 3D CT from pathological size was reported to be 7.7 mm [17]. CT is more accurate than MMG or ultrasonography (US) in determining the extent of invasive lobular carcinoma, with or without neoadjuvant chemotherapy [18].

CT has been shown to detect multiple lesions that are undetectable by conventional methods in 6 18.6% of breast cancer cases [13, 19]. The sensitivity, specificity, and accuracy of the CT diagnosis of otherwise occult sites of cancer have been shown to be 93.3, 98.3, and 97.3%, respectively [13].

## High sensitivity may not be enough

It was believed that the incidence of positive margins was certain to decrease if they could be depicted accurately. MRI is the most sensitive modality available to date for identifying the extent of cancer within the breast. However, findings reported in 2008 that were related to the retrospective analysis of preoperative MRI as compared with no MRI were received with great disappointment, because use of MRI failed to reduce the incidence of positive margins [20]. Subsequently, two randomized control studies that assessed the effectiveness of preoperative MRI in terms of the need for re-excision were reported [21, 22]. The COMICE trial included 1623 women with biopsy-proven primary breast cancer who were randomly assigned to MRI and non-MRI groups before surgery [21]. Addition of MRI to conventional triple assessment was not significantly associated with a reduction in the need for reoperation, with 19% of patients in the MRI group requiring reoperation compared with 19% in the non-MRI group [21]. The primary endpoint of another clinical study, the MONET trial, also involved assessment of the need for additional surgical procedures (re-excision and conversion to mastectomy) for non-palpable breast tumors. The need for additional surgical intervention after initial BCS was 45% in the MRI group versus 28% in the conventional non-MRI group. Thus, addition of MRI to routine clinical care in patients with non-palpable breast cancer was paradoxically associated with an increase in the need for re-excision.

Positive results had been expected from these two randomized controlled trials. Why did MRI fail to reduce the incidence of positive margins and re-excision in BCS despite excellent sensitivity? One reason is speculated to be the change of the shape of the breast because of the different positions used during MRI examination and subsequent surgery. Thus, there is a possibility that even if the lesion can be revealed by MRI, the extent of excision cannot be accurately determined. We should therefore be very careful in not only depicting the tumor margins but also in preventing errors in determining the excision margins that are associated with changes in position of the breast.

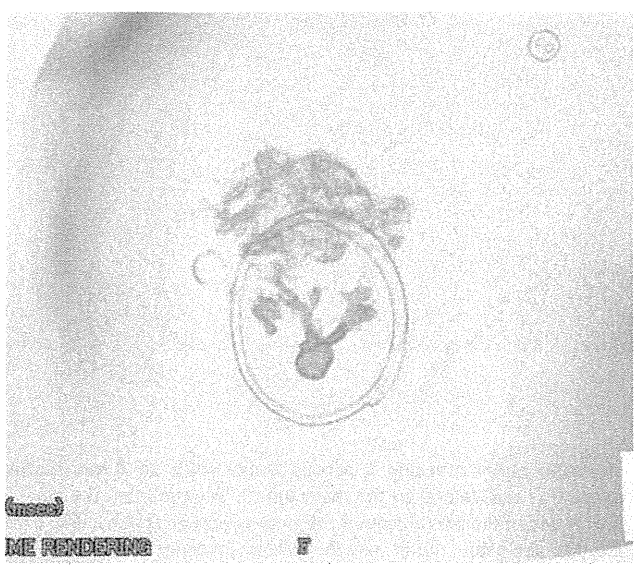


**Fig. 1** Reconstructed 3D CT image. Intraductal extension continuous from the index cancer

## Important factors in determining the extent of surgery

The accuracy with which the surgery is aligned with the image-detected lesion is an important concern. Accurate

**Table 1** Sensitivity, specificity, and accuracy of detection of intraductal spread by CT

| | Published in | No. of patients | Sensitivity | Specificity | Accuracy |
|---|---|---|---|---|---|
| Akashi Tanaka | 1998 | 122 | 91 | 79 | |
| Uematsu | 2001 | 135 | 77 | 87 | |
| Fujita | 2005 | 81 | 81 | 68 | 73 |
| Doihara | 2006 | 72 | 72 | 86 | |