of the disease, but also to the development of new strategies for diagnosis and therapy.

**Acknowledgments** We thank Dr. Yutaka Kondo for technical advice on MCAM analysis and Masami Ashida for technical assistance. This study was supported in part by a Grant-in-Aid for Scientific Research (B) from the Japan Society for Promotion of Science (Y. Shinomura), a Grant-in-Aid for the Third-term Comprehensive 10-year Strategy for Cancer Control (M. Toyota and H. Suzuki), and a Grant-in-Aid for Cancer Research from the Ministry of Health, Labor, and Welfare, Japan (M. Toyota and H. Suzuki).

**Conflicts of interest** None

## References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74–108.
2. Chen CJ, Yu MW, Liaw YF. Epidemiological characteristics and risk factors of hepatocellular carcinoma. J Gastroenterol Hepatol. 1997;12:S294–308.
3. Montesano R, Hainaut P, Wild CP. Hepatocellular carcinoma: from gene to public health. J Natl Cancer Inst. 1997;89:1844–51.
4. Thorgeirsson SS, Grisham JW. Molecular pathogenesis of human hepatocellular carcinoma. Nat Genet. 2002;31:339–46.
5. Jones PA, Baylin SB. The fundamental role of epigenetic events in cancer. Nat Rev Genet. 2002;3:415–28.
6. Cordaux R, Batzer MA. The impact of retrotransposons on human genome evolution. Nat Rev Genet. 2009;10:691–703.
7. Yang AS, Estecio MR, Doshi K, Kondo Y, Tajara EH, Issa JP. A simple method for estimating global DNA methylation using bisulfite PCR of repetitive DNA elements. Nucleic Acids Res. 2004;32:e38.
8. Takai D, Yagi Y, Habib N, Sugimura T, Ushijima T. Hypomethylation of line1 retrotransposon in human hepatocellular carcinomas, but not in surrounding liver cirrhosis. Jpn J Clin Oncol. 2000;30:306–9.
9. Kim MJ, White-Cross JA, Shen L, Issa JP, Rashid A. Hypomethylation of long interspersed nuclear element-1 in hepatocellular carcinomas. Mod Pathol. 2009;22:442–9.
10. Kaneto H, Sasaki S, Yamamoto H, Itoh F, Toyota M, Suzuki H, Ozeki I, Iwata N, Ohmura T, Satoh T, Karino Y, Toyota J, Satoh M, Endo T, Omata M, Imai K. Detection of hypermethylation of the p16(ink4a) gene promoter in chronic hepatitis and cirrhosis associated with hepatitis B or C virus. Gut. 2001;48:372–7.
11. Takagi H, Sasaki S, Suzuki H, Toyota M, Maruyama R, Nojima M, Yamamoto H, Omata M, Tokino T, Imai K, Shinomura Y. Frequent epigenetic inactivation of sfrp genes in hepatocellular carcinoma. J Gastroenterol. 2008;43:378–89.
12. Lee HS, Kim BH, Cho NY, Yoo EJ, Choi M, Shin SH, Jang JJ, Suh KS, Kim YS, Kang GH. Prognostic implications of and relationship between CpG island hypermethylation and repetitive DNA hypomethylation in hepatocellular carcinoma. Clin Cancer Res. 2009;15:812–20.
13. Gao W, Kondo Y, Shen L, Shimizu Y, Sano T, Yamao K, Natsume A, Goto Y, Ito M, Murakami H, Osada H, Zhang J, Issa JP, Sekido Y. Variable DNA methylation patterns associated with progression of disease in hepatocellular carcinomas. Carcinogenesis. 2008;29:1901–10.
14. Arai E, Ushijima S, Gotoh M, Ojima H, Kosuge T, Hosoda F, Shibata T, Kondo T, Yokoi S, Imoto I, Inazawa J, Hirohashi S, Kanai Y. Genome-wide DNA methylation profiles in liver tissue at the precancerous stage and in hepatocellular carcinoma. Int J Cancer. 2009;125:2854–62.
15. Deng YB, Nagae G, Midorikawa Y, Yagi K, Tsutsumi S, Yamamoto S, Hasegawa K, Kokudo N, Aburatani H, Kaneda A. Identification of genes preferentially methylated in hepatitis C virus-related hepatocellular carcinoma. Cancer Sci. 2010;101:1501–10.
16. Goto Y, Shinjo K, Kondo Y, Shen L, Toyota M, Suzuki H, Gao W, An B, Fujii M, Murakami H, Osada H, Taniguchi T, Usami N, Kondo M, Hasegawa Y, Shimokata K, Matsuo K, Hida T, Fujimoto N, Kishimoto T, Issa JP, Sekido Y. Epigenetic profiles distinguish malignant pleural mesothelioma from lung adenocarcinoma. Cancer Res. 2009;69:9073–82.
17. Suzuki H, Yamamoto E, Nojima M, Kai M, Yamano HO, Yoshikawa K, Kimura T, Kudo T, Harada E, Sugai T, Takamaru H, Niinuma T, Maruyama R, Yamamoto H, Tokino T, Imai K, Toyota M, Shinomura Y. Methylation-associated silencing of microrna-34b/c in gastric cancer and its involvement in an epigenetic field defect. Carcinogenesis. 2010;31:2066–73.
18. Nishida N, Nagasaka T, Nishimura T, Ikai I, Boland CR, Goel A. Aberrant methylation of multiple tumor suppressor genes in aging liver, chronic hepatitis, and hepatocellular carcinoma. Hepatology. 2008;47:908–18.
19. Wong IH, Zhang J, Lai PB, Lau WY, Lo YM. Quantitative analysis of tumor-derived methylated p16ink4a sequences in plasma, serum, and blood cells of hepatocellular carcinoma patients. Clin Cancer Res. 2003;9:1047–52.
20. Zhang YJ, Wu HC, Shen J, Ahsan H, Tsai WY, Yang HI, Wang LY, Chen SY, Chen CJ, Santella RM. Predicting hepatocellular carcinoma by detection of aberrant promoter methylation in serum DNA. Clin Cancer Res. 2007;13:2378–84.
21. Carotta S, Holmes ML, Pridans C, Nutt SL. Pax5 maintains cellular identity by repressing gene expression throughout B cell differentiation. Cell Cycle. 2006;5:2452–6.
22. Palmisano WA, Crume KP, Grimes MJ, Winters SA, Toyota M, Esteller M, Joste N, Baylin SB, Belinsky SA. Aberrant promoter methylation of the transcription factor genes pax5 alpha and beta in human cancers. Cancer Res. 2003;63:4620–5.
23. Lazzi S, Bellan C, Onnis A, De Falco G, Sayed S, Kostopoulos I, Onorati M, D'Amuri A, Santopietro R, Vindigni C, Fabbri A, Righi S, Pileri S, Tosi P, Leoncini L. Rare lymphoid neoplasms coexpressing B- and T-cell antigens. The role of pax-5 gene methylation in their pathogenesis. Hum Pathol. 2009;40:1252–61.
24. Liu W, Li X, Chu ES, Go MY, Xu L, Zhao G, Li L, Dai N, Si J, Tao Q, Sung JJ, Yu J. Paired box gene 5 is a novel tumor suppressor in hepatocellular carcinoma through interaction with p53 signaling pathway. Hepatology. 2011;53:843–53.
25. Li X, Cheung KF, Ma X, Tian L, Zhao J, Go MY, Shen B, Cheng AS, Ying J, Tao Q, Sung JJ, Kung HF, Yu J. Epigenetic inactivation of paired box gene 5, a novel tumor suppressor gene, through direct upregulation of p53 is associated with prognosis in gastric cancer patients. Oncogene. 2011. doi:10.1038/onc.2011.511.
26. Morris MR, Ricketts CJ, Gentle D, McRonald F, Carli N, Khalili H, Brown M, Kishida T, Yao M, Banks RE, Clarke N, Latif F, Maher ER. Genome-wide methylation analysis identifies epigenetically inactivated candidate tumour suppressor genes in renal cell carcinoma. Oncogene. 2011;30:1390–401.
27. Ueki T, Toyota M, Skinner H, Walter KM, Yeo CJ, Issa JP, Hruban RH, Goggins M. Identification and characterization of differentially methylated cpg islands in pancreatic carcinoma. Cancer Res. 2001;61:8540–6.
28. Goo YA, Goodlett DR, Pascal LE, Worthington KD, Vessella RL, True LD, Liu AY. Stromal mesenchyme cell genes of the human prostate and bladder. BMC Urol. 2005;5:17.

29. Chung JH, Lee HJ, Kim BH, Cho NY, Kang GH. DNA methylation profile during multistage progression of pulmonary adenocarcinomas. Virchows Arch. 2011;459:201–11.
30. Chung W, Bondaruk J, Jelinek J, Lotan Y, Liang S, Czerniak B, Issa JP. Detection of bladder cancer using novel DNA methylation biomarkers in urine sediments. Cancer Epidemiol Biomarkers Prev. 2011;20:1483–91.
31. Kishida Y, Natsume A, Kondo Y, Takeuchi I, An B, Okamoto Y, Shinjo K, Saito K, Ando H, Ohka F, Sekido Y, Wakabayashi T. Epigenetic subclassification of meningiomas based on genome-wide DNA methylation analyses. Carcinogenesis. 2012;33:436–41.
32. McTavish N, Copeland LA, Saville MK, Perkins ND, Spruce BA. Proenkephalin assists stress-activated apoptosis through transcriptional repression of nf-kappab- and p53-regulated gene targets. Cell Death Differ. 2007;14:1700–10.
33. Gastwirt RF, McAndrew CW, Donoghue DJ. Speedy/ringo regulation of CDKs in cell cycle, checkpoint activation and apoptosis. Cell Cycle. 2007;6:1188–93.
34. Zucchi I, Mento E, Kuznetsov VA, Scotti M, Valsecchi V, Simionati B, Vicinanza E, Valle G, Pilotti S, Reinbold R, Vezzoni P, Albertini A, Dulbecco R. Gene expression profiles of epithelial cells microscopically isolated from a breast-invasive ductal carcinoma and a nodal metastasis. Proc Natl Acad Sci U S A. 2004;101:18147–52.
35. Golipour A, Myers D, Seagroves T, Murphy D, Evan GI, Donoghue DJ, Moorehead RA, Porter LA. The spy1/ringo family represents a novel mechanism regulating mammary growth and tumorigenesis. Cancer Res. 2008;68:3591–600.
36. Ke Q, Ji J, Cheng C, Zhang Y, Lu M, Wang Y, Zhang L, Li P, Cui X, Chen L, He S, Shen A. Expression and prognostic role of spy1 as a novel cell cycle protein in hepatocellular carcinoma. Exp Mol Pathol. 2009;87:167–72.
37. Lin CH, Hsieh SY, Sheen IS, Lee WC, Chen TC, Shyu WC, Liaw YF. Genome-wide hypomethylation in hepatocellular carcinogenesis. Cancer Res. 2001;61:4238–43.
38. Park IY, Sohn BH, Yu E, Suh DJ, Chung YH, Lee JH, Surzycki SJ, Lee YI. Aberrant epigenetic modifications in hepatocarcinogenesis induced by hepatitis B virus X protein. Gastroenterology. 2007;132:1476–94.
39. Calvisi DF, Simile MM, Ladu S, Pellegrino R, De Murtas V, Pinna F, Tomasi ML, Frau M, Virdis P, De Miglio MR, Muroni MR, Pascale RM, Feo F. Altered methionine metabolism and global DNA methylation in liver cancer: relationship with genomic instability and prognosis. Int J Cancer. 2007;121:2410–20.
40. Tangkijvanich P, Hourpai N, Rattanatanyong P, Wisedopas N, Mahachai V, Mutirangura A. Serum line-1 hypomethylation as a potential prognostic marker for hepatocellular carcinoma. Clin Chim Acta. 2007;379:127–33.

CURRENT OPINION

# 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].

Department of Breast Surgical Oncology, Showa University School of Medicine, Tokyo, Japan

Correspondence to Seigo Nakamura, Department of Breast Surgical Oncology, Showa University School of Medicine, 1-5-8 Hatanodai Shinagawa-ku, Tokyo 142-8666, Japan. Tel: +81 3 3784 8000; fax: +81 3 3784 8707; e-mail: seigonak@med.showa-u.ac.jp

**Curr Opin Obstet Gynecol** 2013, 25:000–000
DOI:10.1097/GCO.0b013e32834f3608

## 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%

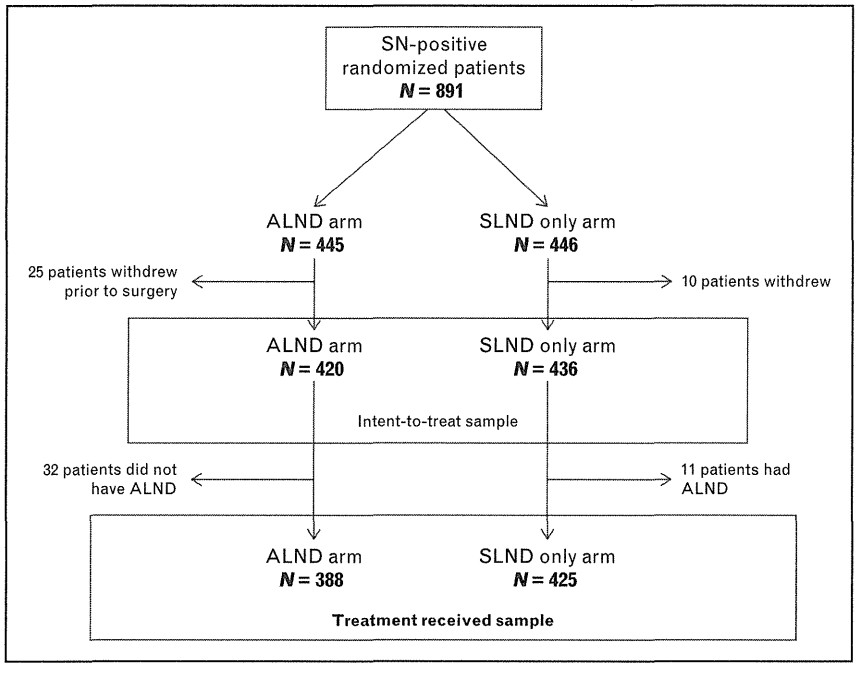



FIGURE 1. ACOSOSG Z0011 patient accrual. Adapted from [20▪▪].

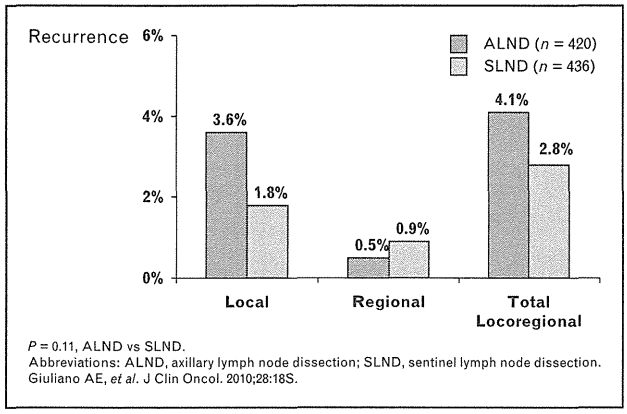



FIGURE 2. ACOSOG Z0011: 5-year recurrence rates. Adapted from [32].

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

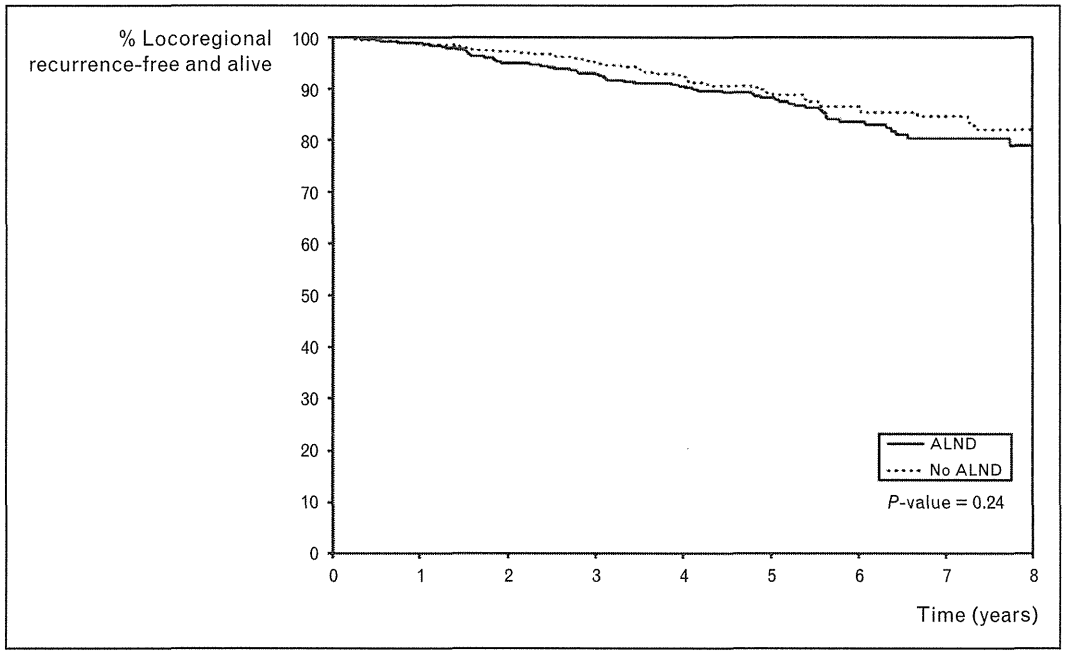



FIGURE 3. ACOSOG Z0011: recurrence-free survival. Adapted from [20▪▪].

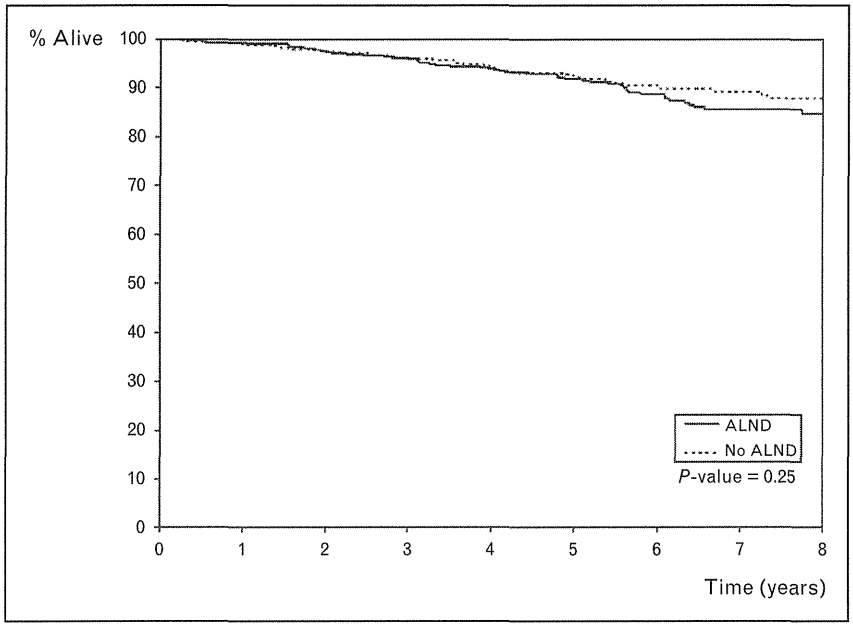



FIGURE 4. ACOSOG Z0011: overall survival. Adapted from [33].

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.

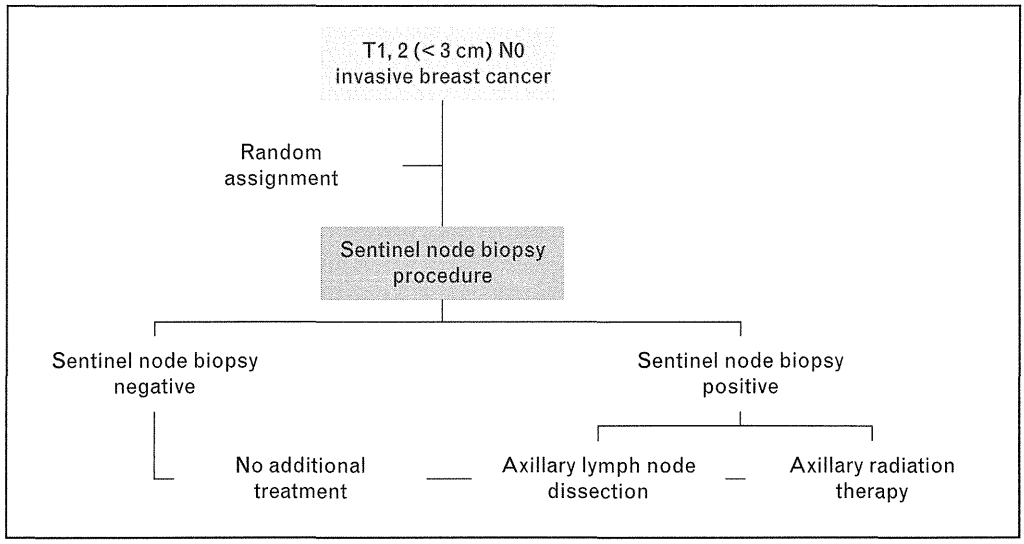



FIGURE 5. AMAROS study design. American Society of Clinical Oncology.

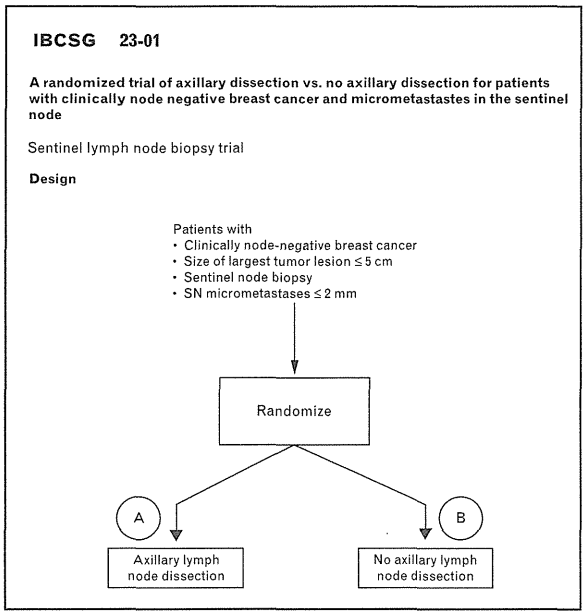



FIGURE 6. IBCSG23-01 study design. http://www.ibcsg.org/Public/Health_Professionals/Closed_Trials/IBCSG%2023-01/Pages/IBCSG23-01.aspx.

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).

1. Giuliano AE, Dale PS, Turner RR, *et al.* Improved axillary staging of breast cancer with sentinel lymphadenectomy. Ann Surg 1995; 222:394–399.
2. Giuliano AE, Kirgan DM, Guenther JM, *et al.* Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg 1994; 220:391–398.
3. Veronesi U, Paganelli G, Viale G, *et al.* A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 2003; 349:546–553.
4. Mansel RE, Fallowfield L, Kissin M, *et al.* Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC trial. J Natl Cancer Inst 2006; 98:599–609.
5. ▪▪ Kell MR, Burke JP, Barry M, *et al.* Outcome of axillary staging in early breast cancer: a meta-analysis. Breast Cancer Res Treat 2010; 120:441–447.

The review found that SNB was equivalent to ALND for detection of lymph node metastasis in early-stage breast cancer with lower morbidity.

6. McLaughlin SA, Wright MJ, Morris KT, *et al.* Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements. J Clin Oncol 2008; 26:5213–5219.
7. Erickson VS, Pearson ML, Ganz PA, *et al.* Arm edema in breast cancer patients. J Natl Cancer Inst 2001; 93:96–111.
8. Giuliano AE, Haigh PI, Brennan MB, *et al.* Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node-negative breast cancer. J Clin Oncol 2000; 18:2553–2559.
9. Goyal A, Newcombe RG, Chhabra A, Mansel RE. Morbidity in breast cancer patients with sentinel node metastases undergoing delayed axillary lymph node dissection (ALND) compared with immediate ALND. Ann Surg Oncol 2008; 15:262–267.
10. Bear HD. Completion axillary lymph node dissection for breast cancer: immediate versus delayed versus none. J Clin Oncol 2008; 26:3483–3484.
11. Krag DN, Julian TB, Harlow SP, *et al.* NSABP-32: phase III, randomized trial comparing axillary resection with sentinel lymph node dissection: a description of the trial. Ann Surg Oncol 2004; 11:208S–210S.
12. Krag DN, Anderson SJ, Julian TB, *et al.* Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 2010; 11:927–933.
13. Chu KU, Turner RR, Hansen NM, *et al.* Do all patients with sentinel node metastasis from breast carcinoma need complete axillary node dissection? Ann Surg 1999; 229:536–541.
14. Chu KU, Turner RR, Hansen NM, *et al.* Sentinel node metastasis in patients with breast carcinoma accurately predicts immunohistochemically detectable nonsentinel node metastasis. Ann Surg Oncol 1999; 8:756–761.
15. Grube BJ, Giuliano AE. Observation of the breast cancer patient with a tumor-positive sentinel node: implications of the ACOSOG Z0011 trial. Semin Surg Oncol 2001; 20:230–237.
16. Park J, Fey JV, Naik AM, *et al.* A declining rate of completion axillary dissection in sentinel lymph node-positive breast cancer patients is associated with the use of a multivariate nomogram. Ann Surg 2007; 245:462–468.
17. Van Zee KJ, Manasseh DM, Bevilacqua JL, *et al.* A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. Ann Surg Oncol 2003; 10:1140–1151.
18. Lyman GH, Giuliano AE, Somerfield MR, *et al.* American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 2005; 23:7703–7720.
19. Giuliano AE, McCall L, Beitsch P, *et al.* Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg 2010; 252:426–432.
20. ▪▪ Giuliano AE, Hunt KK, Ballman KV, *et al.* Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011; 305:569–575.

Among patients with limited SLN metastatic breast cancer treated with breast conservation and systemic therapy, the use of SLND alone compared with ALND did not result in inferior survival.

**21.** Caudle AS, Hunt KK, Kuerer HM, *et al.* Multidisciplinary considerations in the ▪ implementation of the findings from the American College of Surgeons Oncology Group (ACOSOG) Z0011 Study: a Practice-Changing Trial. Ann Surg Oncol 2011; 18:2407–2412.
The omission of cALND according to ACOSOG Z0011 in selected patients has become part of the national practice pattern including MD Anderson Cancer Center.
**22.** Tan LK, Giri D, Hummer AJ, *et al.* Occult axillary node metastases in breast cancer are prognostically significant: results in 368 node-negative patients with 20-year follow-up. J Clin Oncol 2008; 26:1803–1809.
**23.** de Boer M, van Dijck JA, Bult P, *et al.* Breast cancer prognosis and occult lymph node metastases, isolated tumor cells, and micrometastases. J Natl Cancer Inst 2010; 102:410–425.
**24.** Weaver DL, Ashikaga T, Krag DN, *et al.* N. Effect of occult metastases on survival in node-negative breast cancer. N Engl J Med 2011; 364:412–421.
**25.** Mamounas EP, Wolmark N. Effect of occult metastases on survival in node-negative breast cancer. N Engl J Med 2011; 364:412–421.
**26.** Veronesi U, Viale G, Paganelli G, *et al.* Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. Ann Surg 2010; 251:595–600.
**27.** Spiguel L, Yao K, Winchester DJ, *et al.* Sentinel node biopsy alone for node- ▪ positive breast cancer: 12-year experience at a single institution. J Am Coll Surg 2011; 213:122–128.
Axillary recurrence is rare after SNB alone. This might be related to favorable tumor and patient characteristics and frequent use of adjuvant therapy.
**28.** Schem C, Jonat W, Ostertag H, et al. Observation or standard axillary ▪ dissection after sentinel-node biopsy in breast cancer: Final results from the German KISS study. J Clin Oncol 2011; 29 (suppl; abstr 1012). http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=102&abstractID=83261
No significant differences in DFS and OS between the SAD group and the observation group.
**29.** Kim J, Lee J, Chang E, *et al.* Selective sentinel node plus additional non-sentinel node biopsy based on an FDG-PET/CT scan in early breast cancer patients: single institutional experience. World J Surg 2009; 33:943–949.
**30.** Straver ME, Meijnen P, van Tienhoven G, *et al.* Role of axillary clearance after a tumor-positive sentinel node in the administration of adjuvant therapy in early breast cancer. JCO 2010; 28:731–737.
**31.** Galimberti V, Botteri E, Chifu C, *et al.* Can we avoid axillary dissection in the micrometastatic sentinel node in breast cancer? Breast Cancer Res Treat 2012; 131:819–825.
**32.** Giuliano AE, JcCall L, Beistsch P, *et al.* Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg 2010; 252:426–432.
**33.** Giuliano AE, Hunt KK, Ballman KV, *et al.* Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011; 305:569–575.

Original Article

# Analysis of Ki-67 Expression With Neoadjuvant Anastrozole or Tamoxifen in Patients Receiving Goserelin for Premenopausal Breast Cancer

Hiroji Iwata, MD[1]; Norikazu Masuda, MD[2]; Yasuaki Sagara, MD[3]; Takayuki Kinoshita, MD[4]; Seigo Nakamura, MD[5]; Yasuhiro Yanagita, MD[6]; Reiki Nishimura, MD[7]; Hirotaka Iwase, MD[8]; Shunji Kamigaki, MD[9]; Hiroyuki Takei, MD[10]; Hitoshi Tsuda, MD[11]; Nobuya Hayashi, BA[12]; and Shinzaburo Noguchi, MD[13]

**BACKGROUND:** The increasing costs associated with large-scale adjuvant trials mean that the prognostic value of biologic markers is increasingly important. The expression of nuclear antigen Ki-67, a marker of cell proliferation, has been correlated with treatment efficacy and is being investigated for its value as a predictive marker of therapeutic response. In the current study, the authors explored correlations between Ki-67 expression and tumor response, estrogen receptor (ER) status, progesterone receptor (PgR) status, and histopathologic response from the STAGE study (Study of Tamoxifen or Arimidex, combined with Goserelin acetate to compare Efficacy and safety). **METHODS:** In a phase 3, double-blind, randomized trial (National Clinical Trials identifier NCT00605267), premenopausal women with ER-positive, early stage breast cancer received either anastrozole plus goserelin or tamoxifen plus goserelin for 24 weeks before surgery. The Ki-67 index, hormone receptor (ER and PgR) status, and histopathologic responses were determined from histopathologic samples that were obtained from core-needle biopsies at baseline and at surgery. Tumor response was determined by using magnetic resonance imaging or computed tomography. **RESULTS:** In total, 197 patients were randomized to receive either anastrozole plus goserelin (n = 98) or tamoxifen plus goserelin (n = 99). The best overall tumor response was better for the anastrozole group compared with the tamoxifen group both among patients who had a baseline Ki-67 index ≥20% and among those who had a baseline Ki-67 index <20%. There was no apparent correlation between baseline ER status and the Ki-67 index in either group. Positive PgR status was reduced from baseline to week 24 in the anastrozole group. **CONCLUSIONS:** In premenopausal women with ER-positive breast cancer, anastrozole produced a greater best overall tumor response compared with tamoxifen regardless of the baseline Ki-67 index. ***Cancer* 2013;119:704-13.** © *2012 American Cancer Society.*

**KEYWORDS:** anastrozole, aromatase inhibitor, biomarker, neoadjuvant, Ki-67, premenopausal breast cancer.

## INTRODUCTION

In addition to ablative surgery, radiotherapy, and cytotoxic chemotherapy, an additional standard treatment option for premenopausal women with estrogen receptor (ER)-positive breast cancer is the ER antagonist tamoxifen, either alone or in combination with ovarian function suppression.[1] Temporary and potentially reversible ovarian suppression can be achieved by treatment with a luteinizing hormone-releasing hormone analog, such as goserelin. Goserelin in combination with tamoxifen has demonstrated improved progression-free survival and disease-free survival compared with goserelin alone in premenopausal women with hormone receptor-positive (ER-positive and/or progesterone receptor [PgR]-positive) breast cancer in the advanced[2] and adjuvant[3] settings.

Nonsteroidal aromatase inhibitors (AIs), including anastrozole and letrozole, and the irreversible steroidal aromatase inactivator exemestane have demonstrated improved efficacy compared with tamoxifen in the advanced[4-7] and adjuvant[8-

**Corresponding author:** Shinzaburo Noguchi, MD, Department of Breast and Endocrine Surgery, Osaka University Graduate School of Medicine, 2-15 Yamadaoka Suita City, Osaka 565-0871, Japan; Fax: (011) 81-6-6789-3779; noguchi@onsurg.med.osaka-u.ac.jp

[1]Department of Breast Oncology, Aichi Cancer Center Hospital, Aichi, Japan; [2]Department of Surgery, Breast oncology, National Hospital Organization, Osaka National Hospital, Osaka, Japan; [3]Department of Breast Surgery, Sagara Hospital, Kagoshima, Japan; [4]Division of Breast Surgery, National Cancer Center Hospital, Tokyo, Japan; [5]Department of Breast Surgical Oncology, St. Luke's International Hospital, Tokyo, Japan; [6]Department of Breast Oncology, Gunma Cancer Center, Gunma, Japan; [7]Department of Breast and Endocrine Surgery, Kumamoto City Hospital, Kumamoto, Japan; [8]Department of Breast and Endocrine Surgery, Kumamoto University Hospital, Kumamoto, Japan; [9]Department of Surgery, Sakai Municipal Hospital, Osaka, Japan; [10]Department of Breast Surgery, Saitama Cancer Center, Saitama, Japan; [11]Department of Pathology and Clinical Laboratories, National Cancer Center Hospital, Tokyo, Japan; [12]Department of Research and Development, AstraZeneca, Osaka, Japan; [13]Department of Breast and Endocrine Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

Seigo Nakamura's current address: Department of Breast Surgical Oncology, Showa University Hospital, Tokyo, Japan.

Presented as an oral presentation at the 47th Annual Meeting of the American Society of Clinical Oncology; June 3-7, 2011; Chicago, IL.

We thank Takayuki Kobayashi, Harumi Nakamura, Masafumi Kurosumi, and Futoshi Akiyama for their roles as members of the Central Pathological Review Committee. We also thank Simon Vass, PhD, from Complete Medical Communications, who provided medical writing support that was funded by AstraZeneca.

**DOI:** 10.1002/cncr.27818, **Received:** May 18, 2012; **Revised:** August 9, 2012; **Accepted:** August 13, 2012, **Published online** September 12, 2012 in Wiley Online Library (wileyonlinelibrary.com)

[12] treatment settings. Therefore, AIs in combination with ovarian suppression have been evaluated for the treatment of premenopausal women with ER-positive breast cancer.[13,14]

Neoadjuvant treatment for breast cancer provides an opportunity for downstaging of large tumors to allow patients to undergo breast-conserving surgery rather than mastectomy. Chemotherapy can offer an effective neoadjuvant treatment; however, increasing evidence suggests that ER-positive tumors are less sensitive to chemotherapy.[15] It has been demonstrated that neoadjuvant endocrine therapy has efficacy in the treatment of ER-positive disease among postmenopausal women, resulting in similar objective response rates and rates of breast-conserving surgery for AIs compared with more cytotoxic chemotherapy.[16] Therefore, the role of neoadjuvant endocrine therapy in premenopausal women is also of interest.

With the increasing costs associated with large-scale adjuvant trials, both the prognostic value of biologic markers and the long-term predictive value of short-term trials are increasingly important. The expression of nuclear antigen Ki-67, a marker of cell proliferation, reportedly has been correlated with treatment efficacy and is being investigated for its value as a predictive marker of therapeutic response.[17] In a cross-trial comparison, an increased reduction in Ki-67 expression after neoadjuvant treatment with anastrozole compared with tamoxifen was observed consistently; and increased progression-free survival has been reported for anastrozole versus tamoxifen in the adjuvant Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial.[8,18,19]

The STAGE study (Study of Tamoxifen or Arimidex Combined With Goserelin Acetate to Compare Efficacy and Safety) was the first randomized trial to compare anastrozole plus goserelin versus tamoxifen plus goserelin in the neoadjuvant setting (24 weeks of therapy) in premenopausal women with ER-positive and human epidermal growth factor receptor 2 (HER2)-negative, operable breast cancer. The patients who received anastrozole plus goserelin in that trial had a superior best overall tumor response compared with the patients who received tamoxifen plus goserelin, as measured on magnetic resonance imaging (MRI) or computed tomography (CT) studies (anastrozole plus goserelin, 64.3%; tamoxifen plus goserelin, 37.4%; estimated difference, 26.9%; 95% confidence interval [CI], 13.5-40.4; $P < .001$). The treatment effect was consistently in favor of anastrozole, regardless of the measurement methods (caliper and ultrasound). The histopathologic response rate also was better in the anastrozole group (anastrozole plus goserelin, 41.8%; tamoxifen plus goserelin, 27.3%; estimated difference, 14.6%; 95% CI, 1.4-27.7; $P = .032$). Both treatment regimens were well tolerated, consistent with the known safety profiles of anastrozole, tamoxifen, and goserelin.[20] The geometric mean Ki-67 index at baseline was 21.9% in the anastrozole group and 21.6% in the tamoxifen group. At week 24, the Ki-67 index was reduced in both treatment groups (to 2.9% in the anastrozole group and to 8% in the tamoxifen group). The reduction from baseline to week 24 was significantly greater with anastrozole than with tamoxifen. The estimated ratio of reduction between groups was 0.35 (95% CI, 0.24-0.51; $P < .001$).[20] Here, we report an exploratory analysis of the STAGE study that investigated potential correlations between the Ki-67 index and the best overall tumor response, ER status, PgR status, or histopathologic response.

## MATERIALS AND METHODS

### *Study Design and Patients*

In this phase 3, double-blind, randomized, parallel-group, multicenter trial, the participating patients were premenopausal women ≥20 years with ER-positive and HER2-negative breast cancer who had operable and measurable lesions (tumors measuring 2-5 cm, negative lymph node status [N0], and no metastases [M0]). Inclusion and exclusion criteria have been described previously.[20]

Patients were randomized 1:1 to receive either oral anastrozole 1 mg daily with a tamoxifen placebo or oral tamoxifen 20 mg daily with an anastrozole placebo. Both treatment groups received goserelin 3.6 mg as a subcutaneous injection every 28 days. Treatment continued for 24 weeks before surgery or until patients met any criterion for discontinuation.

The primary study endpoint was the best overall tumor response during the 24-week neoadjuvant treatment period. Secondary endpoints included histopathologic response, changes in estrone ($E_1$) and estradiol ($E_2$) serum and breast tumor tissue concentrations, changes in Ki-67 expression, and tolerability. For this exploratory analysis, we assessed correlations between Ki-67 expression and tumor response, ER status, PgR status, or histopathologic response.

The protocol was approved by an institutional review board at all study sites, and all enrolled patients provided written informed consent. The study (National Clinical Trials identifier NCT00605267) was conducted in accordance with the Declaration of Helsinki and good clinical practice, the applicable local regulatory requirements, and the AstraZeneca policy on Bioethics.

### *Assessments*

Tumor measurements were performed using caliper measurements, ultrasound, or MRI or CT studies. The

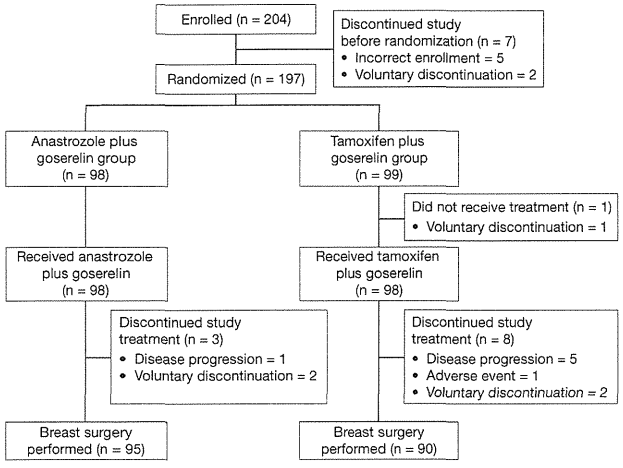



**Figure 1.** This is a CONSORT (Consolidated Standards of Reporting Trials) diagram of the current study.

primary analysis indicated that the best overall tumor response for anastrozole versus tamoxifen was consistent, regardless of the measurement method used.[20] We present tumor response data from the MRI or CT measurements at day 0 and at 24 weeks. The objective tumor response was assessed according to modified Response Evaluation Criteria in Solid Tumors (RECIST).[21]

The status of Ki-67, ER, and PgR was determined using histopathologic core-needle biopsy specimens that were collected at baseline and at surgery. Tissue sections were fixed in formalin and stored at room temperature before immunohistochemical staining. Ki-67 expression was determined by staining sections with an anti-MIB-1 antibody at a central laboratory (SRL Inc., Tokyo, Japan) for assessment by a central review board. For all slides, photomicrographs were taken from 3 to 5 hotspots at $\times$20 magnification using light microscopy. Two pathologists independently assessed the photomicrographs, and the Ki-67 index was calculated as the ratio of Ki-67-positive cancer cells from a total of 1000 cancer cells. ER-positive status and PgR-positive status at baseline were defined as $\geq$10% staining of cancer cell nuclei determined by a pathologist at each individual study site (nuclei were assessed using mouse monoclonal antibody clones 6F11 and 16, respectively). Staining for ER and PgR also was assessed in parallel using Allred scores by the Central Pathologist Review Committee.[22] An Allred score (the proportion score plus the intensity score) of $\geq$3 defined ER or PgR positivity, a score from $\geq$3 to $<$7 indicated medium expression, and a score of $\geq$7 indicated rich expression.

Histopathologic effects were assessed by comparing histopathologic samples that were obtained at baseline and at surgery. For the assessment of histopathologic response, the following categories were used: grade 0 indicated no response; grade 1a, marked change in $<$1 of 3 cancer cells; grade 1b, marked changes in $\geq$1 of 3 but $<$2 of 3 cancer cells; grade 2, marked changes in $\geq$2 of 3 cancer cells; and grade 3, necrosis or disappearance of all cancer cells and replacement of all cancer cells by granuloma-like and/or fibrous tissue. The histopathologic response was defined as the proportion of patients whose tumors were classified as grade 1b, 2, or 3.[23,24]

Post hoc subset analyses were used to determine correlations between the baseline Ki-67 index ($\geq$20% vs $<$20%) and the best overall tumor response. The percentage change in the Ki-67 index for responders (patients whose best overall tumor response was a complete or partial response) versus nonresponders (patients whose best overall tumor response was stable or progressive disease) also was compared. Correlations between the baseline Ki-67 index and the histopathologic response at week 24 also were evaluated, and we used post hoc analyses to investigate correlations between changes in the Ki-67 index from baseline to week 24 and ER or PgR status at baseline. Positive ER and PgR status (Allred score $\geq$3) also was assessed at baseline and at week 24. Preoperative Endocrine Prognostic Index (PEPI) scores, which were calculated post hoc as the sum of risk points weighted by the size of the hazard ratio for tumor size, pathologic lymph node status, ER status, and Ki-67 expression for both recurrence-free and breast cancer-specific survival, were determined for each patient at surgery according to the methods described by Ellis and colleagues.[25]

### *Statistical Analysis*

The sample size calculation and the main statistical analyses have been described previously.[20] All randomized patients were included in the intent-to-treat analysis set.

In a post hoc exploratory analysis, chi-square tests were performed to compare the best overall tumor response at week 24 between baseline Ki-67 index categories ($\geq$20% vs $<$20%) within each treatment group and between treatment groups within each baseline Ki-67 index category. A chi-square test also was used to compare the histopathologic response at 24 weeks between the baseline Ki-67 index categories within each treatment group. All tests were made at the nominal 2-sided significance level of .05.

## RESULTS

### *Patients*

In total, 197 patients were randomized to receive either anastrozole plus goserelin (n = 98) or tamoxifen plus goserelin (n = 99) (Fig. 1). Patient demographics and

**TABLE 1.** Patient Demographics and Baseline Tumor Characteristics

| Characteristic | No. of Patients (%) | |
|---|---|---|
| | Anastrozole Plus Goserelin | Tamoxifen Plus Goserelin |
| No. of patients | 98 | 99 |
| Age: Median [range] | 44 [28-54] | 44 [30-53] |
| Body mass index: Mean±SD, kg/m$^2$ | 22.2±3.5 | 22.1±3.3 |
| Histology type | | |
| Infiltrating ductal carcinoma | 87 (88.8) | 91 (91.9) |
| Infiltrating lobular carcinoma | 3 (3.1) | 3 (3) |
| Other[a] | 8 (8.2) | 5 (5.1) |
| Tumor grade | | |
| 1 | 42 (42.9) | 48 (48.5) |
| 2 | 36 (36.7) | 26 (26.3) |
| 3 | 4 (4.1) | 14 (14.1) |
| Not assessable | 1 (1) | 0 (0) |
| Not done | 15 (15.3) | 11 (11.1) |
| Hormone receptor status | | |
| ER positive | 98 (100) | 99 (100) |
| PgR positive | 93 (94.9) | 87 (87.9) |
| HER2 negative | 98 (100) | 99 (100) |

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; SD, standard deviation.
[a] Other included adenocarcinoma (n = 3).

baseline characteristics generally were well balanced between the treatment groups (Table 1). Paired samples for calculating changes in the Ki-67 index from baseline to week 24 were available for 89 patients in the anastrozole plus goserelin group and for 86 patients in the tamoxifen plus goserelin group.

### *Correlation of the Baseline Ki-67 Index and Best Overall Tumor Response*

With a mean baseline Ki-67 index of 21.9% and 21.6% in the anastrozole and tamoxifen treatment groups, respectively, we used post hoc subset analyses to compare patients according to their baseline Ki-67 index (≥20 vs <20%). For anastrozole versus tamoxifen, best overall tumor response from baseline to week 24 was better with anastrozole plus goserelin versus tamoxifen plus goserelin both in patients who had a baseline Ki-67 index ≥20% (73.2% vs 44.8%; $P = .002$) and in patients who had a baseline Ki-67 index <20% (52.5% vs 29%; $P = .035$) (Fig. 2A).

Within the treatment groups, the best overall tumor response from baseline to 24 weeks, as measured by MRI or CT, was significantly better with anastrozole plus goserelin for patients who had a baseline Ki-67 index ≥20% than for those who had a baseline Ki-67 index <20% (73.2% vs 52.5%; $P = .036$). Among patients in the tamoxifen plus goserelin group, the best overall tumor response was 44.8% for patients who had a baseline Ki-67 index ≥20% and 29% for those who had a baseline Ki-67 index <20% ($P = .118$) (Fig. 2A).

### *Correlation of the Baseline Ki-67 Index and Histopathologic Response*

There was no significant difference in the histopathologic response between patients who had a baseline Ki-67 index ≥20% versus patients who had a baseline Ki-67 index <20% in either treatment group (Fig. 2B).

### *Correlation of Change in the Ki-67 Index and Responders/Nonresponders*

A waterfall plot of changes in the Ki-67 index for individual patients, illustrated according to responders or nonresponders, is provided in Figure 3. There was no apparent relation between a change in Ki-67 expression from baseline to week 24 for responders and nonresponders in either treatment group.

### *Correlation of the Baseline Ki-67 Index and Estrogen Receptor or Progesterone Receptor Status*

In both treatment groups, positive ER status, as determined by the Allred score, was observed in 100% of patients at baseline and at week 24, and >90% of patients in both treatment groups were ER rich (baseline Allred score, ≥7). Therefore, it was not possible to determine any potential relation between the baseline ER Allred score and the percentage change in Ki-67 expression from baseline to week 24 in either treatment group.

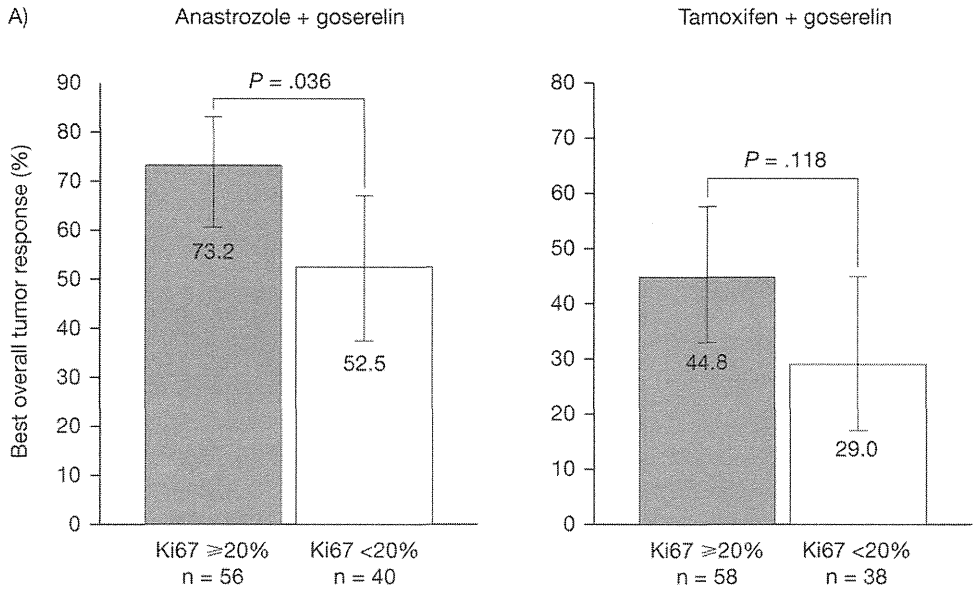
In the anastrozole plus goserelin group, 98.9% of patients were positive for PgR expression at baseline, and 34.4% were positive for PgR expression at week 24. The percentage of patients with positive PgR status was not altered from baseline (91.9%) to week 24 (89.5%) in the tamoxifen plus goserelin group (Fig. 4A). In both treatment groups, the mean decrease in the Ki-67 index was greater in patients who had a baseline PgR Allred score ≥7 (anastrozole group, −88.8%; tamoxifen group, −67.6%), compared with patients who had a baseline PgR Allred score <7 (anastrozole group, −74.1%; tamoxifen group, −32.8%) (Fig. 4B).

### *Preoperative Endocrine Prognostic Index Score*

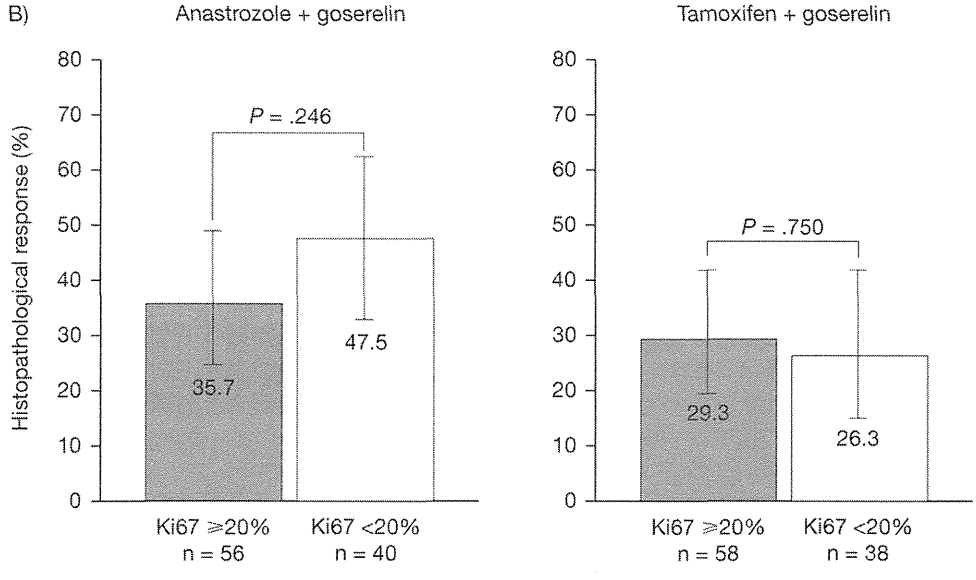
In the anastrozole treatment group, 33.3% of patients had a PEPI score of 0 compared with 11.4% in the tamoxifen group. Fewer patients (21.4%) had a PEPI score ≥4 in the anastrozole group compared with patients in the tamoxifen group (36.7%; $P = .002$) (Table 2).

## DISCUSSION

In this exploratory analysis, we investigated changes in Ki-67 expression among patients from the STAGE study, a




Baseline Ki67 ⩾20%: $P = .002$ between treatment groups.
Baseline Ki67 <20%: $P = .035$ between treatment groups ($X^2$ test).




Baseline Ki67 ⩾20%: $P = .053$ between treatment groups.
Baseline Ki67 <20%: $P = .465$ between treatment groups ($X^2$ test).

**Figure 2.** These charts illustrate the baseline Ki-67 index (≥20% vs <20%) according to (A) the best overall tumor response and (B) the histopathologic response at 24 weeks. Magnetic resonance imaging or computed tomography was used to measure responses. The best tumor response was defined a complete or partial response during the 24-week treatment period.

phase 3 randomized trial that compared tumor response for anastrozole plus goserelin versus response tamoxifen plus goserelin during 24 weeks of neoadjuvant treatment in premenopausal women with ER-positive breast cancer. The primary analysis indicated that the reduction in the Ki-67 index for patients who received goserelin was greater with anastrozole coadministration compared with tamoxifen, suggesting a greater inhibitory effect on tumor cell proliferation with this treatment combination.[20] Given the reported clinical prognostic value of Ki-67 expression after short-term neoadjuvant endocrine therapy for breast cancer,[19] this is in concordance with our finding that anastrozole combined with goserelin demonstrates a superior best overall tumor response compared with tamoxifen plus goserelin. Although Ki-67 is perceived as a reliable predictive endpoint, the outcomes of

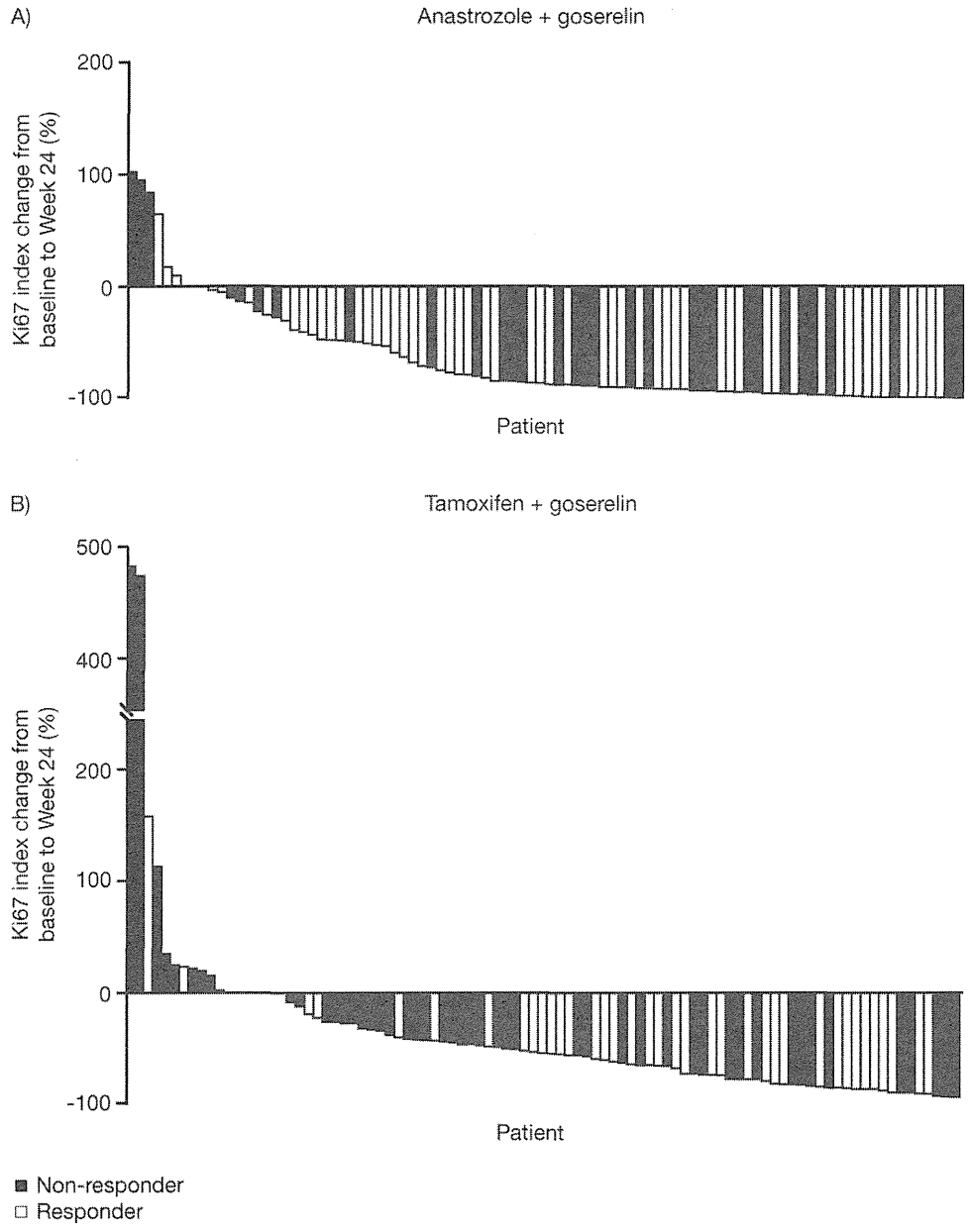



**Figure 3.** This is a waterfall plot of reductions in nuclear antigen Ki-67 levels in (A) the anastrozole plus goserelin treatment group and (B) the tamoxifen plus goserelin treatment group. Magnetic resonance imaging or computed tomography was used to measure responses. Responders were defined as those patients who had a complete or partial response during the 24-week treatment period.

the parallel adjuvant trial by the Austrian Breast and Colorectal Cancer Study Group (ABCSG) did not reflect outcomes related to the Ki-67 changes we observed: Results from the ABCSG-12 study indicated that there was no difference in disease-free survival between patients who received anastrozole versus tamoxifen (hazard ratio, 1.08; 95% CI, 0.81-1.44; $P = .591$).[26] The reason for this difference is not clear, although there were differences in the baseline characteristics of patients in each study: the STAGE study assessed a more hormone-dependent phenotype of tumor (ER-positive/HER2-negative in the STAGE study vs ER-positive/HER2-negative and ER-positive/HER2-positive in the ABCSG-12 trial), and the proportion of women with a body mass index >25 kg/m$^2$ was lower in the STAGE study (17% vs 33%). The ABCSG-12 group did not assess Ki-67 levels. It is also interesting to note that, as recently pointed out by Goncalves et al,[27] in our study, serum estradiol suppression

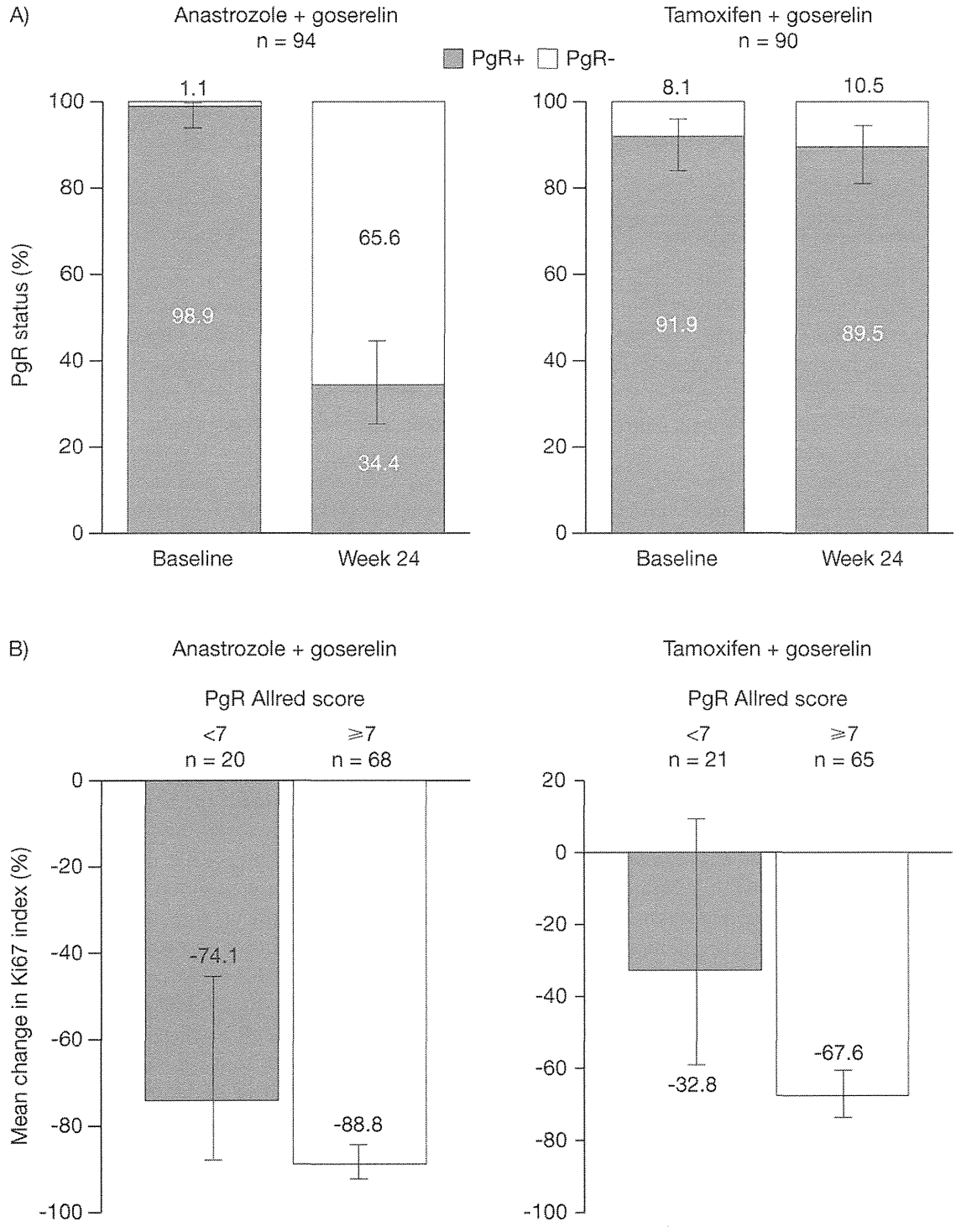



**Figure 4.** (A) Progesterone receptor status is illustrated at baseline and at 24 weeks. (B) Changes in the Ki-67 index and the baseline PgR Allred score are illustrated. PgR-positive (PgR+) indicates an Allred score >3; PgR-negative (PgR−), an Allred score <2.

appeared to decrease at week 24 compared with week 4, although the suppression was not statistically significant. This suggests the possibility of a gradual tachyphylaxis of the estrogen-suppressing effects of combined goserelin and anastrozole treatment, which potentially may explain the difference in outcomes between the ABCSG-12 and STAGE studies. However, further investigations would be required to confirm this.

**TABLE 2.** Preoperative Endocrine Prognostic Index Score

| Treatment Group | No. of Patients | PEPI Score: No. of Patients (%) | | |
|---|---|---|---|---|
| | | 0 | 1-3 | ≥4 |
| Anastrozole plus goserelin | 84 | 28 (33.3) | 38 (45.2) | 18 (21.4) |
| Tamoxifen plus goserelin | 79 | 9 (11.4) | 41 (51.9) | 29 (36.7) |
| *P* for anastrozole vs tamoxifen | | — | — | .002 |

Abbreviation: PEPI, Preoperative Endocrine Prognostic Index.
[a]*P* values were determined using the chi-square test.

In the current study, the best overall tumor response was superior with anastrozole compared with tamoxifen, irrespective of the baseline Ki-67 index. Within the anastrozole treatment group, we observed that the best overall tumor response was significantly better in patients who had a baseline Ki-67 index ≥20% versus patients who had a baseline Ki-67 index <20%. However, in the anastrozole group, we observed a numerically lower histopathologic response in patients who had a baseline Ki-67 index ≥20% compared with those who had a baseline Ki-67 index <20%. It was reported previously that baseline Ki-67 expression was not associated with outcome after neoadjuvant endocrine treatment (including anastrozole, letrozole, and tamoxifen) in ER-positive, postmenopausal women who had breast cancer.[19,25]

There was no apparent relation between a reduction in the Ki-67 index for responders and nonresponders in either treatment group. Although there tended to be more nonresponders among patients in the tamoxifen group who had less of a reduction in the Ki-67 index, the Spearman rank-correlation between the percentage change in the Ki-67 index and the best percentage change in greatest tumor dimension for the tamoxifen group was a modest 0.314. This observation is essentially consistent with what was reported previously by Dowsett et al, who conducted a similar analysis of postmenopausal patients who received neoadjuvant tamoxifen, anastrozole, and the tamoxifen/anastrozole combination.[28] This variation in the Ki-67 index change between responders and nonresponders indicates that the mechanism of estrogen-dependent growth is heterogeneous among breast tumors. Tumor growth is determined by a balance between cell proliferation and apoptosis. Stimulation of cell proliferation by estrogen may be dominantly implicated in tumor growth in some tumors, whereas inhibition of apoptosis by estrogen may be dominantly implicated in other tumors. Thus, a responder does not necessarily have a greater reduction in the Ki-67 index compared with a nonresponder if apoptosis is induced more strongly in the former than the latter after treatment.

In the neoadjuvant setting, endocrine therapy has demonstrated greater (or equivalent) efficacy in postmenopausal women with a lower Ki-67 index.[29,30] In contrast, in our study, both anastrozole and tamoxifen produced greater response rates in premenopausal women with a higher Ki-67 index. It is therefore possible that the main pathways of proliferative stimulation (and the effectiveness of endocrine treatments) may differ between premenopausal and postmenopausal women with ER-positive breast cancer, according to their level of Ki-67 expression. In general, high Ki-67 expression is traditionally is believed to offer a poor prognosis and is predictive of response to chemotherapy regimens.[31] However, our results suggest that endocrine therapy has at least comparable effectiveness for premenopausal patients with ER-positive breast cancer who have a high Ki-67 index.

No correlation could be determined between a change in the Ki-67 index and baseline ER status in either treatment group. However, the number of patients who were identified as PgR-positive decreased at week 24 in the anastrozole treatment group, an effect that was not observed in the patients who received tamoxifen plus goserelin. PgR expression also was reduced under neoadjuvant AI treatment for breast cancer in the ABCSG 17 study, although it remains to be determined whether the down-regulation of PgR may be used as a marker of clinical efficacy.[32] In our study, the reason why the positive rate of PgR was reduced in the anastrozole plus goserelin arm compared with the tamoxifen plus goserelin arm is most likely because of the estrogenic action of tamoxifen, which would induce PgR expression.

Although there may be a potential correlation between a reduction in Ki-67 and the baseline PgR Allred score in patients who receive anastrozole plus goserelin versus tamoxifen plus goserelin, further analyses will be required to determine whether a Ki-67 reduction in patients with high baseline PgR expression translates into a clinical benefit.

After treatment with anastrozole, a lower proportion of patients had a PEPI score ≥4 (indicating a high risk of

recurrence) compared with the tamoxifen treatment group. The PEPI model has been validated previously and has indicated significant differences in recurrence-free survival in the adjuvant setting between 3 PEPI risk groups (PEPI risk scores of 0, 1-3, and $\geq$4), with a PEPI score of 0 indicating a very low risk of relapse.[25] Data from the adjuvant treatment setting will provide added knowledge for the individualization of future adjuvant treatments after neoadjuvant therapy for breast cancer.

Currently, very little is known about the prognostic effect of Ki-67 in premenopausal women. However, in 1 recent study, the prognostic significance of Ki-67 was investigated in women with ER-positive breast cancer who had received short-term presurgical tamoxifen, and Decensi and colleagues reported that the Ki-67 response was a good predictor of recurrence-free survival and overall survival.[33]

To our knowledge, this is the first randomized study to investigate the potential of Ki-67 as a clinical biomarker for AI efficacy in premenopausal women with ER-positive breast cancer. It has been demonstrated that a reduction in Ki-67 expression as a result of neoadjuvant AI treatment can be a potentially useful marker of improved surgical outcomes in postmenopausal women with ER-positive breast cancer, and such a reduction has been identified as predictive of favorable outcomes in the adjuvant treatment period.[34] A reduction in Ki-67 expression during neoadjuvant treatment reportedly was greater with anastrozole versus tamoxifen in postmenopausal women who had ER-positive breast cancer,[18] and a parallel result also was observed in the corresponding adjuvant trial, in which recurrence-free survival also was greater for those who received anastrozole.[8] Yet another similar result was observed for letrozole, in which a greater Ki-67 reduction was observed compared with tamoxifen in the neoadjuvant setting.[35] Greater clinical effectiveness also was observed for letrozole in the neoadjuvant setting, both in terms of the objective response rate and the rate of breast-conserving surgery.[36]

In conclusion, tumor response was greater with anastrozole compared with tamoxifen, regardless of the baseline Ki-67 index, in premenopausal women who received goserelin as neoadjuvant therapy for ER-positive, early stage breast cancer. The current results indicate that endocrine therapy may offer a more tolerable treatment option than cytotoxic chemotherapy as neoadjuvant treatment for these patients, and further studies of the anastrozole plus goserelin treatment combination in this setting are warranted.

## FUNDING SOURCES

This work was supported by AstraZeneca.

## CONFLICT OF INTEREST DISCLOSURES

Dr. Iwase has received honoraria from AstraZeneca and research funding from AstraZeneca; Chugai Pharmaceutical Company, Ltd.; Novartis; and Takeda. Mr. Hayashi is an employee and holds stock ownership with AstraZeneca. Dr. Noguchi has received honoraria and research funding from and has acted in a consultant or in an advisory role for AstraZeneca.

## REFERENCES

1. Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thurlimann B, Senn H-J. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. *Ann Oncol.* 2009;20:1319-1329.
2. Jonat W, Kaufmann M, Blamey RW, et al. A randomised study to compare the effect of the luteinising hormone releasing hormone (LHRH) analogue goserelin with or without tamoxifen in pre- and perimenopausal patients with advanced breast cancer. *Eur J Cancer.* 1995;31A:137-142.
3. Jakesz R, Hausmaninger H, Kubista E, et al. Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer—Austrian Breast and Colorectal Cancer Study Group Trial 5. *J Clin Oncol.* 2002;20:4621-4627.
4. Mouridsen H, Gershanovich M, Sun Y, et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol.* 2001;19:2596-2606.
5. Nabholtz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. *J Clin Oncol.* 2000;18:3758-3767.
6. Bonneterre J, Thurlimann B, Robertson JF, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol.* 2000;18:3748-3757.
7. Paridaens RJ, Dirix LY, Beex LV, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *J Clin Oncol.* 2008;26:4883-4890.
8. Baum M, Budzar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet.* 2002;359:2131-2139.
9. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet.* 2005;365:60-62.
10. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol.* 2010;28:509-518.
11. Cuzick J, Sestak I, Baum M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol.* 2010;11:1135-1141.
12. van de Velde CJ, Rea D, Seynaeve C, et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. *Lancet.* 2011;377:321-331.
13. Forward DP, Cheung KL, Jackson L, Robertson JF. Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer. *Br J Cancer.* 2004;90:590-594.
14. Gnant M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med.* 2009;360:679-691.

15. Tan MC, Al Mushawah F, Gao F, et al. Predictors of complete pathological response after neoadjuvant systemic therapy for breast cancer. *Am J Surg.* 2009;198:520-525.
16. Semiglazov VF, Semiglazov VV, Dashyan GA, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. *Cancer.* 2007;110:244-254.
17. Weigel MT, Dowsett M. Current and emerging biomarkers in breast cancer: prognosis and prediction. *Endocr Relat Cancer.* 2010;17:R245-R262.
18. Dowsett M, Smith IE, Ebbs SR, et al. Short-term changes in Ki-67 during neoadjuvant treatment of primary breast cancer with anastrozole or tamoxifen alone or combined correlate with recurrence-free survival. *Clin Cancer Res.* 2005;11:951s-958s.
19. Dowsett M, Smith IE, Ebbs SR, et al. Prognostic value of Ki-67 expression after short-term presurgical endocrine therapy for primary breast cancer. *J Natl Cancer Inst.* 2007;99:167-170.
20. Masuda N, Sagara Y, Kinoshita T, et al. Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a double-blind, randomised phase 3 trial. *Lancet Oncol.* 2012;13:345-352.
21. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000;92:205-216.
22. Allred DC, Harvey JM, Berardo M, Clark GM. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. *Mod Pathol.* 1998;11:155-168.
23. Sakamoto G, Inaji H, Akiyama F, et al. General rules for clinical and pathological recording of breast cancer 2005. *Breast Cancer.* 2005;12(suppl):S1-S27.
24. Kurosumi M, Takatsuka Y, Watanabe T, et al. Histopathological assessment of anastrozole and tamoxifen as preoperative (neoadjuvant) treatment in postmenopausal Japanese women with hormone receptor-positive breast cancer in the PROACT trial. *J Cancer Res Clin Oncol.* 2008;134:715-722.
25. Ellis MJ, Tao Y, Luo J, et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. *J Natl Cancer Inst.* 2008;100:1380-1388.
26. Gnant M, Mlineritsch B, Stoeger H, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. *Lancet Oncol.* 2011;12:631-641.
27. Goncalves R, Ma C, Luo J, Suman V, Ellis MJ. Use of neoadjuvant data to design adjuvant endocrine therapy trials for breast cancer. *Nat Rev Clin Oncol.* 2012;9:223-229.
28. Dowsett M, Smith IE, Ebbs SR, et al. Proliferation and apoptosis as markers of benefit in neoadjuvant endocrine therapy of breast cancer. *Clin Cancer Res.* 2006;12:1024s-1030s.
29. Endo Y, Toyama T, Takahashi S, et al. High estrogen receptor expression and low Ki-67 expression are associated with improved time to progression during first-line endocrine therapy with aromatase inhibitors in breast cancer. *Int J Clin Oncol.* 2011;16:512-518.
30. Toi M, Saji S, Masuda N, et al. Ki-67 index changes, pathological response and clinical benefits in primary breast cancer patients treated with 24 weeks of aromatase inhibition. *Cancer Sci.* 2011;102:858-865.
31. Urruticoechea A, Smith IE, Dowsett M. Proliferation marker Ki-67 in early breast cancer. *J Clin Oncol.* 2005;23:7212-7220.
32. Mlineritsch B, Tausch C, Singer C, et al. Exemestane as primary systemic treatment for hormone receptor positive post-menopausal breast cancer patients: a phase II trial of the Austrian Breast and Colorectal Cancer Study Group (ABCSG-17). *Breast Cancer Res Treat.* 2008;112:203-213.
33. Decensi A, Guerrieri-Gonzaga A, Gandini S, et al. Prognostic significance of Ki-67 labeling index after short-term presurgical tamoxifen in women with ER-positive breast cancer. *Ann Oncol.* 2011;22:582-587.
34. Ellis MJ, Suman VJ, Hoog J, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype—ACOSOG Z1031. *J Clin Oncol.* 2011;29:2342-2349.
35. Ellis MJ, Ma C. Letrozole in the neoadjuvant setting: the P024 trial. Breast Cancer Res. *Treat.* 2007;105(suppl 1):33-43.
36. Eiermann W, Paepke S, Appfelstaedt J, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: a randomized double-blind multicenter study. *Ann Oncol.* 2001;12:1527-1532.

Breast Cancer (2013) 20:21–25
DOI 10.1007/s12282-011-0306-1

SPECIAL FEATURE

**Preoperative evaluation for intraductal spread of breast cancer through current imaging tests: their strengths and limitations**

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

**Sadako Akashi-Tanaka**

Received: 24 August 2011 / Accepted: 27 September 2011 / Published online: 10 December 2011


**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 |

S. Akashi-Tanaka
Division of Breast Surgery, National Cancer Center Hospital, 5-chome 1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

S. Akashi-Tanaka (✉)
Department of Breast Surgical Oncology, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan
e-mail: sakashi@med.showa-u.ac.jp

## 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