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Paradigm shift in axilla surgery for breast cancer patients treated with sentinel node biopsy

Shigeru Imoto · Hirotsugu Isaka · Noriko Sakemura · Hiroki Ito · Kentaro Imi · Kaisuke Miyamoto

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Abstract
Background Sentinel node biopsy (SNB) is a standard technique for the diagnosis of regional lymph node metastases in clinically node-negative breast cancer patients. In the case of pathologically negative sentinel lymph nodes (SLN), axillary lymph node dissection (ALND) can be avoided.
Methods Recent clinical studies on SNB in breast cancer were reviewed regarding the pathological and molecular diagnosis of SLN, the tools used to predict non-SLN metastases, the prognostic significance of isolated tumor cells (ITC) and micrometastases (MIC), and axilla surgery.
Results ITC or MIC in SLN was associated with worse survival in patients treated with SNB alone or SNB followed by ALND. However, this effect was limited and adjuvant therapy improved survival. If T1 and one SLN-positive breast cancer patients are treated with whole-breast irradiation and adjuvant therapy, additional ALND may not be necessary.
Conclusions SNB without ALND can be adopted for patients with a small number of SLN metastases. Although the lack of apparent regional lymph node recurrence, similar to tumor dormancy, cannot be fully explained, ALND should be performed in cases that are highly suspected to be non-SLN metastases.

Keywords Breast cancer · Micrometastases · Isolated tumor cells · Sentinel lymph nodes

S. Imoto (✉) · H. Isaka · N. Sakemura · H. Ito · K. Imi · K. Miyamoto
Department of Breast Surgery, School of Medicine, Kyorin University, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan
e-mail: imoto@ks.kyorin-u.ac.jp

Introduction

Forty years ago, the National Surgical Adjuvant Bowel and Breast Project (NSABP) B-04 was planned to evaluate the utility of extensive breast surgery [1]. On the basis of the results of 25 years of follow-up, total mastectomy followed by immediate axillary lymph node dissection (ALND) did not affect overall survival (OS) for clinically node-negative and node-positive breast cancer patients in comparison with delayed ALND in cases of regional lymph node recurrence [2]. This result should be considered with caution, because adjuvant therapy was not performed in the 1970s. However, the initial recurrence rate of regional lymph nodes was unexpectedly low (18%) for clinically node-negative breast cancer patients treated with total mastectomy alone, in whom the incidence of nodal metastases had been estimated to be 30% based on the pathological results of patients who had been randomized to receive radical mastectomy. Although this discrepancy, similar to tumor dormancy, is not understood, it raises the clinical issue of whether ALND is appropriate for clinically node-negative breast cancer patients. A new era of axilla surgery has arisen since the sentinel node concept in breast cancer was proposed 20 years ago [3]. Sentinel lymph nodes (SLN) are defined as the first nodes that drain lymphatic flow from solid tumors [4]. This concept was proven and accepted in early stages of breast cancer and melanoma on the basis of the results of feasibility studies on SNB followed by regional lymph node dissection [5, 6]. To evaluate the necessity of axilla surgery for clinically node-negative breast cancer patients, several randomized trials compared SNB with SNB followed by ALND in breast cancer at the end of the 1990s [7–10]. In this article, optimal surgical management in the axilla will be discussed from the perspective of the SLN concept in breast cancer.

Current status of sentinel node biopsy in Japan

To confirm the reliability and safety of SNB in Japanese breast cancer patients, a prospective study on SNB was organized in 2008 by our society, the Japanese Breast Cancer Society. Eighty-one institutes and community hospitals participated in the study. The overall success rate was 98% in over 11,000 cases of dye-guided and/or radioisotope (RI)-guided SNB [11]. In addition, indigocarmine and indocyanine green (Daiichi Sankyo Co., Tokyo, Japan) used for dye-guided SNB were less allergic than isosulfan blue when injected transcutaneously. On the basis of these results, the Japan Ministry of Health, Labour, and Welfare approved dye-guided and/or RI-guided SNB in September 2009. Indigocarmine, indocyanine green, 99m-technetium-labelled tin colloid and 99m-technetium-labelled phytate (Nihon Medi-Physics, Tokyo, Japan) are available as tracers for lymphatic mapping in breast cancer, and national health insurance covers the cost of SNB.

Clinical relevance of micrometastases in sentinel lymph nodes

Although ALND is not recommended for SLN-negative [pN0(sn)] breast cancer at a routine pathological examination, occult metastases could be found more frequently if SLN are examined in greater detail. On the basis of some retrospective studies, the prognostic significance of occult metastases detected in pathologically node-negative breast cancer remains debatable [12, 13]. Unfortunately, there has been no large prospective study on occult metastases, because a detailed pathological examination of all lymph nodes obtained by ALND is considered to be too time-consuming for an institutional laboratory. In contrast, an average of only 2 nodes are needed for the SLN approach to breast cancer. Thus, a more detailed examination in SLN can provide more precise information on nodal metastases. In 2002, the International Union Against Cancer (now the Union for International Cancer Control, UICC) proposed a new classification of lymph node metastases, especially SLN metastases (Table 1) [14]. Isolated tumor cells (ITC) were thought to have no apparent biological activity to disseminate into tumor lymphatics and vessels, but this hypothesis remains uncertain. Regarding the intervals and sections of lymph node specimens and staining methods for detecting ITC and micrometastases (MIC), a standardized pathological examination is not yet available. The American Society of Clinical Oncology recommended pathological examination of SLN at an interval of 2 mm in tissue specimens [15]. On the other hand, the European working group of breast pathology recommended 2 mm as a minimum standard for the identification of SLN metastases,

Table 1 Pathological nodal classification according to TNM staging organized by UICC

Classification	Size of metastases
Isolated tumor cells (i)	>0, ≤0.2 mm or cluster of fewer than 200 cancer cells
Micrometastases (mi)	>0.2, ≤2 mm and in 1–3 lymph nodes
Macrometastases	>2 mm
Non-morphological (mol)	>0 mm

Designated code abbreviations are given in parentheses

because some institutes in Europe have used heterogeneous definitions of ITC and MIC [16]. This group concluded that ITC and MIC in SLN might be shown to have clinical relevance in the future.

Usually hematoxylin–eosin (HE) staining is performed in practice and immunohistochemistry (IHC) staining is helpful for clearly detecting ITC and MIC in SLN. Veronesi et al. [7] first reported a randomized trial to compare SNB with SNB followed by immediate ALND for stage I breast cancer patients. In this study, a pathological examination was performed for both SLN and non-SLN. They examined SLN metastases in 15 pairs of frozen sections cut at 50-μm intervals. If residual tissue was left, additional pairs of sections were made at 100-μm intervals until the SLN had been sampled completely. If the SLN stained with HE were diagnosed as negative, an additional diagnosis was performed based on IHC staining in SLN. In addition, non-SLN were diagnosed by HE staining in 3–6 sections cut several 100 μm apart. A detailed examination revealed that 175 of 516 cases (34%) with stage I disease had positive nodes. Sixty of these (34%) had ITC or MIC in SLN alone and only 10 (17%) had additional metastases in non-SLN. On the basis of these results, occult metastases in SLN could be frequently found even in a small disease, but additional ALND could be omitted in cases with ITC or MIC in SLN alone.

Instead of a pathological workup, there have been rapid advancements in the molecular diagnosis of SLN. The one-step nucleic acid amplification (OSNA) assay is commercially available in Japan and Europe. This assay is highly sensitive and specific for the diagnosis of SLN metastases and has been shown to be highly reproducible in inter-institutional studies [17–19]. However, it has some limitations compared to the pathological diagnosis of SLN by HE staining. First, the OSNA assay measures the expression of cytokeratin (CK) 19 mRNA, and some breast cancer cases exhibit a very low expression of this mRNA. In CK19-negative cases, SN metastases may be overlooked. Second, the cutoff point of this assay is set for the

Table 2 Concordance between pathological nodal diagnosis and OSNA assay

OSNA assay	Pathological diagnosis (no. of nodes)				Concordance		
	NEG	ITC	MIC	MAC	Sensitivity (%)	Specificity (%)	Accuracy (%)
Ref. [17]							
−	263	13	2	0			
+	4	0	3	6	95.6	98.6	98.2
++	0	0	0	34			
Ref. [18]							
−	348	0	6	4			
+	18	3	7	–	87.7	94.3	93.1
++	0	0	–	64			
Ref. [19]							
−	854	14	22	9			
+	29	0	12	9	77.5	95.8	93.4
++	8	1	9	77			

NEG negative, *ITC* isolated tumor cells, *MIC* micrometastases, *MAC* macrometastases, *OSNA* one-step nucleic acid amplification

	Histology	NG	LVI	Mulifocality	ER/PR	HER2	SLN mets	T size	SLN size	Method	Age
MSKCC nomogram [22]	✔	✔	✔	✔	✔		✔	✔	✔	✔	
MD Anderson score [23]			✔	✔	✔	✔	✔	✔		✔	✔
Mayo nomogram [24]					✔		✔		✔	✔	
Tenon score [25]							✔		✔	✔	
Masaryk nomogram [26]	✔		✔	✔			✔	✔	✔		
Stanford nomogram [27]			✔					✔	✔		

Check mark represents factors for predicting non-SLN metastases.

NG nuclear grade, *LVI* lympho-vascular invasion, *SLN mets* number or proportion of positive SLN in all SLN detected, *T size* tumor size, *SLN size* size of the largest SLN metastases including extracapsular invasion, *Method* method for the detection of SLN metastases, *MSKCC* Memorial Sloan-Kettering Cancer Center

Fig. 1 Factors used in predictive tools for non-sentinel lymph node involvement in breast cancer

detection of MIC in lymph nodes. ITC in SLN may sometimes show negative results with the use of this assay (Table 2). However, a recent study demonstrated that this assay using a whole SLN detected cases with MIC more frequently than intraoperative diagnosis of SLN using frozen sections cut at 2-mm intervals did (8.7 vs. 4.5%) [20]. Thus, this assay is as reliable as a breast pathological examination for the detection of SLN metastases. If ITC in SLN is essential when considering adjuvant therapy to achieve a cure, a permanent diagnosis in SLN stained with HE and/or IHC should not be discarded in favor of an OSNA assay.

Tools for predicting non-sentinel lymph node metastases

In general, SLN metastases are identified in about 30% of clinically node-negative breast cancer patients, and half of those with positive SLN have only SLN metastases [5]. On the other hand, 40% of cases with macrometastases (MAC) in SLN have a higher probability of non-SLN metastases. Wada et al. [21] calculated the probability of non-SLN metastases using predictive factors for SLN-positive breast cancer patients who underwent SNB followed by ALND. Of the 185 cases analyzed in their study, 81 (44%) had SLN and non-SLN metastases, including 9 (26%) of the 34 cases with ITC or MIC in SLN and 72 (48%) of the 151 cases with MAC in SLN. A multivariate analysis demonstrated that tumor size, size of the largest SLN metastases, proportion of positive SLN in all SLN detected, and lymphatic invasion of the tumor were independent predictive factors of non-SLN metastases. When one predictive factor, among tumor size greater than 2.0 cm, MAC in SLN, all positive SLN (100%), or positive lymphatic invasion, was identified, the probability of non-SLN metastases was calculated to be 25%. Many investigators have proposed tools for predicting non-SLN metastases [22–27] (Fig. 1). Lympho-vascular invasion, multifocality, number or proportion of positive SLN, tumor size, size of the largest SLN

metastases, and methods for the detection of SLN metastases are common factors that are used for calculations with these tools, and with any tool the area under the receiver operating characteristic curve is around 0.8. Ultrasound, CT, and MRI are also important for detecting nodal metastases in axilla. Retrospective studies have shown that the incidence of MAC in non-SLN ranges from 0 to 13% and from 0 to 18% for breast cancer patients with ITC and MIC in SLN, respectively [21, 28]. Even if the probability of non-SLN metastases is very low using these tools and diagnostic imaging, occult metastases in non-SLN may continue to survive in ITC- or MIC-positive breast cancer patients treated with SNB alone.

Prognostic significance of sentinel lymph node metastases

Recently, several randomized trials have compared SNB with SNB followed by ALND for T1-2N0 breast cancer patients. NSABP B32 demonstrated that ALND did not improve the prognosis for pN0(sn) breast cancer patients [8]. OS at 8 years after randomization was 91.8% in 1,975 patients treated with SNB followed by ALND and 90.3% in 2,011 patients treated with SNB, and the unadjusted hazard ratio was 1.20 ($p = 0.12$). In this study, the prognostic significance of occult metastases was also evaluated prospectively in a blinded manner [29]. Paraffin blocks of SLN were routinely sliced at approximately 2.0-mm intervals and were diagnosed as negative by HE staining. In addition, sections of pathologically negative SLN were sliced at approximately 0.5 and 1.0 mm deeper in the surface and centrally reviewed pathologically using HE and IHC staining. Of the 3,887 breast cancer patients with pN0(sn) at a routine examination, 616 (15.9%) showed occult metastases in SLN: ITC and associated clusters in 430 (11.1%), MIC in 172 (4.4%), and MAC in 14 (0.4%) were detected in SLN. The estimated 5-year OS and 5-year disease-free survival (DFS) in breast cancer patients with occult metastases and those with no occult metastases were 94.6 and 95.8%, and 89.2 and 92.5%, respectively. Log-rank tests demonstrated that occult metastases in SLN significantly lowered OS and DFS in patients who were diagnosed as pN0(sn) at a routine examination ($p = 0.03$ and 0.02). However, the absolute difference in the 5-year OS (1.2%) was too small to justify a detailed examination of initially negative SLN. Interestingly, adjuvant endocrine therapy improved OS for hormone-sensitive breast cancer patients despite occult metastases in SLN. An SNB trial in the Netherlands reported a similar finding that adjuvant therapy improved DFS in breast cancer patients with ITC or MIC in SLN [30]. Those results suggest that, in clinical practice, the pathological examination of SLN should involve HE staining of tissue specimens cut at 2-mm intervals. Additional IHC staining is not recommended for the diagnosis of SLN metastases. Adjuvant therapy based on the tumor characteristics is essential for improving the patient's outcome.

How should we perform axilla surgery for breast cancer patients?

The American College of Surgeons Oncology Group (ACOSOG) Z0011 conducted a study in 1999 to optimize axilla surgery for early breast cancer patients who had a small number of positive SLN. Patients who had one or two positive SLN were eligible and randomized to receive either SNB alone or SNB followed by ALND. Adjuvant therapy was performed at the physician's discretion. OS was the primary endpoint, which led to a one-sided hazard ratio of less than 1.3, indicating that SNB alone is not inferior to ALND. Although 1,900 patients were required to confirm this hypothesis, the study was closed in 2004 because of the unexpectedly low number of deaths in the two treatment groups. Eventually, 891 patients were enrolled. At a median follow-up of 6 years, 5-year OS was 91.8% for 445 patients treated with SNB followed by ALND and 92.5% for 446 patients treated with SNB alone. Locoregional recurrence was seen in 16 and 12 patients, respectively [31]. The hazard ratio for OS was 0.87 after adjusting for age and adjuvant therapy (90% confidence interval, 0.62–1.23). These results suggest that breast cancer patients with one or two positive SLN can avoid ALND to prevent regional lymph node recurrence. However, this study has some limitations. First, approximately 70% of patients had T1 breast cancer, 60% had one positive SLN only, and 35% had MIC in SLN only. Such cases were expected to have a low risk of additional metastases in non-SLN. Second, whole-breast irradiation was a protocol treatment and level I axilla might be irradiated with a standard opposing tangential field. Third, the 5-year OS was similar among patients who underwent SNB alone in NSABP B32 and ACOSOG Z0011, even though they were in different cohorts of nodal metastases (95.0 and 92.5%). The risk of recurrence does not seem to have been high for patients in the latter study compared to those in the former study.

Conclusions

SNB can be used to avoid unnecessary ALND for patients with ITC as well as those with pN0(sn). ITC or MIC in SLN influences the patient's outcome regardless of the pathological or molecular diagnosis, and thus adjuvant

therapy should be used in such cases. If T1 and one SLN-positive breast cancer patients are treated with whole-breast irradiation and adjuvant therapy, additional ALND may not be necessary. Although non-SLN metastases exist in the axilla for some SLN-positive breast cancer patients, low locoregional recurrence was observed after a long follow-up in both NSABP B32 and ACOSOG Z0011, as well as in NSABP B04. This phenomenon, which resembles tumor dormancy, should be further investigated to better understand the relationship and interaction between the host defense and breast cancer.

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Conflict of interest None declared.

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International Multicenter Tool to Predict the Risk of Nonsentinel Node Metastases in Breast Cancer

Tuomo J. Meretoja, Marjut H. K. Leidenius, Päivi S.Heikkilä, Gabor Boross, István Sejben, Peter Regitnig, Gero Luschin-Ebengreuth, Janez Žgajnar, Andraz Perhavec, Barbara Gazic, György Lázár, Tibor Takács, Andras Vörös, Zuhair A. Saidan, Rana M. Nadeem, Isabella Castellano, Anna Sapino, Simonetta Bianchi, Vania Vezzosi, Emmanuel Barranger, Ruben Lousquy, Riccardo Arisio, Maria Pia Foschini, Shigeru Imoto, Hiroshi Kamma, Tove F. Tvedskov, Niels Kroman, Maj-Brit Jensen, Riccardo A. Audisio, Gabor Cserni

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Correspondence to: Tuomo J. Meretoja, MD, PhD, Helsinki University Central Hospital, Breast Surgery Unit, PO Box 140, FI-00029 HUS, Finland (e-mail: tuomo.meretoja@fimnet.fi).

Background Axillary treatment of breast cancer patients is undergoing a paradigm shift, as completion axillary lymph node dissections (ALNDs) are being questioned in the treatment of patients with tumor-positive sentinel nodes. This study aims to develop a novel multi-institutional predictive tool to calculate patient-specific risk of residual axillary disease after tumor-positive sentinel node biopsy.

Methods Breast cancer patients with a tumor-positive sentinel node and a completion ALND from five European centers formed the original patient series (N = 1000). Statistically significant variables predicting nonsentinel node involvement were identified in logistic regression analysis. A multivariable predictive model was developed and validated by area under the receiver operating characteristics curve (AUC), first internally in 500 additional patients and then externally in 1068 patients from other centers. All statistical tests were two-sided.

Results Nine tumor- and sentinel node–specific variables were identified as statistically significant factors predicting nonsentinel node involvement in logistic regression analysis. A resulting predictive model applied to the internal validation series resulted in an AUC of 0.714 (95% confidence interval [CI] = 0.665 to 0.763). For the external validation series, the AUC was 0.719 (95% CI = 0.689 to 0.750). The model was well calibrated in the external validation series.

Conclusions We present a novel, international, multicenter, predictive tool to assess the risk of additional axillary metastases after tumor-positive sentinel node biopsy in breast cancer. The predictive model performed well in internal and external validation but needs to be further studied in each center before application to clinical use.

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Axillary treatment of breast cancer patients is undergoing a paradigm shift, with the main question under scrutiny being how to treat the axilla of a patient with tumor-positive sentinel node biopsy (SNB). Since the introduction of SNB as a procedure to stage the axilla of breast cancer patients, the gold standard of treatment has been completion axillary lymph node dissection (ALND) for all cases with metastasis in the sentinel node (SN) or when the identification of SNs has failed.

Since then, many centers have developed their own predictive tools to identify patients with low risk of additional axillary metastases in whom completion ALND could be omitted (1–16). With a growing body of literature, many centers have abandoned completion ALND in patients with a low risk of nonsentinel node metastases (17). The results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial further shook the completion ALND concept by showing that even a subset of patients with macrometastases in their SN do not benefit from completion ALND in terms of recurrence rate or overall survival (18,19).

Some centers have abandoned predictive tools altogether after the results of the ACOSOG Z0011 trial were published. However, vivid discussion continues on the generalization of the ACOSOG Z0011 results because the study only included patients who had undergone breast-conserving surgery followed by whole-breast radiation (18,19). Furthermore, contradicting results have been published recently, including the current analysis of the Dutch MIRROR cohort study, which showed an increased 5-year regional recurrence rate in patients with micrometastases in their SN and no completion ALND performed (20).

Most of the current predictive tools estimating the likelihood of additional axillary metastases after tumor-positive SNB have been developed from single-institution patient series and thereafter validated in other centers. Current predictive tools have also

been developed to identify patients with low risk of residual disease, rather than those with high risk, and tend to perform worse in a high-risk setting (21).

In light of the ACOSOG Z0011 trial, this study aims to examine factors associated with a high risk of additional axillary metastases and to identify such high-risk patients for whom completion ALND might be warranted. This study further aims to develop a novel international and multi-institutional predictive tool to calculate a patient-specific risk of residual disease. Finally, we aim to validate the novel predictive tool first internally and then externally in various institutions.

Methods

Original Patient Series

Five European centers collected retrospective data, each on 200 consecutive women with invasive breast cancer with one or more tumor-positive SNs and a completion ALND, contributing a total of 1000 patients who were operated on between January 2004 and January 2011. Patients with macrometastasis, micrometastasis, or isolated tumor cells/clusters (ITC) in their SN were included. Patients who had neoadjuvant treatment or previous axillary surgery were excluded. These data were originally collected to assess the impact of differences in the SNB procedure and pathology practices on the performance of existing predictive models for nonsentinel node involvement (22). Although the tools performed well in the institution in which they were developed, subsequent validation produced less-satisfactory and variable results. Hence, we decided to develop a novel predictive tool with emphasis on high-risk patients (22).

The participating centers in the collection of this original patient series were Bács-Kiskun County Teaching Hospital, Kecskemét, Hungary; Helsinki University Central Hospital, Finland; Medical University of Graz, Austria; Institute of Oncology, Ljubljana, Slovenia; and University of Szeged, Hungary.

The collected data were based on known risk factors for additional axillary metastases after tumor-positive SNB (1–15). Primary tumor-specific variables included pathological tumor size, multifocality, histological and nuclear grade, histological type (ductal, lobular, mixed, or other), estrogen and progesterone receptor status, human epidermal growth factor receptor 2 (HER-2) status, and presence of lymphovascular invasion. Lymph node–specific variables included the number of tumor-positive and tumor-negative SNs and nonsentinel nodes, method of detection of the SN metastasis, size of the largest SN metastasis (ITC vs micrometastasis vs macrometastasis) (23), and presence of extra-capsular extension of the SN metastasis. The method of detection of the SN metastases was categorized as intraoperative (frozen section/imprint cytology), paraffin standard staining, serial sectioning, or immunohistochemistry. Patient, tumor, and lymph node characteristics from different centers are given in Table 1.

Surgical techniques and pathological work-ups of the primary tumors and the axillary specimen were conducted according to each center's protocols (22).

Internal Validation Patients

Additional consecutive patients with similar inclusion and exclusion criteria to the original series were gathered from each center to form an internal validation series. The surgical treatment and methods of pathological assessment were similar to the original patient series. Data were collected on 500 additional patients who had surgery between 2003 and 2011.

External Validation Patients

Eight different centers, mainly from Europe but also from Japan, participated in the external validation of the predictive tool. Each external validation center provided consecutive patient series with similar inclusion criteria to the original series. The number of patients included from each center was not restricted because the performance of the predictive tool was examined separately in each center in addition to pooled performance. Altogether, 1068 patients were included in the external validation (Supplementary Data 1, available online).

The participating centers in the collection of the external surgically treated validation patient series were Lariboisiere Hospital, Paris, France (patients surgically treated from 2007 to 2011); Lancashire Teaching Hospitals, Chorley, United Kingdom (2006 to 2011); Azienda Ospedaliera Universitaria San Giovanni Battista di Torino, Turin, Italy (2005 to 2011); Careggi Hospital and University of Florence, Italy (2003 to 2009); Sant'Anna Hospital, Turin, Italy (2010 to 2011); Bellaria Hospital, University of Bologna, Italy (2009 to 2011); Kyorin University Hospital, Tokyo, Japan (2007 to 2010); and Copenhagen University Hospital, Denmark (2010 to 2011).

Statistical Analyses

A univariate analysis of the original patient series was conducted to examine individual risk factors for additional axillary metastases after tumor-positive SNB. Distribution of continuous variables (patient age, prevalence of nonsentinel node metastases in each center's patient series, histological size of the primary tumor, number of negative and positive SNs harvested) was analyzed using the Mann–Whitney U test, and the χ^2 test was used for categorical variables (multifocality of the primary tumor, lymphovascular invasion in the primary tumor, estrogen and progesterone receptor status, HER-2 status, nuclear and histological grade of the primary tumor, histology of the primary tumor, detection method of the SN metastasis, and extra-capsular extension of the SN metastasis). All statistical tests were two-sided with P values less than .05 considered significant.

All variables with a P value less than .1 in the univariate analysis were included in a logistic regression analysis using a backward stepwise likelihood ratio method. Variables with a P value less than .05 were included in the final predictive model.

The resulting multivariable predictive model was then validated both internally and externally by the independent patient series. Discrimination of the model was assessed by area under the receiver operating characteristic curve (AUC), and the calibration of the model was assessed by the Hosmer–Lemeshow goodness-of-fit test. Sensitivity and specificity of the model was determined for various cutoff values.

IBM SPSS Statistics version 20 (SPSS Inc., Chicago, IL) software was used to conduct the statistical analyses.

Ethical Considerations

The patient series were gathered retrospectively with no influence on patient therapy. Institutional review boards and ethical committees

Table 1. Patient, tumor, and lymph node characteristics in the original patient series of 1000 patients*

Patient, tumor and lymph node characteristics	Center A: Bács-Kiskun	Center B: Helsinki	Center C: Graz	Center D: Ljubljana	Center E: Szeged
Patient enrollment period	2005–2010	2010	2010–2011	2005–2008	2004–2010
Patient age, mean (SD), y	58 (12)	59 (11)	57 (13)	58 (10)	56 (11)
Histological size of the primary tumor, mean (SD), mm	20 (14)	21 (18)	18 (9)	22 (11)	22 (11)
Multifocal primary tumor, no. (%)	57 (29%)	47 (24%)	30 (15%)	53 (27%)	19 (10%)
Lymphovascular invasion in the primary tumor, no. (%)	76 (38%)	52 (26%)	51 (26%)	80 (40%)	57 (29%)
Estrogen receptor positive, no. (%)	178 (89%)	189 (95%)	161 (81%)	181 (91%)	152 (76%)
Progesterone receptor positive, no. (%)	157 (79%)	146 (73%)	152 (76%)	156 (78%)	149 (75%)
HER-2 positive, no. (%)	17 (9%)	23 (12%)	26 (13%)	20 (10%)	33 (17%)
Nuclear crade of the primary tumor, no. (%)					
Grade 1	15 (8%)	24 (12%)	45 (23%)	4 (2%)	10 (5%)
Grade 2	79 (40%)	101 (51%)	91 (46%)	124 (62%)	76 (38%)
Grade 3	106 (53%)	75 (38%)	64 (32%)	72 (36%)	114 (57%)
Histological grade of the primary tumor, no. (%)					
Grade 1	48 (24%)	50 (25%)	20 (10%)	27 (14%)	21 (11%)
Grade 2	85 (43%)	89 (45%)	91 (46%)	104 (52%)	100 (50%)
Grade 3	67 (34%)	61 (31%)	64 (32%)	69 (35%)	79 (40%)
Histology of the primary tumor, no. (%)					
Ductal	143 (72%)	149 (75%)	160 (80%)	168 (84%)	169 (85%)
Lobular	21 (11%)	31 (16%)	15 (8%)	21 (11%)	13 (7%)
Mixed	10 (5%)	4 (2%)	21 (11%)	9 (5%)	4 (2%)
Other	26 (13%)	16 (8%)	4 (2%)	2 (1%)	14 (7%)
Detection method of the sentinel node metastasis, no. (%)					
Intraoperative analysis (frozen section/ imprints)	98 (49%)	178 (89%)	111 (56%)	52 (26%)	Not done
Paraffin standard staining	56 (28%)	5 (3%)	4 (2%)	49 (25%)	189 (95%)
Paraffin immunohistochemistry	30 (15%)	17 (9%)	33 (17%)	88 (44%)	11 (5%)
Serial sectioning	16 (8%)	Not done	52 (26%)	11 (6%)	Not done
Size of the sentinel node metastasis, no. (%)					
Isolated tumor cells	1 (1%)	42 (21%)	19 (10%)	1 (1%)	5 (3%)
Micrometastasis	56 (28%)	43 (22%)	54 (27%)	62 (31%)	29 (25%)
Macrometastasis	143 (72%)	115 (58%)	126 (63%)	137 (69%)	166 (83%)
Extracapsular extension of sentinel node metastasis present, no. (%)	90 (45%)	54 (27%)	43 (22%)	53 (27%)	36 (18%)
Sentinel nodes harvested, mean (SD), no.	1.9 (1.0)	2.4 (1.4)	1.8 (1.2)	1.8 (1.0)	1.9 (1.0)
Nonsentinel nodes harvested, mean (SD), no.	12 (5)	19 (6)	15 (6)	17 (6)	10 (5)
Nonsentinel node positive patients	79 (40%)	55 (28%)	70 (35%)	53 (27%)	70 (35%)

* HER-2 = human epidermal growth factor receptor 2.

were consulted in each center as required, and no ethical objections were raised. All patient information was gathered anonymously.

Results

In the original patient series, 327 (32.7%) patients were found to have additional axillary metastases in their completion ALND. This proportion varied between centers from 27% to 40%. Variables associated with additional metastases in univariate analysis with a *P* value less than .1 were prevalence of nonsentinel node metastases in each center's series, size of primary tumor, multifocality, lymphovascular invasion, HER-2 status, histological and nuclear grade, SN metastatasis detection method, SN metastasis size, extracapsular extension of the SN metastasis, and number of tumor-negative and -positive SNs (Table 2).

Prevalence of nonsentinel node metastases in each center's series, primary tumor diameter, multifocality, lymphovascular invasion, HER-2 status, SN metastasis size, extracapsular extension of the SN metastasis, and number of tumor-negative and -positive SNs remained statistically significant risk factors in the logistic regression analysis (Table 3). The Hosmer–Lemeshow test produced a *P* value of .58, indicating that the multivariable model fits and calibrates well for the patient population. The AUC for the original patient series was 0.756 (95% confidence interval [CI] = 0.725 to 0.787), suggesting good discrimination. The following mathematical model was produced from the logistic regression analysis to predict the presence of additional axillary metastases, with p denoting the probability of nonsentinel node metastases:

$$\mathit{logit}(p) = -6.391 + 0.036 \times a + 0.321 \times b + 0.420 \times c - 0.594 \times d - 0.216 \times e + 0.278 \times f + 0.021 \times g + 1.274 \times h + 0.655 \times i$$

The letters in the equation denote the variables: a = prevalence of nonsentinel node metastases in patient series (percentage of patients); b = lymphovascular invasion (1 if present, 0 if not); c = multifocality (1 if multifocal, 0 if not); d = HER-2 status (1 if positive, 0 if negative); e = number of negative SN; f = number of positive SN; g = histological size of the primary tumor in millimeters; h = SN metastasis size (1 if ITC, 2 if micrometastasis, 3 if macrometastasis); and i = extracapsular extension of SN metastasis (1 if present, 0 if not). The predictive model is given as a supplementary Excel file calculator (Supplementary Data 2, available online) and at the website of the Breast Surgery Unit of Helsinki University Central Hospital (http://www.hus.fi/breastsurgery/predictivemodel).

Each patient's information from the internal and external validation patient series was then introduced into the multivariable equation to perform validation of the predictive model. AUC values with confidence intervals for each center are given in Table 4, and receiver operating characteristic curves are given in Figure 1. The prevalence of nonsentinel node metastases ranged from 20.8% to 36.0% between centers in the internal validation series and from 30.2% to 53.0% in the external validation series. Similarly, the AUC values ranged from 0.458 to 0.841 in the internal validation series between different centers and from 0.577 to 0.949 in the different external validation centers. Overall, internal validation of the predictive model yielded an AUC of 0.714 (95% CI = 0.665 to 0.763), whereas the external validation AUC was 0.719 (95% CI = 0.689 to 0.750) (Table 4).

The model generates a probability of additional metastases, which can be termed a risk estimate score, and the sensitivity and specificity of the predictive model may be calculated for any given cutoff value of the risk estimate score. For example, when applied to the external validation series, our model has a sensitivity of 67.6% and a specificity of 65.8% for a cutoff value of more than 50% of the risk score. The sensitivity and specificity of the model in the external validation series for different cutoff values are: greater than 10% risk (98.2% sensitivity and 7.5% specificity), greater than 20% risk (89.4% sensitivity and 31.6% specificity), greater than 30% risk (83.1% sensitivity and 43.9% specificity), greater than 40% risk (70.3% sensitivity and 61.6% specificity), greater than 60% risk (27.3% sensitivity and 91.4% specificity) and greater than 70% risk (12.4% sensitivity and 97.2% specificity).

Calibration of the predictive model was examined by grouping patients in each series into quintiles according to the predicted probabilities of additional metastases. A calibration plot was acquired by plotting the mean predicted probability of each quintile against the actual proportion of patients with additional metastases in each quintile (Figure 2).

Discussion

Our predictive model is presented in the form of a multivariable equation that produces the probability of additional axillary metastases. Most of the previous models were given in the form of scores or nomograms that were always approximations of the original mathematical model (1–15). In the contemporary era, we feel that the predictive equation is the most appropriate form because it produces the most accurate prediction and can be easily incorporated into various platforms, including computers and mobile devices. Moreover, by producing a probability of additional metastases, our predictive model is not tied into specific cutoff points because the thresholds for clinical decision making may well change in the future and increasingly become more patient specific.

The present model performed relatively well both in the internal and external validation. In fact, the model performed equally or even better in the external patient series than it did in the internal setup in terms of AUC. Furthermore, the model performed well in both low-risk (up to 10% risk) and high-risk (60% risk and over) conditions, as illustrated by the calibration plot (Figure 2). Other predictive models may not calibrate equally well, as shown by previous validation studies (15,24). In fact, we have recently validated four previous nomograms with the original patient series of this study with resulting AUC values of 0.640 to 0.686 and relatively poor performance in high-risk (>50% risk) settings (21).

The baseline prevalence of additional axillary metastases in our original patient series (32.7%) is substantially lower than that of the external validation series (42.2%). Such baseline differences may be relatively customary and may account for poor performance of previous predictive tools in other centers. In fact, our model is the first predictive tool to incorporate each center's baseline prevalence of nonsentinel node metastases as a coefficient in the equation to calibrate the model.

The exclusion criteria for this study were intentionally minimal to produce a heterogeneous patient population closely resembling real-life patient material. Furthermore, the methodology of the

Table 2. Univariate analysis comparing patients with additional metastases in axillary lymph node dissection to those with no additional metastases in the original patient series*

Patient, tumor, and lymph node characteristics	No additional metastases in ALND, n = 673	Additional metastases in ALND, n = 327	All patients, N = 1000	P
Patient age, y				.35
Mean (range)	57.4 (26–86)	58.1 (27–87)	57.6 (26–87)	
Standard deviation	11.2	11.8	11.4	
Prevalence of nonsentinel node metastases in each center's patient series				
Mean (range)	32.6% (27.0%–40.0%)	33.7% (27.0%–40.0%)	33.0% (27.0%–40.0%)	<.001
Standard deviation	4.8	4.8	4.9	
Histological size of the primary tumor, mm				<.001
Mean (range)	19.3 (0.4–81.0)	23.1 (0.5–200.0)	20.6 (0.4–200.0)	
Standard deviation	10.1	17.4	13.1	
Multifocality of the primary tumor, no.				.003
No	552	242	794	
Yes	121	85	206	
Lymphovascular invasion in the primary tumor, no.				.001
No	484	200	684	
Yes	189	127	316	
Estrogen receptor status, no.				.93
Negative	94	45	139	
Positive	579	282	861	
Progesterone receptor status, no.				.94
Negative	162	78	240	
Positive	511	249	760	
HER-2 status, no.				.04
Negative	583	298	881	
Positive	90	29	119	
Triple negative, no.†				.48
No	622	298	920	
Yes	51	29	80	
Triple positive, no.‡				.50
No	633	311	944	
Yes	40	16	56	
Nuclear grade of the primary tumor, no.				.01
Grade 1	78	20	98	
Grade 2	320	151	471	
Grade 3	275	156	431	
Histological grade of the primary tumor, no.				.003
Grade 1	130	36	166	
Grade 2	310	159	469	
Grade 3	233	132	365	
Histology of the primary tumor, no.				.37
Ductal carcinoma	539	250	789	
Lobular carcinoma	62	39	101	
Mixed	29	19	48	
Other	43	19	62	
Detection method of the sentinel node metastasis, no.				<.001
Frozen section analysis	258	181	439	
Paraffin standard staining	199	104	303	
Paraffin immunohistochemistry	154	25	179	
Serial sectioning	62	17	79	
Size of the sentinel node metastasis, no.				<.001
Isolated tumor cells	64	4	68	
Micrometastasis	215	30	245	
Macrometastasis	394	293	687	
Extracapsular extension of sentinel node metastasis, no.				<.001
No	544	180	724	
Yes	129	147	276	
Number of negative sentinel nodes harvested				<.001
Mean (range)	0.7 (0–11)	0.5 (0–5)	0.7 (0–11)	
Standard deviation	1.1	0.8	1.0	

(Table continues)

Table 2 (Continued).

Patient, tumor, and lymph node characteristics	No additional metastases in ALND, n = 673	Additional metastases in ALND, n = 327	All patients, N = 1000	*P*
Number of positive sentinel nodes harvested				<.001
Mean (range)	1.2 (1–5)	1.4 (1–5)	1.3 (1–5)	
Standard deviation	0.5	0.8	0.6	

* Mann–Whitney *U* test used for continuous variables and χ^2 test for categorical variables. All statistical tests were two-sided. HER-2 = human epidermal growth factor receptor 2.

† Triple negative = estrogen receptor, progesterone receptor, and HER-2 status all negative.

‡ Triple positive = estrogen receptor, progesterone receptor, and HER-2 status all positive.

Table 3. Binary logistic regression analysis using backward stepwise likelihood ratio method in the original patient series*

Variable	Coefficient	Standard error	Wald	*P*	Odds ratio (95% CI)
Prevalence of nonsentinel node metastases in patient series	0.036	0.015	5.340	.02	1.036 (1.005 to 1.068)
Lymphovascular invasion in the primary tumor	0.321	0.159	4.100	.04	1.378 (1.010 to 1.881)
Multifocality of the primary tumor	0.420	0.181	5.397	.02	1.522 (1.068 to 2.169)
HER-2 status	−0.594	0.248	5.732	.02	0.552 (0.340 to 0.898)
Number of negative sentinel nodes	−0.216	0.086	6.327	.01	0.806 (0.681 to 0.954)
Number of positive sentinel nodes	0.278	0.118	5.596	.02	1.321 (1.049 to 1.664)
Histological size of the primary tumor, mm	0.021	0.007	9.897	.002	1.021 (1.008 to 1.034)
Size of the sentinel node metastasis	1.274	0.184	47.907	<.001	3.552 (2.492 to 5.127)
Extracapsular extension of sentinel node metastasis	0.655	0.163	16.074	<.001	1.925 (1.398 to 2.652)
Constant	−6.391	0.764	69.989	<.001	0.002

* Reporting two-sided *P* values. CI = confidence interval; HER-2 = human epidermal growth factor receptor 2.

Table 4. Performance of the predictive model in internal and external validation*

Patient series	No.	Nonsentinel metastases	AUC (95% CI)	Bonferroni corrected CI (99.4%) for AUC	Sensitivity	Specificity
Original patient series	1000	327 (32.7%)	0.756 (0.725 to 0.787)	0.713 to 0.800	38.5%	89.2%
Internal validation series	500	155 (31.0%)	0.714 (0.665 to 0.763)	0.646 to 0.783	36.8%	90.1%
Center A	100	36 (36.0%)	0.692 (0.586 to 0.797)	0.545 to 0.841	41.7%	85.9%
Center B	134	43 (32.1%)	0.760 (0.675 to 0.844)	0.642 to 0.880	39.5%	89.0%
Center C	42	15 (35.7%)	0.841 (0.706 to 0.976)	0.650 to 1.000	46.7%	92.6%
Center D	200	56 (28.0%)	0.686 (0.600 to 0.771)	0.565 to 0.805	32.1%	91.7%
Center E	24	5 (20.8%)	0.458 (0.176 to 0.740)	0.069 to 0.868	0	94.7%
External validation series	1068	451 (42.2%)	0.719 (0.689 to 0.750)	0.676 to 0.762	51.4%	79.4%
Center F	100	53 (53.0%)	0.762 (0.669 to 0.856)	0.629 to 0.892	62.3%	85.1%
Center G	137	51 (37.2%)	0.747 (0.663 to 0.831)	0.625 to 0.861	62.7%	75.6%
Center H	67	30 (44.8%)	0.577 (0.440 to 0.715)	0.389 to 0.775	23.3%	83.8%
Center I	153	64 (41.8%)	0.715 (0.635 to 0.795)	0.603 to 0.827	51.6%	71.9%
Center J	43	13 (30.2%)	0.949 (0.886 to 1.000)	0.866 to 1.000	84.6%	93.3%
Center K	100	47 (47.0%)	0.702 (0.598 to 0.805)	0.557 to 0.847	48.9%	83.0%
Center L	200	64 (32.0%)	0.673 (0.591 to 0.756)	0.556 to 0.789	56.2%	72.1%
Center M	268	129 (48.1%)	0.731 (0.672 to 0.792)	0.648 to 0.817	44.2%	86.3%

* Sensitivity and specificity calculated for a cutoff value of greater than 50% risk estimate score. AUC = area under the receiver operating characteristics curve; CI = confidence interval.

preoperative nodal assessment, such as the use of axillary ultrasound, and the pathological nodal assessment varied considerably between centers, accounting for differences. A high-quality, preoperative, axillary ultrasound blocks a high proportion of women with macrometastases from the SNB procedure, thereby also lowering the proportion of women with additional nonsentinel node metastases.

Differences between the centers both in internal and external validation are apparent, considering the variation of the AUC values in Table 4. These may partly be due to small patient series from some centers, accounting for both very high (external validation Center J; AUC = 0.949) and very low (external validation Center H; AUC = 0.577) AUC values. These are most likely statistical variations that will be leveled with a higher number of patients. On the other hand, the alteration between centers may represent real methodological or population-wise differences, and further validation of the model with reasonably large patient series is of crucial importance before adoption into clinical use.

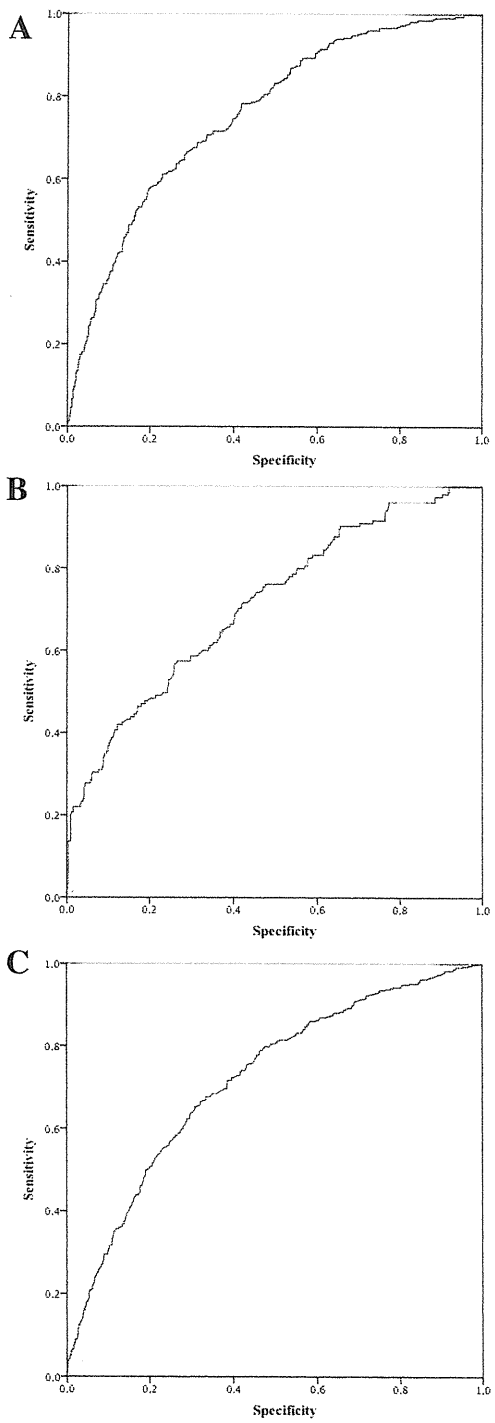

Figure 1. Receiver operating characteristic curves for the original patient series (**A**), the internal validation patient series (**B**), and the external validation patient series (**C**).

Although the present model produces simply the percentile probability of residual disease, the sensitivity and specificity of the model were tested, as an example, for a cutoff value of more than 50% risk score in Table 4. In the wake of the ACOSOG Z0011 trial, such a high cutoff value was chosen because it is being substantially higher than those of previous models (1–16) and also considerably higher than the 27% risk of the ACOSOG patient series (18,19). Our model had a reasonably good sensitivity and specificity at this cutoff point, both in the internal and external validation series.

Nine variables were statistically significant in the logistic regression analysis and were incorporated into our predictive model. The prevalence of nonsentinel metastases is a center- or patient series–specific variable, which is a unique feature in the present model. Most of the other variables included in the model have been found to predict the risk for additional axillary metastases in previously published models (1–15), except for HER-2 status. HER-2 status stood out as an independent factor from estrogen and progesterone receptor status because both triple-negative and triple-positive combinations had similar distributions across the two groups in univariate analysis. The biological explanation behind this phenomenon remains unclear. The implications of HER-2 status on recurrences and survival have been extensively studied (25,26), but the detailed effects of steroid receptor and HER-2 status on axillary lymph node and especially nonsentinel node involvement have not been described in the literature. Triple-positive breast cancer has been shown to lead to highest incidence of tumor-positive lymph nodes in multivariable analysis (27) between different phenotypes, but this study did not find an association between nonsentinel node metastases and triple-negative or triple-positive phenotypes.

Our model includes SN metastasis size as a factor in the predictive equation. In fact, the distinction between ITC, micrometastasis, and macrometastasis as the SN finding greatly affects the probability of additional metastases. Some of the previous models do not take the SN metastasis size into consideration (1,7,11), whereas some models are specifically designed for only ITC or micrometastases (9,15,16).

The ACOSOG Z0011 trial suggested that omitting completion ALND after tumor-positive SNB does not increase regional recurrence rate nor decrease survival rate in general. The prevalence of additional axillary metastases was 27% on the ALND arm of the randomized ACOSOG trial, suggesting a comparable residual disease rate in the SNB-only arm. However, the study only included women having undergone breast-conserving surgery followed by whole-breast radiotherapy including the axilla through a tangential field. The prevalence of nonsentinel node metastases in our unselected patient series was considerably higher than in the ACOSOG trial (33% in our original series, 31% in the internal validation series, and 42% in the external validation series). A meta-analysis of more than 8000 patients reported an additional axillary metastases rate as high as 53% after a tumor-positive SNB (28).

Many factors affect the baseline prevalence of axillary metastases in a given patient population. These include the method of preoperative nodal assessment and many primary tumor-specific factors, such as tumor diameter, which also determines whether a patient undergoes breast-conserving surgery or mastectomy. Therefore, the patient selection of the ACOSOG Z0011 trial may have led to a lower baseline prevalence of nonsentinel node metastases, and the results may not be generalizable to patients with a higher risk of additional metastases than the 27% reported in that study. Moreover, a substantial proportion of patients undergoing mastectomy do not receive radiotherapy and may be at a higher risk of regional recurrence than patients undergoing breast-conserving surgery and radiation (29,30).

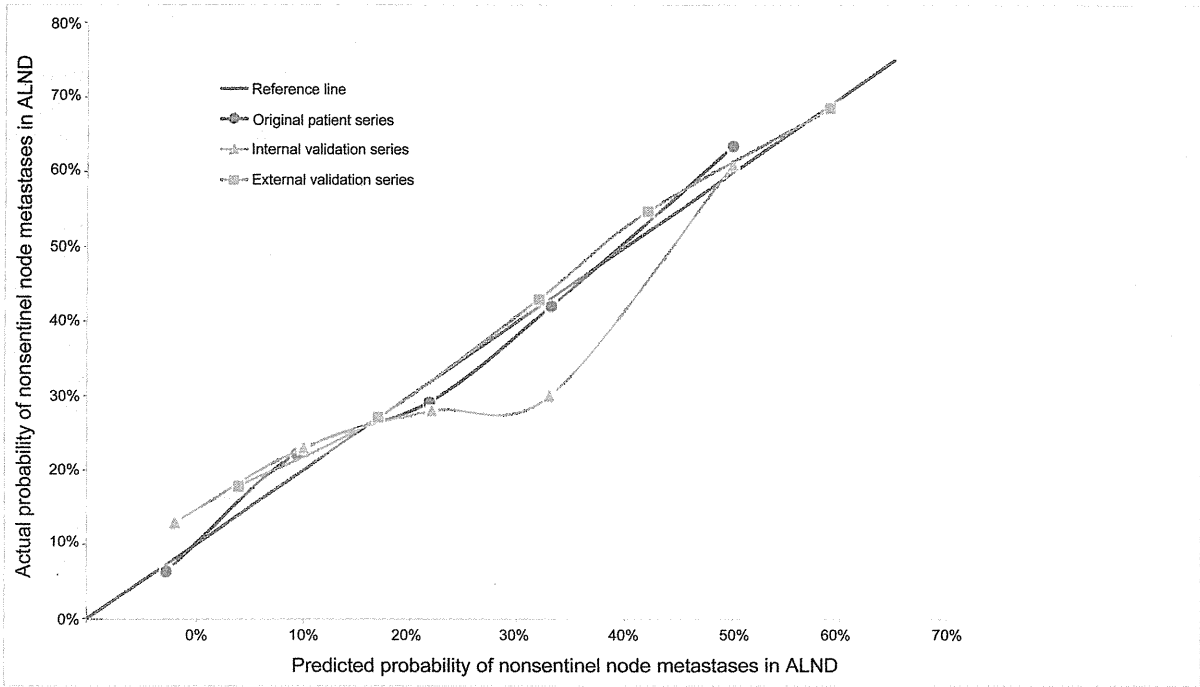

Figure 2. Calibration plot for the predictive model applied to the original patient series, internal validation series, and external validation series, split to quintiles. ALND = axillary lymph node dissection.

Although most axillary recurrences have been reported to occur in the first 5 years after ALND (31), the metastatic tumor load to the axilla is believed to be considerably lower in the SNB era than in the period prior to it. Therefore, the presentation of recurrences may need a longer time than the 6.3 years of median follow-up reported to date (19), despite the fact that at present there is not even a trend toward a decreased survival without completion ALND in the ACOSOG Z0011 trial.

The whole paradigm of axillary treatment of breast cancer patients is changing, but the future may well be multidirectional. In addition to completion ALND, axillary radiotherapy may also be a future option in the treatment of patients with tumor-positive SN. The European Organisation for Research and Treatment of Cancer AMAROS trial (32) is comparing axillary radiotherapy to completion ALND in a randomized set-up, but the final results have not yet been published. Patient-specific prediction of residual axillary disease may become even more relevant in the future because the treatment options of the axilla are under scrutiny. One implication of the ACOSOG Z0011 trial and also of the AMAROS trial is the diminishing role of intraoperative SN analysis and the adaptation of pathology methods to the clinical context (ie, to potential treatment options). Many previous predictive models include SN detection method or the use of frozen section analysis as a factor in the model. These models may become obsolete with possible abandoning of intraoperative SN analysis.

Our study also has limitations. The heterogeneity of our patient series probably reduces the performance of the predictive model in specific subgroups of patients. The subgroup of patients for whom predictive models are especially needed in the future is, however, unclear. Our novel predictive model may perform well in everyday practice with the average patient, but care needs to be taken in special cases with, for example, very large tumors or tumors representing rare histological types. Another limitation of this study is the variance in the patient enrollment times between different centers. This may have a negative impact on the performance of the new model.

We present a novel, international, multicenter, predictive tool to assess the risk of additional axillary metastases after tumor-positive SNB in breast cancer. In the era of changing paradigm, our tool seems to be able to also identify high-risk patients. The predictive model performs well in internal and external validation patient series, but on the basis of our previous results (21,22), it needs to be validated in each center before its application in clinical practice.

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Affiliations of authors: Breast Surgery Unit (TJM, MHKL) and Department of Pathology (PSH), Helsinki University Central Hospital, Helsinki, Finland; Department of Surgery (GB) and Department of Pathology (IS, GC), Bács-Kiskun County Teaching Hospital, Kecskemét, Hungary; Department of Pathology (PR) and Department of Obstetrics and Gynecology (GL-E), Medical University of Graz, Graz, Austria; Department of Surgical Oncology (JZ, AP) and Department of Pathology (BG), Institute of Oncology, Ljubljana, Slovenia; Department of Surgery (GL, TT) and Department of Pathology (AV, GC), University of Szeged, Szeged, Hungary; Department of Breast Surgery, Lancashire Teaching Hospitals, Chorley, United Kingdom (ZAS, RMN); Breast Unit Azienda Ospedaliera Universitaria San Giovanni Battista di Torino, Department of Biomedical Sciences and Human Oncology, University of Turin, Turin, Italy (IC, AS); Section of Pathological Anatomy, Department of Medical and Surgical Critical Care, University of Florence, Florence, Italy (SB, VV); Department of Gynecology and Obstetrics, Lariboisiere Hospital, Paris, France (EB, RL); Department of Pathology, O.I.R.M. -Sant'Anna Hospital, Turin, Italy (RA); Section of Anatomic Pathology at Bellaria Hospital, Department of Biomedical Sciences and Neuromotory Disorders, University of Bologna, Bologna, Italy (MPF); Department of Breast Surgery (SI) and Department of Pathology (HK), Kyorin University School of Medicine, Tokyo, Japan; Department of Breast Surgery (TFT, NK) and Danish Breast Cancer Cooperative Group (M-BJ), Copenhagen University Hospital, Copenhagen, Denmark; Department of Surgery, St Helens Teaching Hospital, St Helens, United Kingdom (RAA).

特集　乳癌を究める

I. 診　断

4. 乳癌センチネルリンパ節生検*

井本　滋**

〔要旨〕センチネルリンパ節生検は，T1-2N0乳癌患者における標準的なリンパ節の転移診断法である．センチネルリンパ節を正確に同定しリンパ節転移の有無を詳細に検討することは，乳癌の集学的治療を検討するうえで重要である．最近の臨床試験の結果から，センチネルリンパ節転移陽性でもリンパ節郭清を行わずに良好な局所コントロールが得られたと報告された．センチネルリンパ節の同定法と転移診断法を紹介し，現時点での腋窩リンパ節郭清の位置づけについて考察する．

はじめに

センチネルリンパ節生検の適応は，臨床的にリンパ節転移を認めない腫瘍径5 cm以下のT1-2N0乳癌である[1]．このうち，病理学的にリンパ節転移を認める症例は30％と推定される．センチネルリンパ節生検に伴う偽陰性率を10％（敏感度90％）と高めに仮定した場合，この方法で腋窩リンパ節転移を見逃す確率は100例中3例（100×0.3×0.1）の3％となる．Rutgersがセンチネルリンパ節生検後の腋窩リンパ節再発の報告を集計した結果，再発率は年率で0.3％，10年で3％と推定された[2]．乳癌の治療戦略は手術・薬物・放射線を適切に組み合わせた集学的治療である．よって，早期乳癌におけるセンチネルリンパ節生検による腋窩リンパ節郭清の個別化は，偽陰性例による再発があるものの妥当である[3]．

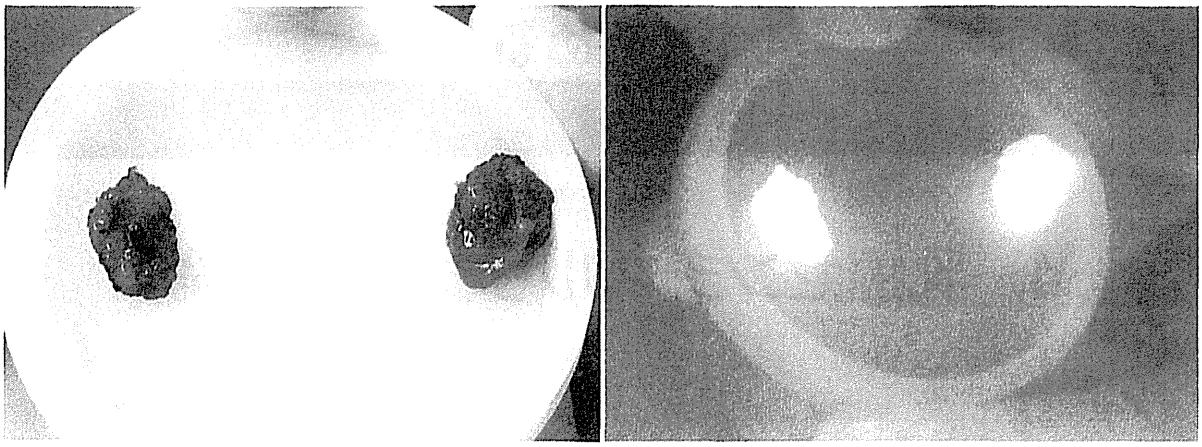
Ⅰ．センチネルリンパ節の生検法

センチネルリンパ節は，色素やアイソトープ（RI）などのトレーサーを用いてリンパ節のマッピングを行い，視覚あるいはγ線を検出する機器によって同定される．しかし，RIは放射線管理区域のない施設では使用できない．そこで，indocyanine greenを用いて近赤外線観察カメラによって蛍光を発するリンパ節を同定する蛍光法[4]（図1）やCT造影剤による方法[5]，さらにsingle-photon emission computed tomography（SPECT）/CTの融合[6]による方法などが開発された．一方，γ線を検出する機器の小型化も図られている（図2）．色素法，RI法，蛍光法の特徴を表1に示す．どの方法も習熟までに症例経験を要するが，同定されずに見逃される転移リンパ節による偽陰性例を防ぐために，可能であれば二つの方法を併用したセンチネルリンパ節生検が望ましい．

キーワード：センチネルリンパ節生検，微小転移，リンパ節郭清

* New era of axilla surgery based on sentinel node concept in early breast cancer

** S. Imoto（教授）：杏林大学外科．



a. 色素法　　b. 蛍光法

図1. 色素法と蛍光法を併用し同定されたセンチネルリンパ節
Indigocarmineによるリンパ節の青染度は右＞左(a)であったが，蛍光法では2個とも明瞭に同定された(b).

図2. 小型化されたγプローブ(荏原実業社)
γ線の検出部と測定部が一体化され操作性に優れている.

トレーサーは，腫瘍周囲，腫瘍直上そして乳輪周囲に投与されることが多い．センチネルリンパ節生検に習熟した外科医であれば，トレーサーの投与部位によるセンチネルリンパ節の同定率に差はほとんどない．ただし，乳輪周囲にトレーサーを投与したほうが腫瘍周囲よりもセンチネルリンパ節におけるRIの集積率が高かった[7]．Sentinel Node Navigation Surgery研究会では，日本で使用可能なトレーサーによるセンチネルリンパ節生検の標準化をめざして，約1,400例のセンチネルリンパ節生検を前向きに集積しその同定率を検討した[8]．その結果，全同定率は98％(1,371/1,393)であったが，上外側腫瘍の症例，リンパ管侵襲やリンパ節転移を伴う症例，ならびに腫瘍周囲に投与した色素法の症例で有意に同定率が低下した．1,000例規模のセンチネルリンパ節生検に関する多施設共同臨床試験の結果では，body mass index，症例経験数，色素法単独，50歳以上例などが有意に同定率を低下させる要因であった(表2)[8]．どの同定法にせよ，センチネルリンパ節以外に硬く触れたり腫れたりして転移を疑うリンパ節が存在した場合は，迷わずにそのリンパ節も生検すべきである．

Ⅱ．センチネルリンパ節の微小転移

Union for International Cancer Control (UICC)第6版から，リンパ節転移はその最大径が0.2 mm以下のisolated tumor cells (ITC)，0.2 mmより大きく2 mm以下のmicrometastases (MIC)，そして2 mmを超えたmacrometastases (MAC)に分類された[9]．センチネルリンパ節を詳細に検討することで，ITCやMICが高率に同定されるようになった．このような微小な癌細胞集塊を診断するために，免疫組織染色はHE染色を補ううえで有用である[10]．しかし，術中に迅速病理診断によって短時間に詳細な転移診断をすることは困難である．そこで，簡便で精度の高い分子マーカーによるリンパ節転移の自動診断法が開

表1. センチネルリンパ節生検法の比較

同定法	トレーサー	習熟までの症例数	同定率	特　徴
色素法	indigocarmine indocyanine green	20例以上	95％以上	機器を要しない 腋窩以外は同定困難
RI法	^{99m}Tc標識スズコロイド ^{99m}Tc標識フチン酸	数例以上	98％以上	同定が容易 微量ではあるが被曝
蛍光法	indocyanine green	10例以上	98％以上	視覚を超えた同定 色素漏出による同定困難

表2. 多施設共同試験におけるセンチネルリンパ節生検の不成功要因

試験名（略称）	登録例数	参加外科医数	同定法（比率）	全成功率	有意な不成功要因
NSABP B32	5,611	226	D and R（100％）	97.2％	50歳以上，T1，内側腫瘍 hot spotsなし
ACOSOG Z0010	5,327	198	D and R（79.4％） D alone（14.8％） R alone（5.7％）	98.7％	BMI≧30 kg/m^2，60歳以上， 経験50例以下
Louisville BCSG	2,148	226	D and R（85.5％） D alone（10.6％） R alone（3.9％）	92.4％	50歳以上，色素法単独，非触知腫瘍，経験20例以下
ALMANAC	842	31	D and R（100％）	96.1％	BMI≧30 kg/m^2，上外側以外の腫瘍，hot spotsなし
German study	1,124	89	D and R（60.9％） D alone（22.4％） R alone（16.7％）	85.2％	色素法単独，腫瘍生検後，経験25例以下
SNAC	1,088	51	D and R（88.1％） D alone（10.9％）	94.5％	体重増加，糖尿病など併存症
SNNS	1,411	62	D and R（78.8％） D alone（16.8％） R alone（3.2％）	98.4％	腫瘍周囲投与色素法，リンパ節転移，リンパ管侵襲，上外側腫瘍

BMI：body mass index，D：色素法，R：RI法

発された．One-step nucleic acid amplification（OSNA）法は，サイトケラチン19のmRNAの増幅測定によってリンパ節を転移診断する方法である[11]．その結果，MACとMIC以下の転移巣とを98％の診断精度をもって区分して診断することができた．偽陽性例はなく，短時間にリンパ節のMACを診断できることから，OSNA法は術中迅速病理診断における病理医の診断能と同等と考えられる．ただし，カットオフ値の設定からMICとITCの検出率は必ずしも高くない．また，数％存在するサイトケラチン19発現が少ない乳癌では，偽陰性になる可能性がある．

センチネルリンパ節生検に関する臨床試験によって，リンパ節微小転移の予後への影響が検証された．National Surgical Adjuvant Breast and Bowel Project Protocol（NSABP）B32試験では，5,611例のT1-2N0乳癌患者を対象にセンチネルリンパ節生検群とリンパ節郭清群の全生存期間が比較された．3,989例が2 mm間隔でのセンチネルリンパ節のHE染色による病理診断において転移陰性であったが，リンパ節郭清群1,978例とセンチネルリンパ節生検群2,011例との8年全生存率はそれぞれ91.8％と90.3％で差がなかった（p＝0.54）[12]．さらに，センチネルリンパ節転移陰性例のうちリンパ節のブロックが回収された3,884例について，再度0.5 mmと1 mmの間隔で深切りを

加えて，HE染色と免疫組織染色によって発見された潜伏転移の意義が検討された[13]．その結果，ITCが430例に，MICが172例に，MACが14例に認められ，潜伏転移616例と非潜伏転移3,268例の5年全生存率はそれぞれ94.6％と95.8％であった（$p=0.03$）．潜伏転移は統計学的に有意な予後不良因子であるが，わずか1.2％の差であり，補助内分泌療法による予後の改善も認められた．以上から，センチネルリンパ節のMACを見逃さないことは重要であるが，ITCあるいはMICは2mm間隔でのHE染色あるいはOSNA法による転移診断が推奨された．免疫組織染色によるリンパ節転移の検索は原則的に行う必要がない．

Ⅲ．センチネルリンパ節転移陽性乳癌におけるリンパ節郭清

センチネルリンパ節に転移を認めても，非センチネルリンパ節に転移がなければリンパ節郭清は不必要である．しかし，センチネルリンパ節ITC例とMIC例における非センチネルリンパ節転移に関する報告から，その転移率はそれぞれ0～26％と6～57％であった[14,15]．一方，術前化学療法によって3割の症例でリンパ節転移が病理学的に完全壊死することが報告された[16]．そこで集学的治療における乳癌のリンパ節郭清の意義を検証するために，センチネルリンパ節転移陽性例におけるリンパ節郭清に関する臨床試験が行われた．

前述のNSABP B32試験では，リンパ節郭清が省略された潜伏転移例での腋窩リンパ節再発は300例中5例（1.7％）であった[13]．American College of Surgeons Oncology Group（ACOSOG）Z0011試験では，T1-2N0乳癌にセンチネルリンパ節生検を施行し，2個までのリンパ節転移陽性例を無作為にリンパ節郭清群と非郭清群に割付けて2群の予後を比較した．当初予定された1,900例の登録は達成されず856例で打ち切られたが，観察期間6年において非郭清群420例のリンパ節再発はわずか4例（1％）であった[17]．5年全生存率も郭清群と非郭清群で92.5％と91.8％とほぼ同等であった．しかし，この試験には課題がある．非郭清群の4割はMIC例であり約8割は1個転移以下の症例であったことから，非センチネルリンパ節への転移率は高くないと予想される．本試験は乳房照射を行う乳房温存手術が適格条件であり，腋窩が照射野の一部に含まれることから再発抑止の効果も予想される．また，リンパ節の転移数あるいは転移径について登録例の1割が不明例であった．さらに，5年生存率はNSABP B32のpN0（sn）非郭清群とACOSOG Z0011の非郭清群で95.0％と92.5％とその差が小さかったことから，後者に登録された症例は比較的予後良好な群であったと考えられる[18]．

以上から，センチネルリンパ節にITC，MIC，1個のMACを認めた乳房温存手術例では，補助薬物療法や乳房照射によって予後の改善が期待されるので，リンパ節郭清を省略することは可能である．しかし，非センチネルリンパ節に転移が遺残する危険性は否定できない．現時点で，リンパ節郭清を省略する症例では，腫瘍の悪性度に応じた適切な補助療法と乳房照射あるいは腋窩照射が必須である．

おわりに

現在，センチネルリンパ節転移陰性に加えて，限局したリンパ節転移を認めた乳癌患者でもリンパ節郭清の省略が行われている．しかし，その前提として腫瘍の悪性度に応じた薬物療法や放射線療法が必須である．リンパ節転移再発だけでは患者の予後に影響しないという見解もあるが，遺残したリンパ節転移巣を起点として全身に癌細胞が播種する可能性はある．リンパ浮腫を予防すべく腋窩への外科的侵襲は最小限にとどめるべきであるが，非センチネルリンパ節に癌細胞が遺残する可能性について症例ごとに十分検討すべきである．

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お知らせ

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　　E-mail：jsct21@surgery.dept.med.gunma-u.ac.jp