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Reduction in the number of sentinel lymph node procedures by preoperative ultrasonography of the axilla in breast cancer

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Abstract

Currently, breast cancer patients without clinically suspicious lymph nodes are candidates for sentinel lymph node procedures (SLNPs). The aims of this study were to investigate whether preoperative axillary ultrasonography and fine-needle aspiration cytology (FNA) can reduce the number of the more time-consuming SLNPs, and to identify a subset of quantitative nodal features to predict metastatic involvement. 268 axillae were ultrasonographically examined. FNA was performed on suspicious nodes (smallest diameter $\geqslant 5$ mm or atypical cortex appearance). SLNP was omitted if a tumour-positive node was found on FNA. Length, width, maximum cortex thickness and appearance of cortex and hilus were ultrasonographically established. In 93 axillae (35%), at least one node was detected with ultrasound. FNA was performed once per axilla on 66 nodes; 37 (56%) contained tumour cells. 31% of all tumour-positive axillae (macro- + micrometastases) was found by ultrasound and FNA (37/121). 41% of all axillae containing macrometastases was found by ultrasound and FNA (36/87). SLNPs were reduced by 14% (37/268). Maximum cortex thickness is the main feature to predict metastatic involvement (area under Receiver Operating Characteristic (ROC) curve (A_Z) = 0.87).

Keywords: Ultrasound; Breast cancer; Sentinel lymph node biopsy; Axilla

1. Introduction

The prognosis of breast cancer patients is for a large part based on the presence of axillary lymph node metastases [1]. For many years, the lymph node status of a breast cancer patient was determined by performing an axillary lymph node dissection (ALND). However, the disadvantage of this method is the significant morbidity that is associated with it, e.g. lymph oedema of the arm with a decreased ability for movement [2–5]. Several studies have shown that a sentinel lymph node procedure (SLNP) can safely replace ALND for axillary staging [6–10]. The selection of patients for SLNP is based on physical examination of the axilla. SLNP is performed only in patients without clinically suspicious nodes. However, the sensitivity of physical examination of the axilla is only 33–68% [11–14].

The sentinel node contains tumour cells in approximately 40% of all breast cancer patients [15]. 50% of these malignant nodes are palpably enlarged during surgery, but are not detected by physical examination preoperatively. By detecting these nodes before surgery, these patients could immediately be scheduled for ALND, which is less labour-intensive than the SLNP plus subsequent ALND if a tumour-positive sentinel node is found. Alternatively, patients may be candidates for neo-adjuvant chemotherapy.

Predictive lymph node characteristics on ultrasound images may provide quantitative guidelines in deciding

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whether or not a node should be aspirated, thereby increasing specificity without compromising sensitivity. This would result in a reduction of the number of fine-needle aspirations (FNAs) on normal nodes. Several authors have studied predictive lymph node characteristics, e.g. length, shape and cortex appearance [16–22]. However, the discriminating power of these features is limited and large variations have been reported. This may be due to subjectivity in the rating of the features.

The first aim of this study was to investigate whether the use of combined preoperative axillary ultrasonography and FNA in breast cancer patients without palpable lymph nodes reduces the number of SLNPs. The second aim was to identify an optimal subset of quantitative features to predict metastatic involvement of a node.

2. Patients and methods

2.1. Study population

Between August 1999 and January 2001, all 265 breast cancer patients who were eligible for a SLNP in our hospital were included in this study. 3 patients had bilateral breast cancer; so 268 axillae were examined. Most patients (82%) had a palpable breast lesion. All patients had a clinically negative axilla. Mean age was 56 years (range 27–91 years). The mean diameter of the primary tumour as measured by the pathologist was 19 mm (range 2–80 mm). The tumour types were invasive ductal carcinomas in 203 cases (76%), invasive lobular carcinomas in 29 cases (11%) and other type of tumours in 30 cases (11%). No histological material of the primary tumour was available in 6 cases (2%). These patients did not have surgery, because they had distant metastases at the time the primary cancer (and the tumour-positive node) was detected.

2.2. Training session

Before starting the study, all seven participating radiologists underwent a training session to become familiar with the area where the sentinel node is situated in the majority of patients. This area is in the lower part of the axilla near or just behind the lateral edge of the major pectoral muscle. In this area, the radiologists have the greatest chance of targeting the sentinel node. Breast cancer patients scheduled for sentinel node lymphoscintigraphy were asked to participate in this training session. The location of the sentinel node was marked on the skin using a ^{57}Cobalt-pen. The radiologists sonographically examined the marked area with a 13-MHz-1.5D transducer (Siemens Elegra, Erlangen, Germany). Each radiologist examined the axillae of at least 5 patients. If a lymph node in the area of the indicated sentinel node was detected by ultrasound, images of the node(s) in two perpendicular directions were obtained. In this training session, no FNA was performed.

2.3. Reduction in SLNPs, study design

The sentinel lymph node area was ultrasonographically examined in two perpendicular directions (longitudinal and transverse) by one of the trained radiologists, using the same transducer that was used in the training session. Fig. 1 shows the flowchart of the study protocol. If no lymph nodes were detected in the axilla by ultrasonography, the patient underwent SLNP several weeks later. If a lymph node was detected in the axilla, the length, width (=smallest diameter) and the maximum cortex thickness of the node were measured (Fig. 2) and images of the node in two perpendicular planes were obtained. The number of visible nodes was established. FNA was only performed on suspicious nodes (smallest diameter of at least 5 mm or atypical cortex appearance [17]). If no FNA was performed, the patient underwent SLNP. If more than one node was detected, radiologist performing the ultrasound examination determined which was the most suspicious and this node was aspirated. In practice, this meant that the node with the most atypical cortex was aspirated. If FNA did not show lymphoid cells or only normal lymphoid cells, the patient underwent SLNP. If tumour cells were found by FNA cytology, the patient underwent ALND. The typical time required for axillary ultrasonography was 5 min without FNA and 10 min with FNA.

2.4. SLNP

In patients scheduled for SLNP, ^{99m}technetium-labelled nanocolloid was injected into the tumour the day

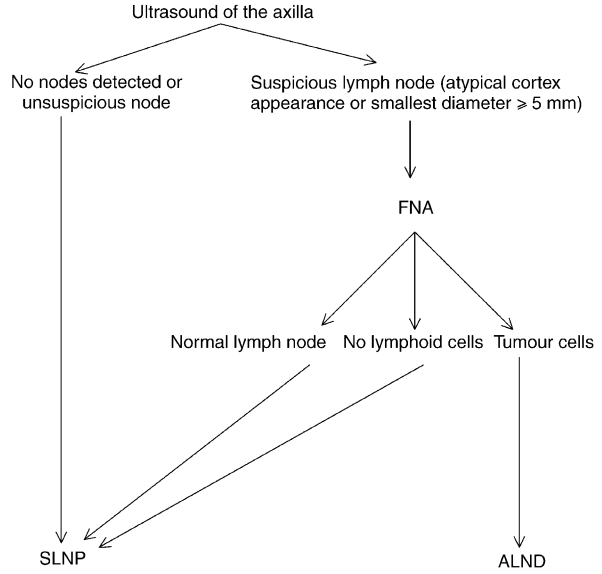

Fig. 1. Flowchart of the study design. FNA, fine-needle aspiration; SLNP, Sentinel Lymph Node Procedure; ALND, Axillary Lymph Node Dissection.

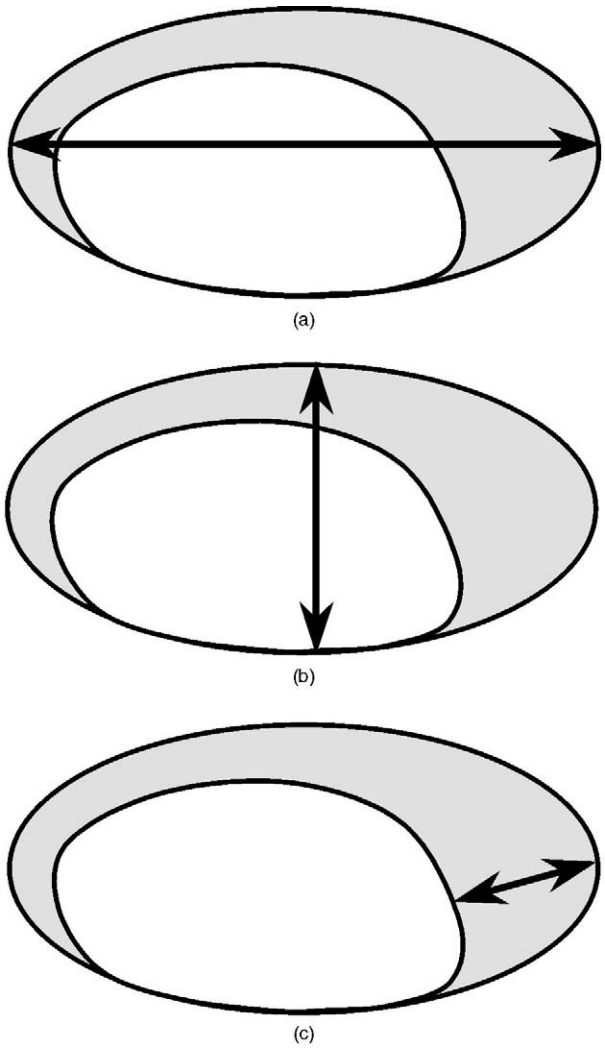

Fig. 2. Schematic representation of lymph node characteristics; (a) length; (b) width; (c) maximum cortex thickness.

before surgery. Scintigraphic images were obtained 20 min, 2 and 4 h after injection. The location of the sentinel node was marked on the skin. During surgery, patent blue dye was injected into the tumour. The sentinel lymph node was detected using a gamma-ray detection probe and by dissecting blue stained lymphatic ducts. Peroperative frozen sectioning of the sentinel node was performed. Patients with a sentinel node containing tumour cells in frozen sections underwent an ALND in the same session. Paraffin sections of the sentinel node of six levels were examined after surgery and immunohistochemistry was used. If the frozen section of the sentinel node did not show a metastasis but the definitive pathological examination did show a metastasis, the patient underwent ALND in a second surgical session or radiotherapy of the axilla.

2.5. Lymph node characteristics, study design

The printed ultrasonographic images of visible nodes were studied. The appearance of the hilus and cortex were established according to the method of Vassallo and colleagues [17]. Length, width and maximum cortex thickness of the node (Fig. 2) were measured by one of the trained radiologists and the length/width ratio, representing the shape of the node, was calculated. The gold standard for the presence of metastasis was ALND ($n=32$) or tumour-positive lymph node at FNA with distant metastases ($n=6$). Because images of three nodes were lost, characteristics of 34 malignant nodes were analysed. The gold standard for benign nodes was SLNP. Thirty-four benign nodes were analysed: 17 showed lymphoid cells or lack of lymphoid cells as well as tumour cells on FNA and 17 were not aspirated. The benign and malignant nodes used for the analysis of lymph node characteristics are indicated in Table 1.

2.6. Statistical analysis

To calculate the reduction in SLNPs, the total number of axillae with a malignant node detected by ultrasound and FNA was divided by the total number of axillae. The Chi-square test was used to compare proportions.

Linear discrimant analysis and step-wise selection were employed with 'appearance of cortex', 'appearance of hilus', 'length', 'width', 'maximum cortex thickness' and 'shape' to identify a statistically significant subset of these features that accurately classifies nodes into normal and malignant. Receiver Operating Characteristic (ROC) analysis [23] was performed to determine the sensitivity and specificity of individual and combined nodal features in the task of distinguishing between malignant and normal lymph nodes. The area under the ROC curve (A_Z) was used to quantify the accuracy of the classification. The ROC technique allows the selection of a cut-off point at a desired trade off between sensitivity and specificity [23]. Prospective estimation of the performance to discriminate between malignant and normal lymph nodes for new

Table 1
Number of ultrasound and fine-needle aspirations (FNAs) (rows) in relation to Axillary Lymph Node status (columns)

Ultrasound	FNA	Axillary lymph node status		Total
		No lymph node metastases	Lymph node metastases (macro + micro)	
No lymph node detected		113	62 (39 + 23)	175
Node(s) detected, but no FNA		17[a]	10 (4 + 6)	27
Node + FNA	No lymphoid cells	1[a]	6 (5 + 1)	7
	Normal node	16[a]	6 (3 + 3)	22
	Malignant node	–	37[a] (36 + 1)	37
Total		147	121 (87 + 34)	268

[a] Benign and malignant nodes used for the analysis of nodal features.

cases was obtained by leave-one-out cross validation [24].

3. Results

3.1. Reduction in SLNPs

Table 1 shows the result of ultrasound and FNA in relation to the axillary lymph node status.

In 93 axillae (35%), at least one lymph node was detected by ultrasonography. The mean number of ultrasonographic visible nodes was 1.6 (range 1–6). Mean length of the lymph nodes was 11.3 mm (range 2.5–33.7 mm); mean width was 6.2 mm (range 1.9–18.2 mm). Twenty-seven lymph nodes (29%) were not aspirated (due to technical problems or unsuspicious nodes with a smallest diameter of <5 mm). FNA was performed on the remaining 66 nodes (71%). Thirty-seven (56%) of these nodes showed tumour cells, 22 (33%) showed normal lymphoid cells and in seven cases (11%) FNA contained neither lymphoid nor tumour cells.

The sentinel nodes of 147 axillae (55%) contained no metastases. In the remaining 121 axillae (45%), at least one lymph node contained a metastasis. Thirty-four of the 121 tumour-positive axillae (28%) contained a micrometastasis (defined as a metastasis smaller than 2 mm) only.

Axillae with ultrasonographically-detected lymph nodes more often had lymph node metastases (macrometastases and micrometastases; 59/93) than axillae without detected lymph nodes (macrometastases and micrometastases; 62/175) ($P<0.0001$).

Forty-eight out of 87 axillae (55%) with a macrometastasis in the sentinel lymph node had visible nodes on ultrasonographic examination, but only 11 out of 34 axillae (32%) with a micrometastasis in the sentinel lymph node had visible nodes ($P=0.024$). Of all axillae with lymph node metastases ($n=121$), 37 (31%) were found by ultrasound and FNA. If only macrometastases are considered, then 41% of patients (36/87) with axillary metastases are identified by preoperative axillary ultrasound and FNA. Altogether, the number of SLNPs was reduced by 14% (37/268), at the expense of FNA in 25% of all axillae (66/268).

3.2. Lymph node characteristics

ROC analysis was performed for all nodal features on the 68 nodes with confirmed histological diagnosis (obtained by SLNP or ALND) or with tumour-positive FNA with distant metastases. Table 2 shows the A_Z values obtained with ROC analysis for the various features individually. An A_Z value of 1.0 corresponds to a 'perfect' ability to predict nodal status, and 0.5 to no ability to predict the status. 'Maximum cortex thickness' and 'appearance of cortex' turned out to be the most effective features to discriminate between normal and malignant nodes. 'Appearance of hilus', 'shape', 'length' and 'width' were also effective features, showing moderate ability to predict metastatic involvement. 'Appearance of cortex' and 'appearance of hilus' were ignored in the step-wise selection procedure. The rationale for this will be discussed in the next section. Of the remaining features, the combination of 'maximum cortex thickness' and 'shape' was found to contribute significantly to the discrimination between malignant and normal lymph nodes (Fig. 3: leave-one-out cross validation: $A_Z=0.89$; Standard Deviation (S.D.) 0.04). The performance obtained by these combined features is comparable to the performance obtained by using 'maximum cortex thickness' alone (Fig. 3: $A_Z=0.87$; S.D. 0.04). The performance of 'shape' (Fig. 3: $A_Z=0.71$; S.D. 0.06) was found to be inferior to that of 'maximum cortex thickness' and also to the combination of 'maximum cortex thickness' and 'shape'.

Table 2
Areas under the ROC curves (A_Z) for individual nodal features

	A_Z (±1 S.D.)
Maximum cortex thickness	0.87 (±0.04)
Appearance of cortex	0.86 (±0.05)
Appearance of hilus	0.75 (±0.06)
Shape	0.71 (±0.06)
Length	0.70 (±0.06)
Width	0.68 (±0.06)

ROC, Receiver Operating Characteristic; S.D., Standard Deviation.

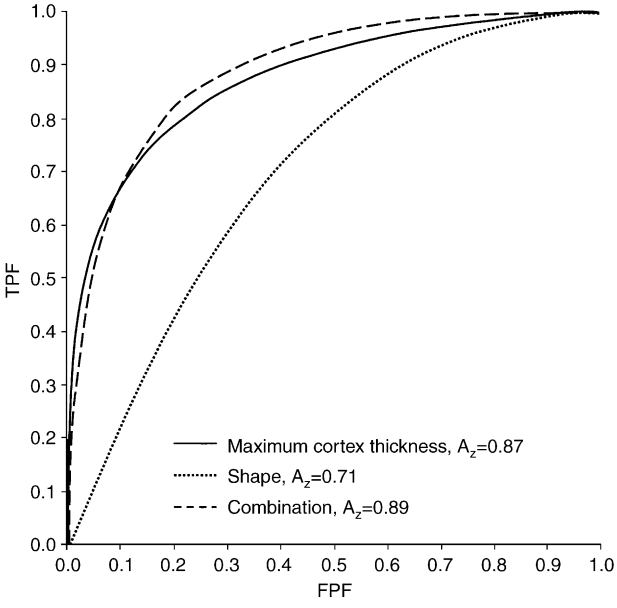

Fig. 3. ROC curves of 'maximum cortex thickness', 'shape' and the combination of 'maximum cortex thickness' and 'shape'. The curves are obtained by leave-one-out cross validation (estimate of prospective performance). ROC, Receiver Operating Characteristic; FPF, False-Positive Fraction; TPF, True-Positive Fraction; A_Z, Area under the ROC curve.

Using the ROC analysis, several cut-off points can be selected to set a corresponding sensitivity and specificity. A cut-off point of maximum cortex thickness with high sensitivity (e.g. 95%) and relatively low specificity (44%) may be chosen. To obtain this sensitivity and specificity, a maximum cortex thickness of 2.3 mm must be applied, i.e. all nodes with a maximum cortex thickness of at least 2.3 mm are to be aspirated. As a consequence, a relatively small fraction of malignant nodes is missed, but FNA is performed on a large proportion of benign nodes. Likewise, a cut-off point of maximum cortex thickness with moderate sensitivity (e.g. 80%) and specificity (80%) may be chosen; a relatively small fraction of benign nodes will be aspirated, but a smaller fraction of malignant nodes will be detected. The maximum cortex thickness for this point on the ROC curve is 4.2 mm. For future clinical implementation, we chose a cut-off point of maximum cortex thickness of 2.3 mm that corresponds to an estimated sensitivity of 95% and specificity of 44%.

4. Discussion

Initial results indicate that a reduction in the number of sentinel lymph node procedures can be obtained by preoperative ultrasonography of the axilla. Because ultrasonographic examination of the axilla is far less time-consuming (5–10 min) than a SLNP, which involves multiple procedures in several departments, we believe that ultrasound is a useful tool for preoperative screening of the axilla in patients scheduled to undergo a SLNP.

To our knowledge, there are only two studies that can be compared with ours: the study of Bonnema and colleagues [25] and of de Kanter and colleagues [26]. The patient populations in these studies also contained breast cancer patients with non-palpable lymph nodes only, but FNA was performed on all sonographically visible nodes. In the study of Bonnema and colleagues [25], positive lymph nodes were identified with ultrasound and FNA in 26% of all axillae. The higher amount of positive nodes found in this study compared with ours can partly be explained by a difference in the patient populations: in their study, 15% of all patients had four or more positive axillary nodes, compared with only 6% in our study. In addition, in their study more patients underwent FNA (54% of all patients compared with 25% in our study).

The reduction in SLNPs in the study of de Kanter and colleagues [26] (17%) was comparable with our findings. However, compared with our study, a larger amount of patients underwent FNA (37% in their study compared with 25% in our study), indicating that a larger reduction in SLNPs is at the expense of a larger fraction of FNA on mostly benign nodes. Cost-benefit considerations should be taken into account when choosing a protocol for combined preoperative ultrasonography and FNA. FNA in all patients with ultrasonographically visible nodes will lead to aspiration of a large amount of benign nodes with an increase in patient distress. In addition, missing a malignant node with ultrasound and FNA has no additional consequences for the patient compared with the current strategy in which only SLNP is employed.

We analysed several nodal features to identify a subset of quantitative features that objectively predicts metastatic involvement of the node. ROC analysis indicates that 'length' and 'width' have a moderate ability to predict metastatic involvement. Some studies indicate a stronger relationship between nodal size and metastatic involvement [19,20], but different patient populations were used in these studies: palpable lymph nodes (non-palpable nodes in our study) and/or a combination of axillary, cervical and inguinal nodes (only axillary nodes in our study).

The feature 'shape' shows moderate ability to predict metastatic involvement as well. These results are in agreement with those reported by other authors [16,17,20], and by authors who used high-resolution helical computed tomography (CT) instead of ultrasound [27].

A good performance in predicting metastatic involvement was found for the feature 'cortex appearance', which confirms results obtained by others [16,17,20–22,27]. However, it is a subjective feature, which may lead to large inter- and intra-observer variations. A more objective measure for the appearance of the cortex is the maximum cortex thickness. The maximum cortex thickness can be measured easily with ultrasound and was a good predictor for metastatic involvement in our patient population ($A_Z = 0.87$). Yang and colleagues [21] indicated that the thickness of the cortex of a normal node is 1–2 mm, which supports our finding that FNA of nodes with maximum cortex thickness of at least 2.3 mm results in a good discrimination (sensitivity 95%, specificity 44%). 'Maximum cortex thickness' by itself and the combination of 'maximum cortex thickness' and 'shape' showed similar A_Z values (0.87 and 0.89, respectively). Therefore, we recommend using the characteristic that is the easiest to implement in clinical practice: 'maximum cortex thickness'.

Several authors have used colour Doppler ultrasound to distinguish between benign and malignant lymph nodes [18,20,28]. In this study, we did not consider colour Doppler because it has been reported that colour Doppler flow is suitable to identify metastatic involvement of palpable axillary nodes, but is less suitable for non-palpable nodes [18].

The use of SLNP is currently proposed in patients with a clinically negative axilla. However, palpation not only has moderate sensitivity, but also has moderate specificity: enlarged nodes may well be cancer-free [12,14]. Although we did not study palpable nodes, it is likely that the combination of ultrasound and FNA might also help to assess the nature of these enlarged nodes.

Although the combination of ultrasound and FNA is a powerful method to reduce the number of SLNPs, a potential drawback is the theoretically possible damage of one of the afferent lymphatic vessels by FNA, resulting in a decreased ability to detect the sentinel node during lymphoscintigraphy and biopsy. However, the follow-up time to determine the amount of false-negative sentinel nodes is too short and definite proof that FNA does not lead to an increase in false-negatives will be obtained from long-term follow-up of these patients. On the other hand, one of the reasons for a false-negative sentinel node (2.5–5%) [6–8] is gross involvement of the node by tumour cells, which prohibits tracer uptake [29–31]. These nodes might be detected before surgery with ultrasonography and FNA, thereby decreasing the false-negative rate of SLNP [32].

It should be noted that the reduction in the number of SLNPs may vary between clinics when conventional assessment of lymph nodes in terms of cortex appearance is used. However, our preliminary results show that the use of quantitative features, maximum cortex thickness in particular, and ROC analysis may lead to a consistent high performance in distinguishing malignant from normal nodes. However, prospective evaluation remains necessary.

References

1. Fisher B, Bauer M, Wickerham DL, *et al*. Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer. An NSABP update. *Cancer* 1983, **52**, 1551–1557.
2. Ivens D, Hoe AL, Podd TJ, Hamilton CR, Taylor I, Royle GT. Assessment of morbidity from complete axillary dissection. *Br J Cancer* 1992, **66**, 136–138.
3. Kissin MW, Querci della Rovere G, Easton D, Westbury G. Risk of lymphoedema following the treatment of breast cancer. *Br J Surg* 1986, **73**, 580–584.
4. Shaw JH, Rumball EM. Complications and local recurrence following lymphadenectomy. *Br J Surg* 1990, **77**, 760–764.
5. Lotze MT, Duncan MA, Gerber LH, Woltering EA, Rosenberg SA. Early versus delayed shoulder motion following axillary dissection: a randomized prospective study. *Ann Surg* 1981, **193**, 288–295.
6. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1994, **220**, 391–398.
7. Veronesi U, Paganelli G, Galimberti V, *et al*. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. *Lancet* 1997, **349**, 1864–1867.
8. Krag D, Weaver D, Ashikaga T, *et al*. The sentinel node in breast cancer—a multicenter validation study. *N Engl J Med* 1998, **339**, 941–946.
9. Veronesi U, Galimberti V, Zurrida S, *et al*. Sentinel lymph node biopsy as an indicator for axillary dissection in early breast cancer. *Eur J Cancer* 2001, **37**, 454–458.
10. 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.
11. Bruneton JN, Caramella E, Hery M, Aubanel D, Manzino JJ, Picard JL. Axillary lymph node metastases in breast cancer: preoperative detection with US. *Radiology* 1986, **158**, 325–326.
12. de Freitas R, Costa MV, Schneider SV, Nicolau MA, Marussi E. Accuracy of ultrasound and clinical examination in the diagnosis of axillary lymph node metastases in breast cancer. *Eur J Surg Oncol* 1991, **17**, 240–244.
13. Perre CI, de Hooge P, Leguit P. [Little extra information with ultrasonic studies of the axillary glands in patients with breast carcinoma]. *Ned Tijdschr Geneeskd* 1991, **135**, 1275–1277.
14. Yang WT, Ahuja A, Tang A, Suen M, King W, Metreweli C. High resolution sonographic detection of axillary lymph node metastases in breast cancer. *J Ultrasound Med* 1996, **15**, 241–246.
15. Tanis PJ, van Sandick W, Nieweg E, *et al*. The hidden sentinel node in breast cancer. *Eur J Nucl Med* 2002, **29**, 305–311.
16. Feu J, Tresserra F, Fabregas R, *et al*. Metastatic breast carcinoma in axillary lymph nodes: in vitro US detection. *Radiology* 1997, **205**, 831–835.
17. Vassallo P, Wernecke K, Roos N, Peters PE. Differentiation of benign from malignant superficial lymphadenopathy: the role of high-resolution US. *Radiology* 1992, **183**, 215–220.
18. Yang WT, Chang J, Metreweli C. Patients with breast cancer: differences in color doppler flow and gray-scale us features of benign and malignant axillary lymph nodes. *Radiology* 2000, **215**, 568–573.
19. Walsh R, Kornguth PJ, Soo MS, Bentley R, DeLong DM. Axillary lymph nodes: mammographic, pathologic, and clinical correlation. *AJR Am J Roentgenol* 1997, **168**, 33–38.
20. Tschammler A, Ott G, Schang T, Seelbach-Goebel B, Schwager K, Hahn D. Lymphadenopathy: differentiation of benign from malignant disease—color doppler US assessment of intranodal angioarchitecture. *Radiology* 1998, **208**, 117–123.
21. Yang WT, Ahuja A, Tang A, Suen M, King W, Metreweli C. Ultrasonographic demonstration of normal axillary lymph nodes: a learning curve. *J Ultrasound Med* 1995, **14**, 823–827.
22. Strauss HG, Lampe D, Methfessel G, Buchmann J. [Preoperative axilla sonography in breast tumor suspected of malignancy—a diagnostic advantage?]. *Ultraschall Med* 1998, **19**, 70–77.
23. Metz CE. ROC methodology in radiologic imaging. *Invest Radiol* 1986, **21**, 720–733.
24. Gong G. Cross-validation, the jackknife, and the bootstrap: excess error estimation in forward logistic regression. *J Am Stat Assoc* 1986, **81**, 108–113.
25. Bonnema J, van Geel AN, van Ooijen B, *et al*. Ultrasound-guided aspiration biopsy for detection of nonpalpable axillary node metastases in breast cancer patients: new diagnostic method. *World J Surg* 1997, **21**, 270–274.
26. de Kanter AY, van Eijck CH, van Geel AN, *et al*. Multicentre study of ultrasonographically guided axillary node biopsy in patients with breast cancer. *Br J Surg* 1999, **86**, 1459–1462.
27. Uematsu T, Sano M, Homma K. In vitro high-resolution helical CT of small axillary lymph nodes in patients with breast cancer: correlation of CT and histology. *AJR Am J Roentgenol* 2001, **176**, 1069–1074.
28. Choi MY, Lee JW, Jang KJ. Distinction between benign and malignant causes of cervical, axillary, and inguinal lymphadenopathy: value of doppler spectral waveform analysis. *AJR Am J Roentgenol* 1995, **165**, 981–984.
29. Tanis PJ, Nieweg OE, Merkus JW, Peterse JL, Kroon BB. False negative sentinel node procedure established through palpation of the biopsy wound. *Eur J Surg Oncol* 2000, **26**, 714–715.
30. Liberman L, Cody III HS. Percutaneous biopsy and sentinel lymphadenectomy: minimally invasive diagnosis and treatment of nonpalpable breast cancer. *AJR Am J Roentgenol* 2001, **177**, 887–891.
31. Boolbol SK, Fey JV, Borgen PI, *et al*. Intradermal isotope injection: a highly accurate method of lymphatic mapping in breast carcinoma. *Ann Surg Oncol* 2001, **8**, 20–24.
32. Parker SH, Dennis MA, Kaske TI. Identification of the sentinel node in patients with breast cancer. *Radiol Clin North Am* 2000, **38**, 809–823.