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Intraoperative frozen section analysis for breast-conserving therapy in 1016 patients with breast cancer

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Abstract

Objective: We evaluate the number of surgical two-stage procedures after FSA during breast-conserving therapy (clinical false negative result of FSA) and investigate the influence of microcalcifications, small tumour diameter, neoadjuvant therapy and preoperative biopsy on the clinical false negative rate of FSA.
Subjects: We retrospectively examined 1016 patients after intraoperative FSA during breast-conserving therapy for breast cancer operated between 1995 and 2001 at the Medical University Vienna.
Results: Only 9% of all patients had to undergo a two-stage operation due to a false negative intraoperative FSA result. The annual local recurrence rate was 1.2% in all patients with no difference between one- and two-stage operated patients. In situ and pT1 lesions were similarly distributed between one-stage and two-stage operated patients. The use of neoadjuvant therapy and stereotactic biopsy (reflecting non-palpable lesions and microcalcifications) were significantly predictive for a false negative FSA result. The use of a preoperative core biopsy, however, reduced the necessity of performing a two-stage operation.
Conclusion: Our study demonstrates that FSA leads to a low rate of two-stage operations. Small lesions and microcalcifications as well as the occurrence of intraductal cancer cells and neoadjuvant therapy increased while preoperative core biopsy reduced the false negative rate of FSA. Overall local recurrence rates after FSA were acceptable.

Keywords: Breast-conserving therapy; Intraoperative management; Frozen section analysis

Introduction

One of the most important factors for adequate oncological surgery in breast cancer patients is the margin status. The standard surgical practice is to obtain microscopically clear margins (R0 $\geq$1 mm) even if this requires a second surgical procedure.[1,2] Frozen section analysis (FSA) guides the surgeon during breast-conserving therapy (BCT) to perform primary tumor resection with clear margins and yields an accuracy of 97%.[3,4] Furthermore, the ''core cut'' FSA results may inform the surgeon immediately about the necessity to perform surgical axillary lymph node dissection in cases of an intraoperatively diagnosed invasive breast cancer. Subsequently, a second operation (two-stage procedure) may be avoided in a considerable number of patients.[5,6] The clinical false negative rate of FSA or the number of two-stage procedures due to a difference between the FSA and the final pathological report, respectively, have been reported to range between 0% and 19% after FSA.[3,4,6–8] Without the use of FSA, a two-stage procedure may become necessary in up to 38–54% of patients undergoing simple lumpectomy.[9–11]

Higher rates of two-stage procedures may account for increased morbidity like wound infection, paraesthesia and scarring. Moreover, due to anatomical disorientation, the volume excised for a re-resection within a one-stage

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procedure may be smaller than that involved in a two-stage procedure which may indirectly affect the cosmetic outcome.[12]

While the accuracy, sensitivity and specificity rates are between 95 and 99%,[3,5,13] several authors raised concerns regarding the use of FSA for non-palpable lesions, tumours below 1 cm in diameter and pure microcalcifications.[4,7,14–18] As a consequence, physicians were concerned about a reduced diagnostic accuracy particularly in these lesions. In addition, pathologists have reported on freezing artefacts, which may cause difficulties in determining both final tumour staging and the smallest free resection margin, thus interfering with tailoring adequate adjuvant therapy and deteriorating oncological outcome. Thus, several breast cancer units have been shifting their policy not to apply FSA on a routine basis.[7]

Recent developments such as preoperative sure cut biopsy and neoadjuvant therapy play an important role in improving operative planning and increase breast-conserving rates. Their influence on FSA, however, is unknown.

We hypothesize that intraoperative high-quality FSA performed by well-trained pathologists on a routine basis yields a low number of two-stage procedures for breast cancer patients. In addition we analysed whether factors such as grading, tumour size, preoperative biopsy and neoadjuvant therapy may interfere with the FSA result.

Patients and methods

Patient collective

A total of 1559 consecutive patients with intraoperative FSA of their breast specimens during breast surgery for malignant and benign disease performed at our institution between 1st January 1995 and 1st August 2001 were analyzed retrospectively. One hundred and sixty-five had open biopsy for benign breast disease, and 378 underwent mastectomy due to breast cancer. Indications for primary mastectomy were either impossibility to gain resection-free margins with an adequate cosmetic result, no change or progressive disease after nedoadjuvant therapy and multicentric disease.[2] Of all patients with breast cancer, 1016 (65%) underwent BCT. These patient data were used for all further analyses.

Diagnosis of breast cancer and indications for surgery were based on the BIRADS system providing surgery for BIRADS IV, V and VI lesions.[19]

Core needle biopsy

Core needle biopsy was offered to all patients with radiological diagnosed BIRADS IV and V breast lesions.[19] Whether a patient underwent core needle biopsy or not was decided based on the patients' personal preference after informed and written consent. The tumour size did not influence the decision for the use of core needle biopsy.

Percutaneous biopsy was performed using stereotactic guidance or ultrasound guidance after written informed consent was obtained from each patient. The choice of guidance depended on a number of factors including lesion location, imaging characteristics, scheduling considerations, and individual preference. All biopsies were performed by one of five of attending radiologists specialized in breast imaging. Stereotactic biopsy was introduced at our institution in 1994. From 1994 to 1997 all biopsies were performed with 14-gauge needle (BIP, Bard Urological, Covington, GA). The 14-gauge vacuum-assisted probe (Mammotome, Ethicon Endosurgery) was introduced in July, and the 11-gauge vacuum-assisted biopsy probe in September 1997. All biopsies were performed after disinfection and local anaesthesia with patients prone on a dedicated examination table (Fischer Imaging Mammotest, Denver, CO).[20]

In cases of palpable lesions, core needle biopsy was immediately performed in the outpatient clinic with a detachable core needle biopsy system (ASAP Detachable; Meditech, Watertown, MA) containing a 14-gauge needle. Briefly, after disinfection and local anaesthesia and written informed consent of each patient the skin was incised with a scalpel and the biopsy system was inserted through the skin incision into the breast. Under control by local palpation, the lesion was punctured 1–3 times (median 2 times).

Neoadjuvant therapy

Patients with a breast/tumour size relation necessitating primary mastectomy were treated with neoadjuvant therapy in a prospective randomized protocol (ABCSG 14) comparing 3 with 6 cycles of epirubicin and docetaxel.[21] The primary outcome was pathological complete response (pCR) defined as no residual invasive or intraductal cancer in the breast.[22]

Breast-conserving therapy (BCT)

BCT was indicated for all patients with a possibility of achieving resection-free margins (>1 mm) with a cosmetically acceptable result. Other exclusion criteria were progressive disease after neoadjuvant therapy, inflammatory carcinoma and multicentric disease.[2] Non-palpable tissue masses or microcalcifications were preoperatively marked using wire-guided localization. During BCT (lumpectomy), the excised tissue specimen was marked with sutures for orientation and immediately sent for pathological examination. In the presence of microcalcifications, the specimens were sent to radiology for specimen radiography. Together with preoperative wire localization technique, this procedure further helped the pathologist to define areas requiring particular attention during FSA. If the result of the FSA showed a benign lesion or clear margins, the surgical procedure was finalized. The time needed from excision of the biopsy until arrival of the FSA report in the operating room via intercom is usually about 30 min. In case of malignant cells on one of the resection margins or close

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to the next margin (below 1 mm), the surgeon immediately performed an additional excision at this specific site in order to establish free margins (>1 mm = R0 resection). These specimens were also evaluated by FSA (suture orientation of the new margin).

In cases of pathologically documented invasive malignancy, a sentinel node biopsy was performed as described elsewhere.[23] In case of nodal involvement, conventional axilla dissection followed.

Histological procedures

After surgical resection, the breast specimen was transported to the pathology department. The margins were marked with ink. The specimen was then serially sectioned in 3–4 mm slices. Next, FSA of up to 3 μm thin slices (1–3 μm; mean 2 μm) from the suspected tissue area (macroscopically suspect lesion, palpable lesion, wire-localized lesion, microcalcification seen on mammogram) was performed to evaluate the closest margin of resection. FSA was performed with a microtom (Kryostat). FSA has only been done for lesions in cases of unknown diagnosis (no preoperative core needle biopsy). Sections were stained with a rapid haematoxylin and eosin procedure. Results of the FSA were defined as benign lesion, intraductal or invasive carcinoma. The distance of the lesion from the nearest margin was also evaluated. The result was reported directly to the surgeon within 20–30 min after excision. The rest of the tissue was not frozen, preventing freezing artefacts in the permanent histology. It was wrapped up in a paper towel to prevent swelling during fixation (2.5% formalin for 24 h). Thereafter the fixed tissue was embedded in paraffin for definitive histological analysis. A median of 11 paraffin blocks were done for all patients. TNM staging and grading were performed according to Bloom and Richardson,[24] receptor status was assessed by immunohistochemistry as already described.[25] A close or positive margin was defined as cancer cells below 1 mm from the next resection-free margin.

Retrospective data evaluation

All patients' characteristics were obtained over the past 10 years by continuous updating of our patient database during follow-up (every 3 months for the first 3 years, every 6 months thereafter and once yearly at 5 years after operation). This file was created in 1990. Patients gave their consent to record and evaluate their data. From 1995 the database has been updated prospectively. All patients with breast operations are routinely implemented in the database by our documentation centre (study nurse). However, there were some missing data which were added either by our study nurse, the first author (O.R.) or a co-author (F.F.). Missing data were imported retrospectively from the central patient database of the Medical University of Vienna with permission of the appropriate authorities.

False negative rate of FSA

We evaluated the clinical false negative rate of the FSA by evaluating the frequency of two-stage procedures resulting due to a discrepancy between the intraoperative FSA result and the definitive histological paraffin section result in terms of resection-free margins or diagnosis of invasive cancer within the breast.

Factors predicting a false negative FSA

In order to evaluate factors which may be correlated with the clinical false negative rate of FSA, we compared the demographic data of patients undergoing a one- vs. two-stage procedure and analysed grading, tumour size, the use of preoperative tumour biopsy, neoadjuvant therapy and the use of a preoperative stereotactic biopsy as an indicator for microcalcifications and non-palpability of the cancer in a univariate and multiple analyses.

Statistical analysis

Categorical data were described with absolute and relative frequencies. Differences of the categorical factors between patients with one- and two-stage procedures were assessed with chi-squared tests. In case of sparse data corresponding exact tests were used. A multiple logistic regression model was used to estimate the effect of prognostic factors on a resulting one- or two-stage procedure. These effects were described with odds ratios, corresponding 95% confidence intervals and p-values. All p-values given were two-sided.

Results

Clinical false negative FSA rate

Within the observation period, 1559 patients had FSA during breast surgery at the Department of General Surgery, Medical University of Vienna. One thousand three hundred and ninety-four patients had invasive or intraductal carcinoma and BCT was administered to 1016 women (65%). In 9% (91 patients) of these primarily breast conserved patients, histological results of FSA differed from the definitive histological result of the paraffin-embedded tissue in terms of margin status or detection of invasive cancer cells. In these patients a second operation ($n = 89$) or even a third operation ($n = 2$) had to be performed to achieve clear margins or to further undergo lymph node surgery (Table 1). In 35 out of these 91 patients a mastectomy had to be performed to finally yield cancer-free margins increasing the total mastectomy rate of the whole cohort (1394 patients) from 27% to 30%.

Demographic data

Table 2 shows the demographic data of breast cancer patients with one- and two-stage procedures. There were

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Table 1
Patient cohort

1 January 1995 to 1 August 2001	*n*	%
Patients with frozen sections	1559	100
Benign breast lesions	165	11
Malignant breast lesions	1394	89
Primary mastectomy	378	27
Primary BCT	1016	73
Invasive carcinoma	930	92
Ductal carcinoma in situ	86	8
One-stage procedure after BCT	925	91
Two-stage procedure after BCT	89	8.8
Three-stage procedure after BCT	2	0.2
Secondary mastectomy after BCT	35	3

no statistically significant differences in age, grading, nodal status or receptor status regarding the likelihood of a patient undergoing a two-stage procedure due to a difference in FSA of the breast specimens when compared with the definitive histological result.

Table 2
Demographic data of breast cancer patients with one- and two-stage procedures

	One-stage procedure		Two-stage procedure		*p*-value
	n	% ($n = 925$)	*n*	% ($n = 91$)	
Age					
<40	59	6	7	8	0.63
Histology					
Lobular	112	12	3	3	0.03
Ductal	813	88	88	97	
pT					
Tis	77	8	9	10	0.09
T1	595	64	50	55	
T2	218	24	25	27	
T3	7	1	2	2	
T4	18	2	5	5	
pCR	10	1	0	0	
pN					
N0	595	64	48	53	0.08
N1	305	33	34	37	
Not done	25	3	9	10	
Grading					
G1/G2/Gx	593	64	61	67	0.57
G3	332	36	30	33	
Receptor status					
ER neg	241	26	18	20	0.11
ER pos	444	48	38	42	
ER strongly pos	221	24	35	38	
PR neg	472	51	44	48	0.22
PR pos	330	36	42	46	
PR strongly pos	92	10	5	5	
Preoperative BX					
Sure cut	223	24	6	7	0.0008
Stereotactic	86	9	8	9	
Open	26	3	3	3	
Neoadjuvant	118	13	43	47	0.0001

Reason for two-stage operation

Seventeen patients with a benign diagnosis at FSA had malignant cells at final paraffin histology. Thirty-six had an intraductal carcinoma at the resection margin while 25 had invasive cancer cells at the resection margin. Thirteen patients had to undergo axillary surgery due to a final diagnosis of invasive cancer cells at paraffin embedded histology, while FSA showed only an intraductal carcinoma.

Prognostic factors for a two-stage operation

Multiple logistic regression analysis demonstrated that patients with a preoperative biopsy had a lower chance of having a clinical false negative FSA while patients with neoadjuvant therapy and patients with microcalcifications, indicated by a preoperatively performed stereotactic biopsy, had an increased risk of having a clinical false negative FSA (Table 3).

Oncologic outcome

After a median follow up of 82.8 months (one-stage group) and 92.8 months (two-stage group) there were 74 local recurrences out of 925 in the one-stage procedure patients (8% local recurrence rate) compared with 9 out of 91 in the two-stage procedure patients (10% local recurrence rate). This reflects an annual local recurrence rate of 1.2 and 1.3, respectively without any statistical differences between the two groups.

Discussion

BCT is only indicated in the presence of resection-free margins. In cases of involved margins diagnosed by paraffin-embedded histology after BCT, the patient has to undergo a second operation (two-stage procedure). Intraoperative FSA serves as a diagnostic tool and guidance for surgeons in the course of breast cancer surgery during open biopsy or BCT, respectively. FSA may inform the surgeon immediately about an involved margin and may thus lead to an immediate re-resection without the necessity of a second operation reducing the two-stage procedures.

Table 3
The likelihood for a patient to undergo a second operation due to false frozen section analysis (FSA) with regard to demographic data

	Odds ratio (95% CI)	*p*
pTis vs others	1.058 (0.445; 2.515)	0.899
pT1 vs others	0.771 (0.458; 1.299)	0.329
G3 vs G1/G2	0.632 (0.3386; 1.035)	0.068
No BX vs BX	7.675 (3.551; 16.587)	<0.0001
Radioguided vs not	5.683 (1.958; 16.494)	0.0014
Neoadjuvant vs not	10.621 (6.321; 17.845)	<0.0001

The table shows *p*-values (<0.05 is significantly different) and the odds ratio (RR) with a 95% confidence interval (CI).

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This hypothesis is based on few studies with small patient numbers.

FSA and two-stage operations

The present report is based on a very large retrospective evaluation of FSA in breast cancer specimens. The efficacy of FSA is reflected in a low clinical false negative rate of 9%. Thus, FSA may ameliorate patients physical and psychological condition, while reducing costs.[5,26] As the amount of dissected breast tissue is larger after re-resection, a two-stage procedure may be associated with a worse cosmetic outcome[27,28,29,30] and FSA may thus improve the cosmetic outcome, however this remains to be determined in further studies.

Other results supporting the use of FSA have already been reported[3,4,6,7,8] demonstrating that intraoperative FSA of breast specimens reduces the need for secondary surgery in 20 to 40%[5,6,8,31,32,33,34] and rapidly achieves optimal oncologic results with clear margins.[35] Others suggested even a 50% reduction of a two-stage procedure by the use of FSA.[9]

FSA in preinvasive and small lesions

Several authors do not recommend FSA in the presence of preinvasive and non-palpable breast cancer. [36] While the accuracy of FSA for invasive breast cancer lesions above 1 cm is about 97%, studies suggest that FSA for smaller non-palpable and preinvasive lesions as well as pure microcalcifications may have a lower accuracy rate and may impair the result of the definitive histology from paraffin-embedded tissue due to freezing artefacts.[4,15,16,17,37,38]

Cheng et al. demonstrated that accuracy of preinvasive lesions may be as low as 55% with a 36% false negative rate. [17] In their report, the authors did not give a full description of the protocol for selecting the tissue areas of interest for FSA. Thus, as already stated in their report, sampling error may be the main reason for the poor results. The use of tissue radiography to detect calcification may add accuracy in this respect. Tinnemans retrospectively reviewed FSA on 321 non-palpable breast lesions of which 36.7% were found to be malignant, 12.4% to be preinvasive and only 15.3% had microcalcifications as solely clinical precursor. [38] They demonstrated an overall false negative rate of 1.9%, yet an accuracy of only 68%, and suggested that FSA should not be used in instances of pure microcalcifications and tiny solid masses of 5 mm or less. However, the number of patients in this study is comparatively small. Furthermore, the authors did not perform FSA on pure microcalcification and in several tiny masses below 5mm, minimizing the evidence for their conclusion. Fessia reviewed 82 preinvasive lesions treated over one decade [4] and found an accuracy rate of 78% and a false negative rate of 11.1%. Due to the low number of preinvasive lesions, it may be suggested that pathologists may not have gained enough routine to achieve optimal accuracy. Pathologists' routine practice in performing FSA, especially for preinvasive lesions, is crucial. The accuracy may drop to 50% if the pathologist is not well trained and if FSA is not performed on a routine base.[6,39,40]

Concerning non-palpable lesions, some authors also reported about good accuracy and low false negative rates of FSA for non-palpable breast tumours. Ferreiro et al. demonstrated a false negative rate of only 0.5% and an accuracy rate of 97%, no matter whether the lesion was smaller or larger than 1 cm [3]. The difference in accuracy of FSA regarding preinvasive and small lesions among these studies may be partly due to differences in the prevalence rate and in the numbers of slides submitted for FSA. The low false negative rate in Ferreiro's study may be related to the unique FSA practice followed at Mayo Clinic, where all tissue of concern and adjacent breast parenchyma where examined by FSA, with the number of slides ranging from 1 to 42 (mean 3.4).

Our data support the evidence that FSA should be used with caution for non palpable tumours and microcalcifications. Although our cohort had a clinical false negative rate of 9% and a similar distribution of in situ lesions between one-stage and two-stage operated patients the use of a preoperative stereotactic biopsy indicating non palpability, a mass below 1 cm or microcalcifications increased the chance for a clinical false negative FSA, and thus, a second operation. This confirms earlier findings.[8,41]

Preoperative diagnostics

In our cohort preoperative sure cut biopsy demonstrated a high probability for a low clinical false negative FSA. Thus, preoperative diagnostic of breast cancer may either warrant the surgeon to immediately perform a resection with larger margins and/or helped the pathologist to perform the FSA. In this regard it is important to remind that recent consensus conferences and guidelines state that 90% of the breast lesions should undergo preoperative sure cut biopsy. Our data support the use of a preoperative biopsy.

Neoadjuvant therapy

The use of neoadjuvant therapy increases every year. Although its use to predict the sensibility of a certain systemic therapy is undisputed, there is only little oncologic advantage for the patients. No study to date has demonstrated that neoadjuvant therapy improves oncologic outcome. The reduced mastectomy rate after neoadjuvant therapy may, however, yield an increase local recurrence rate and even a worse survival.[42] Moreover neoadjuvant therapy may increase morbidity after BCT. In this regard we have to look very carefully whether neoadjuvant therapy may not be harmful for our patients.

This study demonstrates that after neoadjuvant therapy patients have an increased risk of a clinical false negative

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FSA. This increased risk of undergoing a two-stage operation was independent from grading, age, and tumour size. Further research has to address this important question in larger patient series.

Oncologic outcome and final pathology examination

In our patient cohort the local recurrence rate did not differ between one-stage and two-stage operated patients with annual local recurrence rates of 1.2 and 1.3, respectively. Recently, others have demonstrated a low local recurrence rate after intraoperative FSA.[43] Moreover, the final pathological results for all patients were in agreement with FSA with the exception of 31 out of 1016 patients for nodal status (including DCIS cases!) These data suggest that the final pathological results are not altered significantly after the use of FSA even in small and non-palpable lesions.

Conclusion

In conclusion the use of FSA in breast cancer yields excellent clinical false negative rates. In our study a second operation due to a positive resection margin had to be performed in 9% of the patients. Patients with FSA analyses had an annual local recurrence rate of 1.2%. Microcalcifications and small lesions, however, should not routinely be sent to FSA unless they are palpable. Neoadjuvant therapy reduces the quality of the FSA while preoperative sure cut biopsy improves FSA accuracy.

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Conflict of interest

The authors have no conflict of interest.

References

1. Aziz D, Rawlinson E, Narod SA, et al. The role of reexcision for positive margins in optimizing local disease control after breast-conserving surgery for cancer. *Breast J* 2006;**12**:331–7.
2. Fitzal F, Gnant M. Breast conservation: evolution of surgical strategies. *Breast J* 2006;**12**:S165–73.
3. Ferreiro JA, Gisvold JJ, Bostwick DG. Accuracy of frozen-section diagnosis of mammographically directed breast biopsies. Results of 1490 consecutive cases. *Am J Surg Pathol* 1995;**19**:1267–71.
4. Fessia L, Ghiringhello B, Arisio R, Botta G, Aimone V. Accuracy of frozen section diagnosis in breast cancer detection. A review of 4436 biopsies and comparison with cytodiagnosis. *Pathol Res Pract* 1984; **179**:61–6.
5. Weber S, Storm FK, Stitt J, Mahvi DM. The role of frozen section analysis of margins during breast conservation surgery. *Cancer J Sci Am* 1997;**3**:273–7.
6. Sauter ER, Hoffman JP, Ottery FD, et al. Is frozen section analysis of reexcision lumpectomy margins worthwhile? Margin analysis in breast reexcisions. An evaluation of frozen section biopsy in 4434 cases. *Cancer* 1994;**73**:2607–12.
7. Niemann TH, Lucas JG, Marsh Jr WL. To freeze or not to freeze. A comparison of methods for the handling of breast biopsies with no palpable abnormality. *Am J Clin Pathol* 1996;**106**:225–8.
8. Cendan JC, Coco D, Copeland 3rd EM. Accuracy of intraoperative frozen-section analysis of breast cancer lumpectomy-bed margins. *J Am Coll Surg* 2005;**201**:194–8.
9. Huston TL, Pigalarga R, Osborne MP, Tousimis E. The influence of additional surgical margins on the total specimen volume excised and the reoperative rate after breast-conserving surgery. *Am J Surg* 2006;**192**:509–12.
10. Schmidt-Ullrich R, Wazer DE, Tercilla O, et al. Tumor margin assessment as a guide to optimal conservation surgery and irradiation in early stage breast carcinoma. *Int J Radiat Oncol Biol Phys* 1989;**17**:733–8.
11. McLaughlin SA, Ochoa-Frongia LM, Patil SM, Cody 3rd HS, Sclafani LM. Influence of frozen-section analysis of sentinel lymph node and lumpectomy margin status on reoperation rates in patients undergoing breast-conservation therapy. *J Am Coll Surg* 2008;**206**: 76–82.
12. Cochrane RA, Valasiadou P, Wilson AR, Al-Ghazal SK, Macmillan RD. Cosmesis and satisfaction after breast-conserving surgery correlates with the percentage of breast volume excised. *Br J Surg* 2003;**90**:1505–9.
13. Bianchi S, Palli D, Ciatto S, et al. Accuracy and reliability of frozen section diagnosis in a series of 672 nonpalpable breast lesions. *Am J Clin Pathol* 1995;**103**:199–205.
14. Guski H, Winzer KJ, Aldinger HU, Frohberg HD, Bick U. Possibilities and limits of diagnostic frozen section in breast carcinoma. *Zentralbl Chir* 1998;**123**:19–22.
15. Association of Directors of Anatomic and Surgical Pathology. Immediate management of mammographically detected breast lesions. *Am J Surg Pathol* 1993;**17**:850–1.
16. Fechner RE. Frozen section examination of breast biopsies. Practice parameter. *Am J Clin Pathol* 1995;**103**:6–7.
17. Cheng L, Al-Kaisi NK, Liu AY, Gordon NH. The results of intraoperative consultations in 181 ductal carcinomas in situ of the breast. *Cancer* 1997;**80**:75–9.
18. Fechner RE. Frozen section (intraoperative consultation). *Hum Pathol* 1988;**19**:999–1000.
19. Sickles EA. Breast masses: mammographic evaluation. *Radiology* 1989;**173**:297–303.
20. Helbich TH, Matzek W, Fuchsjager MH. Stereotactic and ultrasound-guided breast biopsy. *Eur Radiol* 2004;**14**:383–93.
21. Steger G, Kubista E, Hausmaninger H, et al. 6 vs. 3 cycles of epirubicin/docetaxel +G-CSF in operable breast cancer: results of ABCSG-14. *J Clin Oncol* 2004;**22**:553.
22. Mamounas EP. Overview of National Surgical Adjuvant Breast Project neoadjuvant chemotherapy studies. *Semin Oncol* 1998;**25**:31–5.
23. 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**:546–53.
24. Bloom HJ, Richardson WW. Histological grading and prognosis in breast cancer. *Br J Cancer* 1957;**11**:359–77.
25. Reiner A, Neumeister B, Spona J, Reiner G, Schemper M, Jakesz R. Immunocytochemical localization of estrogen and progesterone receptor and prognosis in human primary breast cancer. *Cancer Res*. 1990; **50**:7057–61.
26. Jeong HJ, Lee KK, Choi IJ. Frozen-section indications, limitations, and accuracy. *Kor J Pathol* 1985;**19**:45–50.
27. Van Limbergen E, Rijnders A, van der Schueren E, Lerut T, Christiaens R, Van Tongelen K. Cosmetic evaluation of breast

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conserving treatment for mammary cancer. 2. A quantitative analysis of the influence of radiation dose, fractionation schedules and surgical treatment techniques on cosmetic results. *Radiother Oncol* 1989;**16**: 253–67.
28. Van Limbergen E, van der Schueren E, Van Tongelen K. Cosmetic evaluation of breast conserving treatment for mammary cancer. 1. Proposal of a quantitative scoring system. *Radiother Oncol* 1989;**16**:159–67.
29. Rose MA, Olivotto I, Cady B, et al. Conservative surgery and radiation therapy for early breast cancer. Long-term cosmetic results. *Arch Surg* 1989;**124**:153–7.
30. Wazer DE, DiPetrillo T, Schmidt-Ullrich R, et al. Factors influencing cosmetic outcome and complication risk after conservative surgery and radiotherapy for early-stage breast carcinoma. *J Clin Oncol* 1992;**10**:356–63.
31. Cabioglu N, Hunt KK, Sahin AA, et al. Role for intraoperative margin assessment in patients undergoing breast-conserving surgery. *Ann Surg Oncol* 2007;**14**:1458–71.
32. Chagpar A, Yen T, Sahin A, et al. Intraoperative margin assessment reduces reexcision rates in patients with ductal carcinoma in situ treated with breast-conserving surgery. *Am J Surg* 2003;**186**:371–7.
33. Pinotti JA, Carvalho FM. Intraoperative pathological monitorization of surgical margins: a method to reduce recurrences after conservative treatment for breast cancer. *Eur J Gynaecol Oncol* 2002;**23**:11–6.
34. Balch GC, Mithani SK, Simpson JF, Kelley MC. Accuracy of intraoperative gross examination of surgical margin status in women undergoing partial mastectomy for breast malignancy. *Am Surg* 2005;**71**:22–7. (discussion 27-8).
35. Klimberg VS, Harms S, Korourian S. Assessing margin status. *Surg Oncol* 1999;**8**:77–84.
36. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Canadian Association of Radiation Oncologists. The management of ductal carcinoma in situ (DCIS). *CMAJ* 1998;**158**:S27–34.
37. Oberman HA. A modest proposal. *Am J Surg Pathol*. 1992;**16**:69–70.
38. Tinnemans JG, Wobbes T, Holland R, et al. Mammographic and histopathologic correlation of nonpalpable lesions of the breast and the reliability of frozen section diagnosis. *Surg Gynecol Obstet* 1987;**165**:523–9.
39. Agnantis NJ, Apostolikas N, Christodoulou I, Petrakis C, Garas J. The reliability of frozen-section diagnosis in various breast lesions: a study based on 3451 biopsies. *Recent Results Cancer Res* 1984;**90**:205–10.
40. Hwang TS, Ham EK, Kim CW, et al. An evaluation of frozen section biopsy in 4434 cases. *J Kor Med Sci* 1987;**2**:239–45.
41. Rosen PP. Frozen section diagnosis of breast lesions. Recent experience with 556 consecutive biopsies. *Ann Surg* 1978;**187**:17–9.
42. van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. *J Clin Oncol* 2001; **19**:4224–37.
43. Olson TP, Harter J, Munoz A, Mahvi DM, Breslin T. Frozen section analysis for intraoperative margin assessment during breast-conserving surgery results in low rates of re-excision and local recurrence. *Ann Surg Oncol* 2007;**14**:2953–60.

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