

Diagnostic Value of Frozen Section in Patients with Non-Palpable Breast Lesions

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Rezumat

Valoarea diagnostică a examenului histopatologic intraoperator extemporaneu la pacienții cu leziuni mamare nepalpabile

Scop: Am analizat rezultatele localizării cu mandren metalic, examenul histopatologic intraoperator extemporaneu și abordarea chirurgicală în cazul leziunilor nepalpabile suspecte de malignitate detectate mamografic și ecografic drept mase tumorale mamare, microcalcificări și distorsiuni arhitecturale.

Material și metode: Am analizat retrospectiv cazurile a o sută de pacienți supuse localizării cu mandren metalic și examenului histopatologic intraoperator extemporaneu în cadrul Secției de Chirurgie Generală Spitalului Goztepe din İstanbul, din cauza prezenței de leziuni mamare nepalpabile suspecte de malignitate.

Rezultate: 75 % din cazuri erau în stadiul BIRADS 4, 21% BIRADS 3 și 3% BIRADS 5, conform clasificării Breast Imaging Reporting and Data System (BIRADS). A existat o corelație cu semnificație statistică între examenul histopatologic la parafină și examenul histopatologic intraoperator extemporaneu (coeficient Kappa: 0,872; $p < 0,01$). În grupul de pacienți în stadiul BIRADS 4 a existat o corelație puternic semnificativă statistic între rezultatele examenului histopatologic la parafină și ale celui histopatologic intra-

operator extemporaneu (raportul de corelație fiind de 85,3% și coeficientul Kappa: 0,853; $p < 0,01$).

Concluzii: În stadiile incipiente ale cancerului mamar localizarea cu mandren metalic și metoda rezecției reprezintă o unealtă diagnostică importantă. La pacienții în stadiul BIRADS 4 cu leziuni mamare nepalpabile localizarea cu mandren metalic, rezecția sub anestezie generală și examenul histopatologic intraoperator extemporaneu pot fi utilizate cu încredere. La pacienții cu cancer mamar în stadiu incipient chirurgia mamară cu conservarea sânului și biopsia de ganglion santinelă pot asigura evitarea disecțiilor inutile de ganglioni axilari.

Cuvinte cheie: cancer mamar, examen histopatologic intraoperator extemporaneu, leziune mamară nepalpabilă, biopsie ghidată imagistic, chirurgie mamară cu conservarea sânului

Abstract

Aim: We analyzed wire-marking, frozen section (FS) and surgical approach in malignancy-suspicious non-palpable lesions detected on mammography (MG) and ultrasonography (US) as breast mass, microcalcifications and distortions.

Material and Methods: A hundred patients in whom wire-marking and frozen section analysis was performed because of non-palpable, malignancy-suspected breast lesions at General Surgery Department, Goztepe Training and Research Hospital, İstanbul were analyzed retrospectively.

Results: Seventy-six % of the cases was in BIRADS 4, 21% in BIRADS 3 and 3% BIRADS 5, according to Breast Imaging Reporting and Data System (BIRADS) classification. There

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was a statistically significant correlation between paraffin block (PB) and frozen section analyses (kappa statistics: 0.872; $p < 0.01$). In BIRADS 4 group of the patients, there was a significant correlation between PB and FS results (Correlation ratio was 85.3% and kappa statistics: 0.853; $p < 0.01$).

Conclusion: In early stage breast cancer wire-marking and resection method is an important diagnostic tool. In BIRADS 4 patients with non-palpable breast lesions, wire marking, resection under general anesthesia and FS can be used trustfully. In patients with early breast cancer, breast-conserving surgery and sentinel lymphnode biopsy may avoid unnecessary axillary lymph node dissection.

Key words: breast cancer, frozen sections, non-palpable breast lesion, image-guided biopsy, breast-conserving surgery

Introduction

Breast cancer is the most frequent cancer of woman in Turkey and in all around the world. It is the second frequently seen cancer following lung cancer in human and the most frequent cause of the cancer death in women (1,2).

Use of wire marking and excision biopsy have been increased in the number of breast lesions which are non-palpable on physical examination but detected on mammographic screening (3,4).

A suspicious microcalcification focus or non-palpable lesion which are suspicious for malignancy are the most frequent indications of wire marking biopsy. The patients in whom wire marking and biopsy were done for non-palpable suspicious lesions and malignancy was diagnosed, were found to have 98% disease free survival (5).

It is doubtful to make FS in non palpable lesions per operatively. It is said that it is possible to skip small carcinoma foci. The success of FS is directly related to experience of the pathologist. If sufficient amount of sample and an important expectation which might change the direction of surgery, are present, FS is suggested (6, 7).

In recent years, by formation of the breast working groups (pathologist, radiologist, general surgeon) breast cancer patients have been started to be treated in a multi-disciplinary fashion. We analyzed results of FS following wire marking and surgical approach in patients with malignancy suspected non-palpable breast lesions like mass, microcalcifications and distortion.

Material and Methods

Pathology reports and files of a hundred patients in whom wire marking, excision and FS analysis were done for malignancy-suspected breast lesions at Goztepe Training and Research Hospital General surgery clinics were analyzed, retrospectively.

All lesions were detected by MG and US imaging and classified according to BIRADS classification. Wire marking was performed in the patients with BIRADS 3, 4 and 5, on suggestion of the radiologist instead of fine needle biopsy or tru-cut biopsy. Wire marking was done for asymmetric density, structural distortion, increased density, malignancy-suspected microcalcification, lobulated mass with irregular margin and mass with spiculated extension, which were detected on MG (SenographeSenix 600T; General Electric CGR, France) or US (7.5mHz, SSA-770A/80 Aplio; Toshiba, Japan, 5 - 11 mHz, Acuson 150; Siemens, MountainView, USA andLogic 9; General Electric, USA) imaging. The lesions which could be detected on one of the imaging modalities only, either MG or US, were marked by using that modality; for the lesions detectable on both, US was used.

Curved end guide wire (Hawkins III Hardwire BLN/Inter-V; Angiotech, Switzerland) was used in localization procedure without giving local anesthesia. Wire marking was successful when curved end of wire is in the lesion. Surgical excision was performed in operation room under general anesthesia following the wire marking.

In patients to whom FS examination was done, excised tissue was sent to pathology without fixation per operatively, frozen and sectioned and analyzed within 20 to 30 minutes.

Wire marked area was excised circumferentially with at least 1 cm healthy margin. Marking stitches was placed for space orientation. Specimen graphy was taken to check if the lesion was excised properly and specimen was sent to pathology per operatively. On benign and suspicious results, skin was closed without drain tube placement into the cavity.

If malignancy was detected on FS, then surgical margin was researched. When positive (i.e. tumor is closer to surgical margin less than 2 mm), re-excision was performed and axillary lymph node dissection was done with a different skin incision. In patients in whom FS was benign but ultimate pathological analysis was malignant, lymph node dissection was performed on a second operation. If FS was benign but ultimate pathological analysis was DCIS, axillary lymph node dissection wasn't performed, provided that surgical margin was free of disease.

All the patients were informed in detail preoperatively about surgery and surgery-related treatment modalities planned if malignancy was detected per operatively. In patients who didn't accept breast conserving surgery (BCS), modified radical mastectomy (MRM) was performed.

NCSS 2007 & PASS 2008 Statistical Software (Utah, USA) program for statistical analysis was used. Along with the descriptive statistical methods (mean, standard deviation, frequency), Ki-square test and McNemar test were used in comparison of qualitative data.

Also, diagnostic screening tests was used in calculation of specificity and sensitivity. Results was evaluated at 95% confidence interval and $p < 0.05$ was significant.

Results

The patients were between 17 to 82 years of age, the mean

Table 1. Lesions classified according to BIRADS classification

BIRADS	n	%
BIRADS 3	21	21,0
BIRADS 4	76	76,0
BIRADS 5	3	3,0

age was 47.71 ± 10.42 . Forty patients (40%) were younger than 45 years of age and 60 (60%) were over 45. Seventy-six patients were in BIRADS 4, 21% in BIRADS 3 and 3% in BIRADS 5 (Table 1).

FS analysis revealed 65% of the cases was benign, 15% suspicious and 20% malignant. PB analysis revealed 72% of the cases as benign and 28% malignant. The surgical margin in seven of 20 patients in whom FS analysis revealed malignancy, was found positive and preoperative re-excision was performed.

Ninety-three point eight (93.8) percent of the cases found benign on FS, were found benign on PB. Sixty-six point seven (66.7) percent of the suspicious cases on FS, were found benign on PB. Ninety-five (95) percent of the cases found malignant on FS, were diagnosed as malignant. There was only case which was found malignant on FS but diagnosed as benign on PB (Table 2).

As FS diagnosed malignancy in 19 out of 23 cases found as malignant on PB, sensitivity of FS was found 82.60%. Its sensitivity was 98.39%; positive predictive value was 95% and negative predictive value was 93.85%. The accuracy was 94.12% (Table 3).

Although cases in BIRADS 3 and BIRADS 5 couldn't be evaluated, there was a statistically significant correlation between the results of PB and FS. PB and FS correlation ratio was 85.3% (kappa statistics: 0.853; $p < 0.01$).

Malignancy types were 73% invasive cancer and 27% were DCIS of the cases diagnosed as malignant on PB. Considering the type of malignancy, the most common was invasive ductal cancer by 77%, followed by invasive ductal+ lobular cancer (mixed type) by 1%.

The types of benign lesions diagnosed on PB were, in order of frequency, fibrocystic changes by 34.7%, fibroadenoma by

Table 2. Frozen section and paraffin block distribution

		Paraffin Block analysis			
		Benign		Malign	
		n	%	n	%
Frozen	Benign	61	93.8	4	6.2
Section	Suspicious	10	66.7	5	33.3
analysis	Malign	1	5,0	19	95,0

27.8% and hyperplasia by 12.5%.

Seventy-three percent of breast cancer cases diagnosed was at stage 0 and 27% was at stage 2.

One patient was underwent MRM, another was underwent BCS with sentinel lymph node sampling and remained all patients underwent BCS plus axillary dissection operation among the malignancy diagnosed ones.

Discussion

Breast cancer is very common in women and cause of serious mortality and morbidity. Early diagnosis is important in its treatment. Frequency of non-palpable breast lesions has been increased as a result of increase in use of screening MG and self-consciousness of women on periodical examination (8).

Today, one of the techniques used in localization of non-palpable breast lesions is wire-marking. A suspicious microcalcification focus or non-palpable lesion are the most common indications for wire-marking biopsy. In our study, malignancy-suspected microcalcifications detected on MG in 37 (37%) patients were the most common indications of wire-marking biopsy.

It was found that patients with non-palpable lesions in whom wire-marking biopsy was done and malignancy was diagnosed, had a high disease-free survival. Thus, it enables to detect malignancy in an early phase and increase success of the treatment and life quality of the patient (9,10). 92.3% of the patients in our study were at stage 0 and I, including DCIS. We could also perform BCS in all these patients which shown the advantage of wire-marking in non-palpable breast lesions.

In non-palpable lesions, per operative FS is frequently used in planning single step surgical treatment, if sufficient tissue is

Table 3. Frozen section and paraffin block sensitivity table

		Paraffin Block analysis						p
		Malign		Benign		Total		
		n	%	n	%	n	%	
Frozen	Malign	19	22,4	1	1,2	20	23,5	0,375
Section	Benign	4	4,7	61	71,8	65	76,5	
analysis	Total	23	27,1	62	72,9	85	100	
Sensitivity		82,60						
Specificity		98,39						
Positive predictive value		95,00						
Negative predictive value		93,85						
Accuracy		94,12						

McNemar's test was used

present (6, 7-11). Today, FS is used widely in BCS for diagnosis, evaluating tumor margin and for detecting metastasis in sentinel lymph biopsy (12).

Accuracy rate of FS is over 90% (96.5-97.9%) and its false positivity is zero or near zero. It was reported that it has a false-positivity of 0.2-0.3% and a false-negativity of 0.5-1.2% (12). In this study, FS was performed in all cases and its results were 65% benign, 15% suspicious and 20% malignant. As FS revealed malignancy in 19 cases of 23 in which PB revealed malignancy, its sensitivity was found 82.60%. Its specificity was 98.39%; positive-predictive value was 95% and negative-predictive value was 93.85%. The accuracy of FS was found 94.12%. False-positivity rate was 1% and false negativity rate of 4%. One patient (5%) in whom FS diagnosed malignancy but PB was benign, underwent unnecessary surgery in this study. False positivity rate was higher than literature. Small number of the patients and insufficient experience of the pathologist might have had a role for this.

Although the cases remained for PB varies between 0.5 to 12% in literature, commonly it is less than 5% (12). Our case number remained for PB was 15 (15%) which was also higher than that of the literature. Diagnosis of papillary lesions and in-situ lobular cancers on FS is difficult. Radial scars and sclerosing adenosis are interfering lesions with tubular cancer.

In our study, results of 6 patients out of 15 in whom lesions were remained for PB were found as adenosis. This result shown that adenosis was a difficult lesion which might interfere with cancer and a definitive diagnosis might be difficult on FS. Thus, if adenosis is thought, more care should be given and in suspicious cases, PB should be performed.

Cancer diagnosis rate of wire-marking was 28% in our study. Studies shown malignancy rate for BIRADS 3 lesions was less than 8%; between 4–34% for BIRADS 4 and between 54–97% for BIRADS 5(13,14). We found that malignancy rates were 0%, 35.5% and 33.3% for BIRADS 3, 4 and 5, respectively. This results correlated to literature, except BIRADS 5. We thought this low rate was due to few numbers of the patients (only 3 patients) in BIRADS 5 group in our study. Also, PB and FS results shown a significant correlation in BIRADS 4, where PB and FS correlation ratio was 85.3% (kappa statistics: 0.853; $p < 0.01$).

Although axillary dissection is necessary for staging certainly, this procedure increases morbidity when performed in unnecessary situations (15). As sentinel node biopsy technique has been performed routinely, classic approaches for axillary dissection have become to change. According to this opinion, breast cancer cells invade axillary nodes in an anatomical sequence, meaning that they generally invade 1 to 3 nodes draining tumor focus and then spread to others. Thus, in cases that sentinel nodes are positive, invasion of other nodes are possible. When sentinel nodes are negative, routine axillary lymph node dissection can be given up (16). We detected axillary lymph node metastasis only in 2 patients in malignancy diagnosed patients with non-palpable breast lesions on FS and PB analysis. This result emphasized that, especially in early stage breast cancers, sentinel node biopsy is important and axillary dissection might be an unnecessary procedure.

Possibility of regional lymph node metastasis, recurrence and mortality rates has been shown to be directly related with tumor size. Especially in lymph node invasion negative cases, size of primary tumor becomes a very important prognostic factor on survival. Although axillary lymph node metastasis risk is 8% for T1a tumors, the risk increases to 12% for T1b tumors (17). In our study, axillary lymph node metastasis was below 1% for T1 tumors but, increased up to 12% for T2 tumors in patients with non-palpable breast cancer diagnosis.

We couldn't find any study researching effect of biopsy type on surgical treatment. The reason for performing mastectomy in common, following preoperative FS might be because of unknowing of certain diagnosis, thus, inability to talk on alternatives with the patient preoperatively (18). We performed MRM in only one patient and BCS in 27 patients in whom malignancy was diagnosed on per operative FS analysis. Informing the patients on treatment if FS of excised lesion revealed malignancy in detail preoperatively, and taking informed consent, enabled us to perform BCS in 96% of the patients. Only in one patient MRM was performed because of patients' refusal of BCS.

Conclusions

Wire-marking and excision of non-palpable breast lesions detected on MG or/and US is a very important method to diagnose early-stage breast cancers. If the surgery is performed on basis of FS analysis and BIRADS classification, it is useful to know that FS and PS analysis has a good correlation in BIRADS 4 patients. Breast conserving surgery and sentinel lymph node sampling should be suggested in malignancy diagnosed patients to avoid unnecessary axillary dissection.

Authors' contributions

Study concept and design: Drs Abuoglu, Yiğitbaşı
 Analysis and interpretation of data: Dr Abuoglu
 Administrative, technical, or material support: Drs Günay, Sunamak
 English editing: Drs Günay, Sunamak

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