Int J Cancer Manag. 2021 November; 14(11):e114082. doi: 10.5812/ijcm.114082.
Published online 2021 November 29. Systematic Review

Diagnostic Value of Intraoperative Frozen Section in Breast-Conserving Surgery: A Systematic Review and Meta-analysis

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Received 2021 May 24; **Revised** 2021 November 13; **Accepted** 2021 November 15.

Abstract

Context: According to previous studies, using the frozen section procedure during breast surgery reduces the rate of error and the need for re-surgery. We aimed at performing a comprehensive systematic review and meta-analysis to provide reliable evidence on the diagnostic value of frozen section procedures in breast-conserving surgery (BCS).
Data Sources: A thorough search was performed in PubMed, Embase, Cochrane Library, and Web of Science databases for human diagnostic studies that used the frozen section in BCS. Meta-analyses were done to find the sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR).
Study Selection: Human diagnostic studies used the frozen section in breast-conserving surgery and studies that reported the sensitivity and specificity of the frozen section in BCS or contained data that could be calculated the desired parameters were selected for this meta-analysis.
Data Extraction: Assessment of studies quality was done and data was extracted from included papers. Then, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to assess the quality of included papers.
Results: Thirty-five papers were entered into our study. The meta-analysis indicated the high sensitivity (83.47, 95%CI 79.61 - 87.32) and specificity (99.29, 95%CI 98.89 - 99.68) for the frozen section in BCS, which resulted in an accuracy of 93.77 (95%CI 92.45 - 95.10). We also found a significant PPV (93.26, 95%CI 91.25 - 95.27), NPV (92.17, 95%CI 90.22 - 94.11), PLR (7.99, 95%CI 6.01 - 9.96), and NLR (0.18, 95%CI 0.14 - 0.23).
Conclusions: The findings showed that intraoperative frozen section analysis has high sensitivity and specificity for evaluating lumpectomy margins in patients with early-stage breast cancer and significantly reduces the need for re-operation. Accordingly, re-operation costs are not imposed on the patient and reduce the anxiety of the patients.

Keywords: Breast Cancer, Breast Neoplasm, Frozen Section

1. Context

Breast cancer is the most prevalent cancer among females worldwide, and it is increasing in developing countries (1, 2). The most common treatment for women with low-grade breast cancer is breast-conserving surgery (BCS) (Lumpectomy or Partial Mastectomy) with radiation therapy (RT) (3). However, based on previous reports, 20 to 25 percent of patients undergoing BCS will need secondary surgeries to reach positive resection margins (4, 5).

Sometimes, some techniques such as clinical examination, ultrasonography, mammography, and biopsy using fine-needle aspiration (FNA), cannot allow accurate diagnosis in a patient with a breast tumor. In this case, a wide local excision and pathology examination will be the final solution. The optimal length of surgical margins varies in different countries and ranges between 2 mm to 10 mm (4, 6, 7).

To perform a successful BCS, the surgeon needs to identify the tissue's distances and margins correctly. In this regard, one of the most effective approaches is the frozen section procedure, which plays a guiding role in the next stages of surgery and prevents patients from re-operation (8-10). However, it is difficult to get a precise diagnosis using a frozen section due to a lack of expert pathologists, especially in developing countries (11, 12).

According to reports, using the frozen section procedure during breast surgery reduces the rate of error and the need for re-surgery (13, 14). Nevertheless, to our knowledge, a large number of surgeons in hospitals in Iran have moved away from this approach, mainly because of the surgery's cost burden and length.

2. Objectives

We aimed at performing a comprehensive systematic review and meta-analysis to provide reliable evidence on the diagnostic value of frozen section procedures in breast-conserving surgery. We hope our findings could advocate this technique and help the surgeons to decide more accurately.

3. Data Sources

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline was used for study design, search strategy, screening, and reporting. We performed a systematic search in PubMed, Embase, Cochrane Library, and Web of Science databases up to May 2019. The search strategy included MeSH descriptors and free keywords as follows: (all available MeSH terms for "Breast-Conserving Surgery") AND ("frozen section" OR "frozen sections"). Our search was limited to studies published in English but was not limited to a specific date. Only diagnostic studies on humans were entered into the study.

4. Criteria Study Selection

Two researchers (A.SH and K.H) selected the studies independently and disagreements were resolved through discussion with the third party (R.AN). Studies that met the following criteria were included: (1) human diagnostic studies used the frozen section in breast-conserving surgery, and (2) studies that reported the sensitivity and specificity of the frozen section in BCS or contained data that could help in calculating the desired parameters (3) English-language studies. Excluded studies were: (1) conference abstracts, letters, comments, case reports, reviews, animal studies, cross-sectional studies, ecological studies, and in vitro studies; (2) duplicate publications, and (3) studies with insufficient data.

5. Data Extraction & Quality Assessment

Two investigators (A.SH and K.H) independently evaluated the quality of publications and extracted data from included articles. The supervisor (Gh.G) resolved any disagreements regarding quality assessment. Data were extracted using a checklist containing the following items: the name of author, publication year, number of patients, mean age, true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN) of the frozen section, clinicopathological features, and correlations. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to assess the quality of included papers.

6. Data Analysis

Sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and accuracy and 95% confidence interval were calculated in MedCalc. We used the STATA v.11 software for data analysis. The I-square (I^2) test was used for heterogeneities assessment. Due to the high heterogeneity, the random-effects model was used for the pooled estimation. The possible publication bias was assessed using Egger's asymmetry test. P-values less than 0.05 were considered statistically significant.

7. Results

7.1. Study Selection Process

Our primary search resulted in 844 studies. After removing duplicated articles, we used title and abstract in order to screen 482 remaining papers. Finally, among 181 papers considered by full text, 35 articles entered into the meta-analysis. The PRISMA flow diagram for selecting eligible studies is presented in Figure 1.

7.2. Study Characteristics

Out of selected studies, a total of 10,100 patients with breast cancer aged 25 - 93 years old were included in the current study. Twenty studies used paraffin block, 12 studies used permanent sections, one study used histopathological examinations as a reference method, and in 2 studies, the reference method was unclear. Characteristics of studies that entered into meta-analysis are displayed in Table 1.

7.3. Quality Assessment & Publication Bias

According to the QUADAS-2 tool's quality assessment, 35 papers received the eligibility score and were included in the meta-analysis. Egger's test showed a significant publication bias for sensitivity ($P < 0.001$), specificity ($P < 0.001$), PPV ($P < 0.001$), NPV ($P = 0.010$), PLR ($P = 0.023$), NLR ($P = 0.005$), and accuracy ($P = 0.001$).

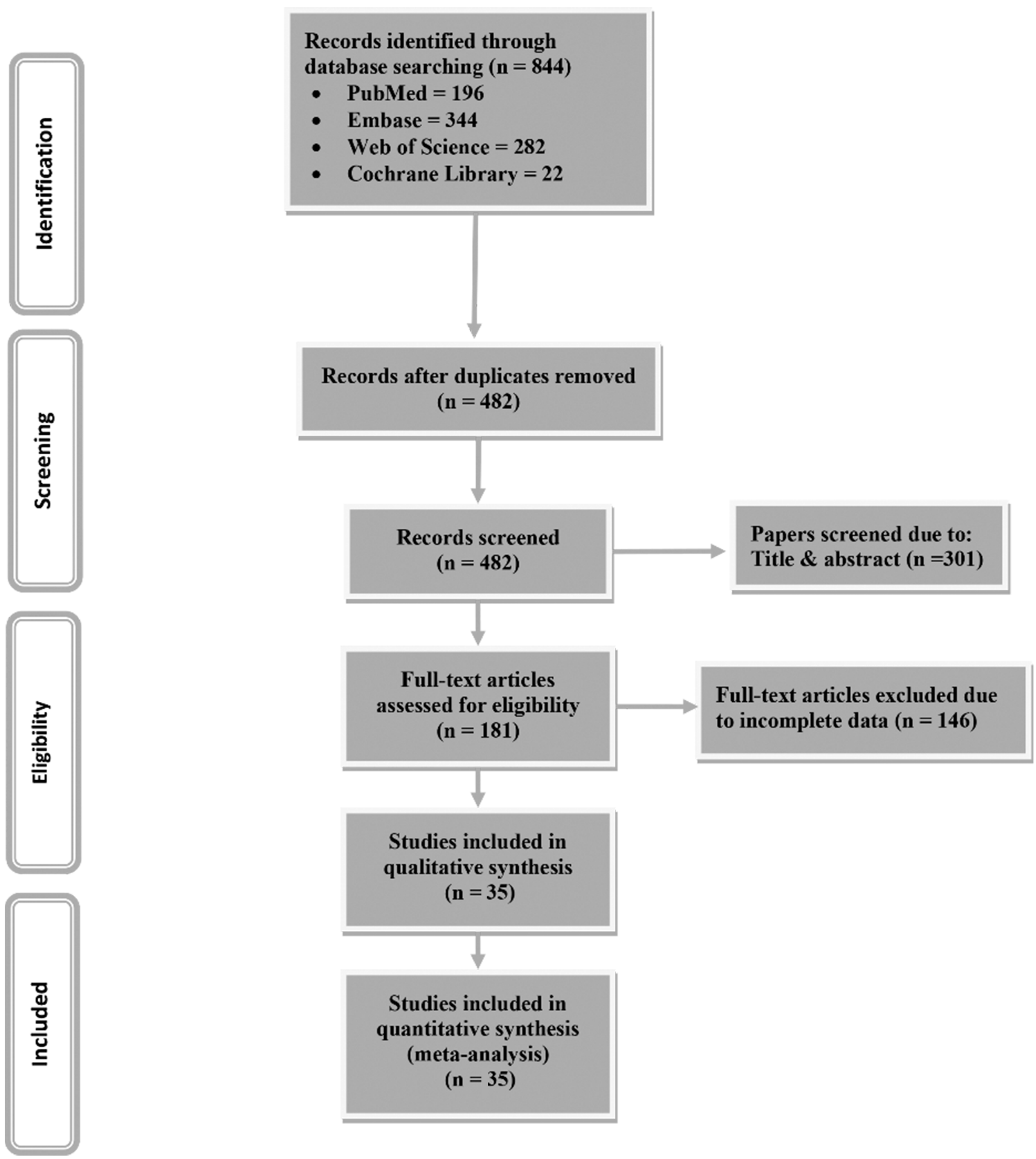

Figure 1. Flowchart of the study selection procedure

Table 1. Characteristics of Studies Entered into the Meta-analysis

Author	Year	Country	No. Patients	Reference Method	TN	TP	FN	FP
Kaufman et al. (15)	1986	Israel	242	PB	166	71	5	0
Cox et al. (16)	1991	USA	114	PS	-	-	-	-
Sauter et al. (17)	1994	USA	107	PS	292	52	6	9
Bianchi et al. (18)	1995	Italy	672	PB	356	267	24	3
Noguchi et al. (A) (19)	1995	Japan	87	PB	63	20	4	10
Noguchi et al. (B) (20)	1995	Japan	95	PS	64	23	1	12
Ikeda et al. (21)	1997	Japan	56	PS	34	17	1	4
Sultana and Kayani (12)	2005	Pakistan	319	PB	29	287	1	2
Cendan et al. (22)	2005	USA	97	PB	-	-	-	-
Olson et al. (23)	2007	USA	292	PB	1228	57	21	5
Cabioglu et al. (24)	2007	USA	264	PS	-	-	-	-
Weber et al. (25)	2008	Switzerland	78	PB	-	-	-	-
Rusby et al. (26)	2008	UK	115	PB	495	39	8	15
Bellolio et al. (27)	2009	-	337	-	-	-	-	-
Fukamachi et al. (28)	2010	Japan	122	PS	-	-	-	-
Jensen et al. (29)	2010	USA	416	PB	287	79	50	0
Jaka et al. (30)	2011	India	114	Histopathology	36	75	3	0
Caruso et al. (31)	2011	Italy	52	PB	44	5	1	3
Barakat et al. (32)	2012	Jordan	440	PB	285	135	26	0
Sabel et al. (33)	2012	USA	139	PS	121	26	2	0
Arlicot et al. (34)	2013	France	672	PB	-	-	-	-
Francissen et al. (35)	2013	Netherland	628	PB	447	101	78	2
Poling et al. (36)	2014	USA	1940	PB	-	-	-	-
Banuelos-Andrio et al. (37)	2014	Spain	370	PB	326	32	16	0
Kikuyama et al. (38)	2014	Japan	220	PB	-	-	-	-
Jorns et al. (39)	2014	USA	46	PS	28	12	6	0
Duarte et al. (40)	2015	Brazil	68	PB	-	-	-	-
Abuoglu et al. (41)	2016	Turkey	100	PB	61	19	4	1
Ahmed and Ahmad (10)	2016	Pakistan	76	PB	15	59	2	0
Kim et al. (42)	2016	South Korea	25	PS	23	3	2	1
Jorns and Kidwell (A) (43)	2016	USA	134	PS	42	8	2	0
Jorns and Kidwell (B) (43)	2016	USA	116	PS	64	10	5	0
Du et al. (44)	2017	China	976	-	-	-	-	-
Ko et al. (45)	2017	Korea	509	PS	338	120	24	1
Mahadevappa et al. (46)	2017	India	62	PB	28	33	0	1

Abbreviations: TN, true negatives; TP, true positives; FN, false negatives; FP, false positives; PB, paraffin block; PS, permanent section.

7.4. Main Outcomes

7.4.1. Sensitivity

Meta-analysis showed a high sensitivity for the frozen section in BCS (Sensitivity: 83.47, 95%CI 79.61 - 87.32). Significant heterogeneity was observed (I^2 = 95.1%, P < 0001, Table 2).

7.4.2. Specificity

Meta-analysis findings revealed a significant specificity for the frozen section in BCS (Specificity: 99.29, 95%CI 98.89 - 99.68). The heterogeneity was substantial (I^2 = 62.8%, P < 0001, Table 2).

7.4.3. PPV & NPV

Considering the diagnostic test performance, meta-analysis indicated the PPV of 93.26 (95%CI 91.25 - 95.27) and the NPV of 92.17 (95%CI 90.22 - 94.11) for the frozen section in BCS. The heterogeneity was found to be significant for both PPV and NPV (I^2 = 88.4%, P < 0001, I^2 = 95.1%, P < 0001, respectively). The PPV was 100 in 13 studies, which did not enter the meta-analysis due to the incalculable CI, and the value obtained in this meta-analysis is underestimated. The NPV was 100 in 2 studies, which did not enter the meta-analysis due to the incalculable CI, and the value obtained in this meta-analysis is underestimated (Table 2).

7.4.4. PLR & NLR

The meta-analysis showed that performing a diagnostic test resulted in sensational PLR 7.99 (95%CI 6.01 - 9.96) and NLR 0.18 (95%CI 0.14 - 0.23) for the frozen section. A low heterogeneity was observed for PLR and a high heterogeneity for NLR (I^2 = 38.5%, P = 0.03, I^2 = 95.0%, P < 0001, respectively) (Table 2).

7.4.5. Accuracy

We found an accuracy of 93.77 (95%CI 92.45 - 95.10) for this procedure by examining sensitivity and specificity. Significant heterogeneity was observed (I^2 = 90.2%, P < 0001) (Table 2).

8. Discussion

In recent years, BCS has been recognized as the standard surgical procedure in patients with early-stage breast cancer. One of the complications of BCS is the risk of local recurrence, in which one of the leading causes is the microscopic involvement of lumpectomy margins (47). According to different studies, the probability of re-operation due to microscopic involvement of margins varied from 24 to 40% (23, 28, 45). The probability of residual tumor in the re-excised specimen varied between 32 - 65% (38). Several parameters are involved in the probability of residue in the margins, such as ductal carcinoma in situ (DCIS), especially extensive intraductal component, patient age, type of tumor pathology (e.g., invasive lobular carcinoma), pathologic tumor size (e.g., PT3), breast density, as well as lymph vascular invasion (48-51). Younger patients are more likely to have marginal involvement. Patients with invasive lobular carcinoma pathology are at increased risk for marginal involvement and recurrence because this type of breast cancer usually is multifocal and multicenter (52-54).

Pre-operative imaging examinations to check the tumor size include mammography, ultrasound, magnetic resonance imaging, and computed tomography scan are not frequent. Due to the limitations of pre-operative imaging and low-quality sonography, it may be difficult to estimate the tumor's extent. All of these factors increase the probability of marginal involvement and increase the need for re-operation. Therefore, intraoperative examination of the margins is needed to reduce the probability of marginal involvement and reduce the need for re-operation (55).

Since there are several techniques for examining the surgical margins in breast cancer treatment, it is crucial to choose the method that has the most diagnostic value in the shortest time while being cost-benefit. At present, methods such as gross examination, imprint cytology, frozen section analysis, near-infrared fluorescence, micro-computed tomography, margin probe diffraction system, high-frequency ultrasound, and cavity shave margin are used, which have their strengths and weaknesses, and so far, the specific method has not been accepted as an international gold standard (56, 57).

According to the controversies over the diagnostic value of frozen sections in studies, we carried out a meta-analysis to combine the available data on the subject and to calculate the test's accuracy. The frozen section method's sensitivity varied from 43.58% (35) to 100% (16, 46) among the reviewed studies. This method's sensitivity for detecting margins with tumor tissue during surgery for breast cancer tumors was estimated to be 83.11% in our meta-analysis. Also, while specificity was ranged from 84.21% to 100% in different studies, pooling data resulted in a very high specificity (99.29%) for the frozen section procedure. Our findings regarding the frozen section's sensitivity and specificity in BCS were in agreement with systematic reviews of Esbona et al. (14) and St John et al. (58). Also, many cohort studies and national databases have examined the diagnostic value of this method (59-61).

In addition, to find the number of actual patients among cases tested positive (62), the meta-analysis indicated the PPV 94.61 (95%CI 92.92 - 96.31), which is very high like sensitivity for the frozen section method and suggest

Table 2. Pooled Estimates of Diagnostic Parameters

Diagnostic Parameter	Number of Studies	I Square	P-Value	Effect Size (95% Confidence Interval)
Sensitivity	35	95.1	0.00	83.47 (79.61 - 87.32)
Specificity	35	62.8	0.00	99.29 (98.89 - 99.68)
Positive predictive value	22	88.4	0.00	93.26 (91.25 - 95.27)
Negative predictive value	33	95.1	0.00	92.17 (90.22 - 94.11)
Positive likelihood Ratio	22	38.5	0.03	7.99 (6.01 - 9.96)
Negative likelihood Ratio	33	95.0	0.00	0.18 (0.14 - 0.23)
serum-HER2 accuracy	35	90.2	0.00	93.77 (92.45 - 95.10)

acceptable performance for this method compared to the reference method. The other way around, NPV was also significantly high (NPV = 92.12; 95%CI 90.24 - 94.01). It demonstrates the frozen section's satisfactory performance in detecting actual healthy individuals among cases tested negative in comparison to the reference method.

Overall, to find the method's capacity in classifying true positive and negative cases among all cases (63, 64), findings showed an accuracy of 93.77 (95%CI 92.45 - 95.10) for the frozen section method, which is substantially high and suggests acceptable performance in this regard.

The likelihood ratio describes the test results probability in cases with the condition to the probability of cases without the condition (65). PLR more than 10 and NLR less than 0.1 are reported to offer strong evidence for diagnosis (66). Herein, the meta-analysis showed the PLR 7.99 (95%CI 6.01 - 9.96) and NLR 0.18 (95%CI 0.14 - 0.23) for the frozen section, which indicates a significant relationship with the presence and absence of the condition, respectively.

Nevertheless, this method is not widely used in the U.S. due to several reasons, including false-positive frozen section analysis in cases such as ductal hyperplasia (e.g., mistaken for DCIS) and in lesions such as micro glandular adenosis, sclerosing adenosis, radial scar, intracystic papilloma, and fat necrosis. Also, the frozen section analysis study showed a potential for overestimation that leads to unnecessary resection and even mastectomy. There is also the possibility of false-negative and lower estimation in lesions such as tubular carcinoma, invasive lobular carcinoma, DCIS, and lesions caused by morphological changes after chemotherapy (9, 67, 68). Therefore, in addition to having the necessary frozen section analysis techniques, a skilled and experienced pathologist is essential.

The next problem is the prolongation of surgery time, which in most studies, extended between 20 and 50 minutes (69-72). According to a reported meta-analysis, the cost-effectiveness of this method depends on the extent of the margin being positive and the need for re-operation without this method. The results showed that it was cost-effective when positive margins were more than 25%, and the probability of re-operation was less than 15% (39, 73). A study examining frozen section analysis reported that this method is cost-effective and cost-saving is $ 400 to $ 600 per patient with breast cancer (33).

Regarding other methods, imprint cytology is one of the approaches for the rapid evaluation of benign and malignant tissues during surgery, which is used to evaluate tissue margins in cases such as sentinel lymph nodes surgery (74), breast mass surgery, and parathyroid (75). Shortcomings of this method include the inability to analyze deep infiltrations (76) and distinguish progressed tumors from dense stromal fibrosis (77). Also, based on available documents, the sensitivity and specificity of intraoperative ultrasound are 59% and 81%, respectively (58), which is significantly weaker in detecting tissue margins than the frozen section and cytology.

Also, the radiography evaluation did not significantly improve the re-operation rate (78). However, it might help decide whether the margins of calcified lesions are correct (79). The results of a meta-analysis study comparing radiographic and pathological evaluation methods of tissue margins showed that the efficiency of this method was lower than pathological methods (80). Another method of examining tissue margins during surgery is radiofrequency spectroscopy, which has also been approved for use in the United States. A randomized trial indicated that this method significantly reduced the re-operation rate compared to the control group (81). In general, based on the available evidence, margin probe tools are more effective in detecting positive margins (81, 82).

Finally, since different diagnostic values are reported for different approaches, and there is no international gold standard yet, considering various factors such as cost, availability of experts to perform the process, and the time required to obtain test results, the most appropriate method for evaluating surgical margins should be accurately chosen. However, due to high sensitivity of the frozen section method for evaluating lumpectomy margins in breast cancer, it is a good choice for low-income countries because of its cost efficiency (73).

8.1. Conclusions and Limitation

Due to the inclusion criteria, English-language studies that assessed the diagnostic value of intraoperative frozen section to evaluate lumpectomy margins in breast cancer surgery were included. We recommended considering more inclusive criteria to include original studies in other languages.

Our systematic review and meta-analysis showed that intraoperative frozen section analysis has high sensitivity and specificity to evaluate lumpectomy margins in patients with early-stage breast cancer and significantly reduce the need for re-operation. Also, re-operation costs are not imposed on the patient and reduce the patient's anxiety. Based on this study, it can be accepted that some patients who have a lower risk of positive marginal lumpectomy benefit less from this method, so this percentage of patients can be excluded. However, in patients who are more likely to have a positive margin based on pre-operative examinations, such as young patients, dense breast, DCIS, invasive lobular carcinoma pathology, presence of microcalcification, and lymph vascular invasion, use of this marginal screening method can significantly reduce re-operation and subsequently reduce the risk of recurrence.

Footnotes

Authors' Contribution: Conception and design: Gh.G, R.A-N, L.Sh; Data Collection: A.Sh, K.H; Data analysis: R.A-N, K.H; Data interpretation: Gh.G, A.Sh, R.A-N, L.Sh; Draft and revise: A.Sh, L.Sh. The final manuscript revised and approved by all authors.

Conflict of Interests: The authors have no conflicts of interest to declare.

Funding/Support: No financial support was received.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;**68**(1):7–30. doi: 10.3322/caac.21442. [PubMed: 29313949].
2. Fan L, Strasser-Weippl K, Li JJ, St Louis J, Finkelstein DM, Yu KD, et al. Breast cancer in China. *Lancet Oncol*. 2014;**15**(7):e279–89. doi: 10.1016/S1470-2045(13)70567-9. [PubMed: 24872111].
3. Habermann EB, Abbott A, Parsons HM, Virnig BA, Al-Refaie WB, Tuttle TM. Are mastectomy rates really increasing in the United States? *J Clin Oncol*. 2010;**28**(21):3437–41. doi: 10.1200/JCO.2009.27.6774. [PubMed: 20548000].
4. Dillon MF, Mc Dermott EW, O'Doherty A, Quinn CM, Hill AD, O'Higgins N. Factors affecting successful breast conservation for ductal carcinoma in situ. *Ann Surg Oncol*. 2007;**14**(5):1618–28. doi: 10.1245/s10434-006-9246-y. [PubMed: 17443388].
5. Kricker A, Armstrong B. Surgery and outcomes of ductal carcinoma in situ of the breast: a population-based study in Australia. *Eur J Cancer*. 2004;**40**(16):2396–402. doi: 10.1016/j.ejca.2004.07.008. [PubMed: 15519511].
6. Pinder SE. Ductal carcinoma in situ (DCIS): pathological features, differential diagnosis, prognostic factors and specimen evaluation. *Mod Pathol*. 2010;**23 Suppl 2**:S8–13. doi: 10.1038/modpathol.2010.40. [PubMed: 20436505].
7. Silverstein MJ, Buchanan C. Ductal carcinoma in situ: USC/Van Nuys Prognostic Index and the impact of margin status. *Breast*. 2003;**12**(6):457–71. doi: 10.1016/s0960-9776(03)00153-x. [PubMed: 14659122].
8. 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**(1):61–6. doi: 10.1016/S0344-0338(84)80062-X. [PubMed: 6504769].
9. Niu Y, Fu XL, Yu Y, Wang PP, Cao XC. Intra-operative frozen section diagnosis of breast lesions: a retrospective analysis of 13,243 Chinese patients. *Chin Med J (Engl)*. 2007;**120**(8):630–5. [PubMed: 17517175].
10. Ahmed S, Ahmad M. Comparison of diagnostic accuracy of touch imprint cytology and frozen section techniques in detecting breast malignancies. *J Pak Med Assoc*. 2016;**66**(3):292–5. [PubMed: 26968279].
11. Wang K, Ren Y, Huang R, He JJ, Feng WL, Kong YN, et al. Application of intraoperative frozen section examination in the management of female breast cancer in China: a nationwide, multicenter 10-year epidemiological study. *World J Surg Oncol*. 2014;**12**:225. doi: 10.1186/1477-7819-12-225. [PubMed: 25034137]. [PubMed Central: PMC4105393].
12. Sultana N, Kayani N. Validity of frozen section in the diagnosis of breast lumps: 5 years experience at the Aga Khan University Hospital. *J Pak Med Assoc*. 2005;**55**(12):533–6. [PubMed: 16438272].
13. Butler-Henderson K, Lee AH, Price RI, Waring K. Intraoperative assessment of margins in breast conserving therapy: a systematic review. *Breast*. 2014;**23**(2):112–9. doi: 10.1016/j.breast.2014.01.002. [PubMed: 24468464].
14. Esbona K, Li Z, Wilke LG. Intraoperative imprint cytology and frozen section pathology for margin assessment in breast conservation surgery: a systematic review. *Ann Surg Oncol*. 2012;**19**(10):3236–45. doi: 10.1245/s10434-012-2492-2. [PubMed: 22847119]. [PubMed Central: PMC4247998].
15. Kaufman Z, Lew S, Griffel B, Dinbar A. Frozen-section diagnosis in surgical pathology. A prospective analysis of 526 frozen sections. *Cancer*. 1986;**57**(2):377–9. doi: 10.1002/1097-0142(19860115)57:2<377::aid-cncr2820570231>3.0.co;2-m. [PubMed: 3942971].
16. Cox CE, Ku NN, Reintgen DS, Greenberg HM, Nicosia SV, Wangensteen S. Touch preparation cytology of breast lumpectomy margins with histologic correlation. *Arch Surg*. 1991;**126**(4):490–3. doi: 10.1001/archsurg.1991.01410280094014. [PubMed: 2009065].
17. Sauter ER, Hoffman JP, Ottery FD, Kowalyshyn MJ, Litwin S, Eisenberg BL. Is frozen section analysis of reexcision lumpectomy margins worthwhile? Margin analysis in breast reexcisions. *Cancer*. 1994;**73**(10):2607–12. doi: 10.1002/1097-0142(19940515)73:10<2607::aid-cncr2820731023>3.0.co;2-1. [PubMed: 8174059].
18. Bianchi S, Palli D, Ciatto S, Galli M, Giorgi D, Vezzosi V, et al. Accuracy and reliability of frozen section diagnosis in a series of 672 nonpalpable breast lesions. *Am J Clin Pathol*. 1995;**103**(2):199–205. doi: 10.1093/ajcp/103.2.199. [PubMed: 7856563].
19. Noguchi M, Minami M, Earashi M, Taniya T, Miyazaki II, Mizukami Y, et al. Pathologic Assessment of Surgical Margins on Frozen and Permanent Sections in Breast Conserving Surgery. *Breast Cancer*. 1995;**2**(1):27–33. doi: 10.1007/BF02966893. [PubMed: 11091529].
20. Noguchi M, Minami M, Earashi M, Taniya T, Miyazaki I, Mizukami Y, et al. Intraoperative histologic assessment of surgical margins and lymph node metastasis in breast-conserving surgery. *J Surg Oncol*. 1995;**60**(3):185–90. doi: 10.1002/jso.2930600309. [PubMed: 7475069].

21. Ikeda T, Enomoto K, Wada K, Takeshima K, Yoneyama K, Furukawa J, et al. Frozen-section-guided breast-conserving surgery: implications of diagnosis by frozen section as a guide to determining the extent of resection. *Surg Today*. 1997;**27**(3):207–12. doi: 10.1007/BF00941646. [PubMed: 9068099].
22. Cendan JC, Coco D, Copeland EM. Accuracy of intraoperative frozen-section analysis of breast cancer lumpectomy-bed margins. *J Am Coll Surg*. 2005;**201**(2):194–8. doi: 10.1016/j.jamcollsurg.2005.03.014. [PubMed: 16038815].
23. 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**(10):2953–60. doi: 10.1245/s10434-007-9437-1. [PubMed: 17674109].
24. Cabioglu N, Hunt KK, Sahin AA, Kuerer HM, Babiera GV, Singletary SE, et al. Role for intraoperative margin assessment in patients undergoing breast-conserving surgery. *Ann Surg Oncol*. 2007;**14**(4):1458–71. doi: 10.1245/s10434-006-9236-0. [PubMed: 17260108].
25. Weber WP, Engelberger S, Viehl CT, Zanetti-Dallenbach R, Kuster S, Dirnhofer S, et al. Accuracy of frozen section analysis versus specimen radiography during breast-conserving surgery for nonpalpable lesions. *World J Surg*. 2008;**32**(12):2599–606. doi: 10.1007/s00268-008-9757-8. [PubMed: 18836763].
26. Rusby JE, Paramanathan N, Laws SA, Rainsbury RM. Immediate latissimus dorsi miniflap volume replacement for partial mastectomy: use of intra-operative frozen sections to confirm negative margins. *Am J Surg*. 2008;**196**(4):512–8. doi: 10.1016/j.amjsurg.2008.06.026. [PubMed: 18809053].
27. Bellolio JE, Guzman GP, Orellana CJ, Roa S, Villaseca HM, Araya O, et al. Diagnostic value of frozen section biopsy during surgery for breast lesions or neoplasms. *Rev Med Chil*. 2009;**137**(9):1173–8. [PubMed: 20011957].
28. Fukamachi K, Ishida T, Usami S, Takeda M, Watanabe M, Sasano H, et al. Total-circumference intraoperative frozen section analysis reduces margin-positive rate in breast-conservation surgery. *Jpn J Clin Oncol*. 2010;**40**(6):513–20. doi: 10.1093/jjco/hyq006. [PubMed: 20189973].
29. Jensen AJ, Naik AM, Pommier RF, Vetto JT, Troxell ML. Factors influencing accuracy of axillary sentinel lymph node frozen section for breast cancer. *Am J Surg*. 2010;**199**(5):629–35. doi: 10.1016/j.amjsurg.2010.01.017. [PubMed: 20466107].
30. Jaka RC, Zaveri SS, Somashekhar SP, Parameswaran RV; Sureshchandra. Value of frozen section and primary tumor factors in determining sentinel lymph node spread in early breast carcinoma. *Indian J Surg Oncol*. 2010;**1**(1):27–36. doi: 10.1007/s13193-010-0008-8. [PubMed: 22930615]. [PubMed Central: PMC3420992].
31. Caruso F, Ferrara M, Castiglione G, Cannata I, Marziani A, Polino C, et al. Therapeutic mammaplasties: full local control of breast cancer in one surgical stage with frozen section. *Eur J Surg Oncol*. 2011;**37**(10):871–5. doi: 10.1016/j.ejso.2011.07.002. [PubMed: 21868188].
32. Barakat FH, Sulaiman I, Sughayer MA. Reliability of frozen section in breast sentinel lymph node examination. *Breast Cancer*. 2014;**21**(5):576–82. doi: 10.1007/s12282-012-0431-5. [PubMed: 23192628].
33. Sabel MS, Jorns JM, Wu A, Myers J, Newman LA, Breslin TM. Development of an intraoperative pathology consultation service at a free-standing ambulatory surgical center: clinical and economic impact for patients undergoing breast cancer surgery. *Am J Surg*. 2012;**204**(1):66–77. doi: 10.1016/j.amjsurg.2011.07.016. [PubMed: 22178485].
34. Arlicot C, Le Louarn A, Arbion F, Leveque J, Lorand S, Kinn J, et al. Evaluation of the two intraoperative examination methods for sentinel lymph node assessment: a multicentric and retrospective study on more than 2,000 nodes. *Anticancer Res*. 2013;**33**(3):1045–52.
35. Francissen CM, van la Parra RF, Mulder AH, Bosch AM, de Roos WK. Evaluation of the benefit of routine intraoperative frozen section analysis of sentinel lymph nodes in breast cancer. *ISRN Oncol*. 2013;**2013**:843793. doi: 10.1155/2013/843793. [PubMed: 24167745]. [PubMed Central: PMC3791598].
36. Poling JS, Tsangaris TN, Argani P, Cimino-Mathews A. Frozen section evaluation of breast carcinoma sentinel lymph nodes: a retrospective review of 1,940 cases. *Breast Cancer Res Treat*. 2014;**148**(2):355–61. doi: 10.1007/s10549-014-3161-x. [PubMed: 25318925]. [PubMed Central: PMC4352298].
37. Banuelos Andrio L, Rodriguez Caravaca G, Arguelles Pintos M, Mitjavilla Casanova M. [Selective biopsy of the sentinel lymph node in breast cancer: without axillary recurrences after a mean follow-up of 4.5 years]. *Rev Esp Med Nucl Imagen Mol*. 2014;**33**(5):259–63. doi: 10.1016/j.remn.2013.11.003. [PubMed: 24560598].
38. Kikuyama M, Akashi-Tanaka S, Hojo T, Kinoshita T, Ogawa T, Seto Y, et al. Utility of intraoperative frozen section examinations of surgical margins: implication of margin-exposed tumor component features on further surgical treatment. *Jpn J Clin Oncol*. 2015;**45**(1):19–25. doi: 10.1093/jjco/hyu158. [PubMed: 25320337].
39. Jorns JM, Daignault S, Sabel MS, Wu AJ. Is intraoperative frozen section analysis of reexcision specimens of value in preventing reoperation in breast-conserving therapy? *Am J Clin Pathol*. 2014;**142**(5):601–8. doi: 10.1309/AJCPRSOA2G8RLEXY. [PubMed: 25319974].
40. Duarte GM, Tomazini MV, Oliveira A, Moreira L, Tocchet F, Worschech A, et al. Accuracy of frozen section, imprint cytology, and permanent histology of sub-nipple tissue for predicting occult nipple involvement in patients with breast carcinoma. *Breast Cancer Res Treat*. 2015;**153**(3):557–63. doi: 10.1007/s10549-015-3568-z. [PubMed: 26358710].
41. Abuoglu HH, Gunay E, Sunamak O, Yigitbasi MR. Diagnostic Value of Frozen Section in Patients with Non-Palpable Breast Lesions. *Chirurgia (Bucur)*. 2016;**111**(6):500–4. doi: 10.21614/chirurgia.111.6.500. [PubMed: 28044952].
42. Kim MJ, Kim CS, Park YS, Choi EH, Han KD. The Efficacy of Intraoperative Frozen Section Analysis During Breast-Conserving Surgery for Patients with Ductal Carcinoma In Situ. *Breast Cancer (Auckl)*. 2016;**10**:205–10. doi: 10.4137/BCBCR.S40868. [PubMed: 27980416]. [PubMed Central: PMC5147452].
43. Jorns JM, Kidwell KM. Sentinel Lymph Node Frozen-Section Utilization Declines After Publication of American College of Surgeons Oncology Group Z0011 Trial Results With No Change in Subsequent Surgery for Axillary Lymph Node Dissection. *Am J Clin Pathol*. 2016;**146**(1):57–66. doi: 10.1093/ajcp/aqw078. [PubMed: 27373347].
44. Du Z, Wan H, Chen Y, Pu Y, Wang X. Bioimpedance spectroscopy can precisely discriminate human breast carcinoma from benign tumors. *Medicine (Baltimore)*. 2017;**96**(4). e5970. doi: 10.1097/MD.0000000000005970. [PubMed: 28121948]. [PubMed Central: PMC5287972].
45. Ko S, Chun YK, Kang SS, Hur MH. The Usefulness of Intraoperative Circumferential Frozen-Section Analysis of Lumpectomy Margins in Breast-Conserving Surgery. *J Breast Cancer*. 2017;**20**(2):176–82. doi: 10.4048/jbc.2017.20.2.176. [PubMed: 28690654]. [PubMed Central: PMC5500401].
46. Mahadevappa A, Nisha TG, Manjunath GV. Intra-operative Diagnosis of Breast Lesions by Imprint Cytology and Frozen Section with Histopathological Correlation. *J Clin Diagn Res*. 2017;**11**(3):EC01–6. doi: 10.7860/JCDR/2017/24454.9323. [PubMed: 28511385]. [PubMed Central: PMC5427311].
47. Horiguchi J, Iino Y, Takei H, Maemura M, Yokoe T, Niibe H, et al. Surgical margin and breast recurrence after breast-conserving therapy. *Oncol Rep*. 1999;**6**(1):135–8. [PubMed: 9864416].
48. Voguet L, Hebert T, Leveque J, Acker O, Mesbah H, Marret H, et al. Patient age and positive margins are predictive factors of residual tumor on mastectomy specimen after conservative treatment for breast cancer. *Breast*. 2009;**18**(4):233–7. doi: 10.1016/j.breast.2009.06.002. [PubMed: 19628389].
49. Campbell ID, Theaker JM, Royle GT, Coddington R, Carpenter R, Herbert A, et al. Impact of an extensive in situ component on the pres-

ence of residual disease in screen detected breast cancer. *J R Soc Med*. 1991;**84**(11):652–6. [PubMed: 1744869]. [PubMed Central: PMC1295466].

50. Holland R, Verbeek AL. Prognostic assessment in node-negative breast cancer patients. *J Clin Oncol*. 1990;**8**(9):1451–3. doi: 10.1200/JCO.1990.8.9.1451. [PubMed: 2391555].
51. Smitt MC, Nowels K, Carlson RW, Jeffrey SS. Predictors of reexcision findings and recurrence after breast conservation. *Int J Radiat Oncol Biol Phys*. 2003;**57**(4):979–85. doi: 10.1016/s0360-3016(03)00740-5. [PubMed: 14575828].
52. Biglia N, Mariani L, Sgro L, Mininanni P, Moggio G, Sismondi P. Increased incidence of lobular breast cancer in women treated with hormone replacement therapy: implications for diagnosis, surgical and medical treatment. *Endocr Relat Cancer*. 2007;**14**(3):549–67. doi: 10.1677/ERC-06-0060. [PubMed: 17914088].
53. Moore MM, Borossa G, Imbrie JZ, Fechner RE, Harvey JA, Slingluff CJ, et al. Association of infiltrating lobular carcinoma with positive surgical margins after breast-conservation therapy. *Ann Surg*. 2000;**231**(6):877–82. doi: 10.1097/00000658-200006000-00012. [PubMed: 10816631]. [PubMed Central: PMC1421077].
54. Singletary SE, Patel-Parekh L, Bland KI. Treatment trends in early-stage invasive lobular carcinoma: a report from the National Cancer Data Base. *Ann Surg*. 2005;**242**(2):281–9. doi: 10.1097/01.sla.0000171306.74366.22. [PubMed: 16041220]. [PubMed Central: PMC1357735].
55. Soucy G, Belanger J, Leblanc G, Sideris L, Drolet P, Mitchell A, et al. Surgical margins in breast-conservation operations for invasive carcinoma: does neoadjuvant chemotherapy have an impact? *J Am Coll Surg*. 2008;**206**(6):1116–21. doi: 10.1016/j.jamcollsurg.2007.12.025. [PubMed: 18501808].
56. Thill M, Baumann K, Barinoff J. Intraoperative assessment of margins in breast conservative surgery–still in use? *J Surg Oncol*. 2014;**110**(1):15–20. doi: 10.1002/jso.23634. [PubMed: 24863286].
57. Jorns JM, Visscher D, Sabel M, Breslin T, Healy P, Daignaut S, et al. Intraoperative frozen section analysis of margins in breast conserving surgery significantly decreases reoperative rates: one-year experience at an ambulatory surgical center. *Am J Clin Pathol*. 2012;**138**(5):657–69. doi: 10.1309/AJCP4IEMXCJ1GDTS. [PubMed: 23086766]. [PubMed Central: PMC3988579].
58. St John ER, Al-Khudairi R, Ashrafian H, Athanasiou T, Takats Z, Hadjiminas DJ, et al. Diagnostic Accuracy of Intraoperative Techniques for Margin Assessment in Breast Cancer Surgery: A Meta-analysis. *Ann Surg*. 2017;**265**(2):300–10. doi: 10.1097/SLA.0000000000001897. [PubMed: 27429028].
59. Tengher-Barna I, Hequet D, Reboul-Marty J, Frassati-Biaggi A, Seince N, Rodrigues-Faure A, et al. Prevalence and predictive factors for the detection of carcinoma in cavity margin performed at the time of breast lumpectomy. *Mod Pathol*. 2009;**22**(2):299–305. doi: 10.1038/modpathol.2008.186. [PubMed: 18997732].
60. Pata G, Bartoli M, Bianchi A, Pasini M, Roncali S, Ragni F. Additional Cavity Shaving at the Time of Breast-Conserving Surgery Enhances Accuracy of Margin Status Examination. *Ann Surg Oncol*. 2016;**23**(9):2802–8. doi: 10.1245/s10434-016-5210-7. [PubMed: 27034079].
61. Kobbermann A, Unzeitig A, Xie XJ, Yan J, Euhus D, Peng Y, et al. Impact of routine cavity shave margins on breast cancer re-excision rates. *Ann Surg Oncol*. 2011;**18**(5):1349–55. doi: 10.1245/s10434-010-1420-6. [PubMed: 21046260].
62. Trevethan R. Sensitivity, Specificity, and Predictive Values: Foundations, Pliabilities, and Pitfalls in Research and Practice. *Front Public Health*. 2017;**5**:307. doi: 10.3389/fpubh.2017.00307. [PubMed: 29209603]. [PubMed Central: PMC5701930].
63. Bossuyt PM. Interpreting diagnostic test accuracy studies. *Semin Hematol*. 2008;**45**(3):189–95. doi: 10.1053/j.seminhematol.2008.04.001. [PubMed: 18582626].
64. Knottnerus JA, van Weel C, Muris JW. Evaluation of diagnostic procedures. *BMJ*. 2002;**324**(7335):477–80. doi: 10.1136/bmj.324.7335.477. [PubMed: 11859054]. [PubMed Central: PMC1122397].
65. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. *BMJ*. 2004;**329**(7458):168–9. doi: 10.1136/bmj.329.7458.168. [PubMed: 15258077]. [PubMed Central: PMC478236].
66. Guyatt G, Rennie D, Meade M, Cook D. *Users' guides to the medical literature: a manual for evidence-based clinical practice*. Chicago: AMA press; 2002.
67. Blair SL, Thompson K, Rococco J, Malcarne V, Beitsch PD, Ollila DW. Attaining negative margins in breast-conservation operations: is there a consensus among breast surgeons? *J Am Coll Surg*. 2009;**209**(5):608–13. doi: 10.1016/j.jamcollsurg.2009.07.026. [PubMed: 19854401].
68. Karve PV, Jambhekar NA, Desai SS, Chinoy RF. Role of frozen section evaluation in patients with breast lumps: A study of 251 cases. *Indian J Surg*. 2005;**67**(5).
69. Houssami N, Morrow M. Margins in breast conservation: a clinician's perspective and what the literature tells us. *J Surg Oncol*. 2014;**110**(1):2–7. doi: 10.1002/jso.23594. [PubMed: 24756965].
70. Yoon JE, Kim JS, Park JH, Lee KB, Roh H, Park ST, et al. Uremic parkinsonism with atypical phenotypes and radiologic features. *Metab Brain Dis*. 2016;**31**(2):481–4. doi: 10.1007/s11011-015-9774-x. [PubMed: 26631408].
71. Klimberg VS, Westbrook KC, Korourian S. Use of touch preps for diagnosis and evaluation of surgical margins in breast cancer. *Ann Surg Oncol*. 1998;**5**(3):220–6. doi: 10.1007/BF02303776. [PubMed: 9607622].
72. Ohno Y, Noguchi M, Yokoi-Noguchi M, Nakano Y, Kosaka T, Kurose N, et al. Tangential Frozen Section Analysis for the Surgical Margins in Breast-conserving Surgery. *Am J Breast Cancer Res*. 2015;**2**:9–20.
73. Osborn JB, Keeney GL, Jakub JW, Degnim AC, Boughey JC. Cost-effectiveness analysis of routine frozen-section analysis of breast margins compared with reoperation for positive margins. *Ann Surg Oncol*. 2011;**18**(11):3204–9. doi: 10.1245/s10434-011-1956-0. [PubMed: 21861234].
74. Henry-Tillman RS, Korourian S, Rubio IT, Johnson AT, Mancino AT, Massol N, et al. Intraoperative touch preparation for sentinel lymph node biopsy: a 4-year experience. *Ann Surg Oncol*. 2002;**9**(4):333–9. doi: 10.1007/BF02573867. [PubMed: 11986184].
75. Westra WH, Pritchett DD, Udelsman R. Intraoperative confirmation of parathyroid tissue during parathyroid exploration: a retrospective evaluation of the frozen section. *Am J Surg Pathol*. 1998;**22**(5):538–44. doi: 10.1097/00000478-199805000-00003. [PubMed: 9591722].
76. Lee TK. The value of imprint cytology in tumor diagnosis: a retrospective study of 522 cases in northern China. *Acta Cytol*. 1982;**26**(2):169–71. [PubMed: 6952718].
77. Khalid A, Haque AU. Touch impression cytology versus frozen section as intraoperative consultation diagnosis. *Int J Pathol*. 2018:63–70.
78. Ihrai T, Quaranta D, Fouche Y, Machiavello JC, Raoust I, Chapellier C, et al. Intraoperative radiological margin assessment in breast-conserving surgery. *Eur J Surg Oncol*. 2014;**40**(4):449–53. doi: 10.1016/j.ejso.2014.01.002. [PubMed: 24468296].
79. Lange M, Reimer T, Hartmann S, Glass A, Stachs A. The role of specimen radiography in breast-conserving therapy of ductal carcinoma in situ. *Breast*. 2016;**26**:73–9. doi: 10.1016/j.breast.2015.12.014. [PubMed: 27017245].
80. Chan BK, Wiseberg-Firtell JA, Jois RH, Jensen K, Audisio RA. Localization techniques for guided surgical excision of non-palpable breast lesions. *Cochrane Database Syst Rev*. 2015;(12). CD009206. doi: 10.1002/14651858.CD009206.pub2. [PubMed: 26718728].
81. Allweis TM, Kaufman Z, Lelcuk S, Pappo I, Karni T, Schneebaum S, et al. A prospective, randomized, controlled, multicenter study of a real-time, intraoperative probe for positive margin detection in breast-conserving surgery. *Am J Surg*. 2008;**196**(4):483–9. doi: 10.1016/j.amjsurg.2008.06.024. [PubMed: 18809049].
82. Karni T, Pappo I, Sandbank J, Lavon O, Kent V, Spector R, et al. A device for real-time, intraoperative margin assessment in breast-conservation surgery. *Am J Surg*. 2007;**194**(4):467–73. doi: 10.1016/j.amjsurg.2007.06.013. [PubMed: 17826057].