Specimen Mammography for Intraoperative Margin Assessment in Breast Conserving Surgery: A Meta-Analysis

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Abstract

Specimen mammography is one of the widely used intraoperative methods assessing margin status in breast conserving surgery. We performed a meta-analysis to evaluate the diagnostic accuracy of specimen mammography. Literature databases including Pubmed, Cochrane Library, Web of Science and EMBASE were searched prior to May 2020. 18 studies with a total of 1142 patients were included. Data was extracted to perform pooled analysis, heterogeneity testing, threshold effect testing, sensitivity analysis, publication bias analysis and subgroup analyses. The pooled weighted values were a sensitivity of 0.55 (95% CI, 0.45–0.64), a specificity of 0.85 (95% CI, 0.77–0.90), a DOR of 7 (95% CI, 4–11) and a pooled positive likelihood ratio of 3.6 (95% CI 2.4-5.3). The area under the receiver operator characteristic curve was 0.75 (95% CI 0.71-0.78). In the subgroup analysis, the pooled specificity in the positive margin defined as tumor at margin subgroup was lower than the other positive margin definition subgroup (0.79 [95% CI: 0.66, 0.91] vs. 0.88 [95% CI: 0.81, 0.95], $p = 0.01$). Our findings indicated specimen mammography to be an accurate and intraoperative imaging technique for margin assessment in breast conserving surgery.

Introduction

Breast cancer is one of the most common cancers worldwide. Breast conserving surgery (BCS) is an important surgical treatment for women with early stage breast cancer. BCS removes the cancer and spares the rest of the breast, balancing oncologic resection and ideal cosmesis. In recent years, more patients are diagnosed with smaller invasive tumors and are therefore likely to receive BCS. The use of neoadjuvant chemotherapy results in tumor downstaging, also leading to more patients receiving BCS. Achieving negative margin is critical in BCS, as positive margin is one of the most significant risk factors for local recurrence. Positive margin occurs in 20%-40% of all patients and 15%-30% patients undergo a reoperation to improve local control¹⁻⁴. Reoperation is associated with higher surgical risk, poorer cosmetic outcome, increased psychological and economic burden⁵. Histopathology serves as the gold standard for margin status assessment, but the analysis takes several days.

In order to reduce the reoperation rate, intraoperative margin assessment methods have been developed to identify positive margins and to enable immediate re-excision. These methods include frozen section, imprint cytology, intraoperative ultrasound, specimen mammography and so forth. Intraoperative pathological assessment such as frozen section and imprint cytology depend on experience of the pathologist and both techniques are time-consuming which add significant time to the operation, often between 20 and 30 min on average⁶. Intraoperative ultrasound has relatively low and variable sensitivity, ranging from 25 to 100%. It works well for lesions presenting as masses but not well enough for calcifications^{6,7}.

Specimen mammography is usually used to confirm excision of the targeted lesion. It is also found to be a method for intraoperative resection margin assessment during BCS. There are mainly two kinds of systems to perform specimen mammography. Standard specimen mammography is the earliest and most widely used system. As this standard system is completed by transporting the specimen to a radiology unit, it is relatively time consuming. Another system, intraoperative specimen mammography, is developed by using a small automatic device placed near the operation room to take images, which saves operation time.

Routine clinical use of specimen mammography for margin assessment rely upon achieving diagnostic accuracy comparable to other methods, especially pathological methods. Several studies showed that specimen

mammography with high sensitivities lowered the rate of re-excision, but also generated a number of false positives leading to unnecessary tissue removal. Other studies showed relatively low sensitivities with high specificities. The aim of this study was to perform a meta-analysis to evaluate pooled diagnostic accuracy for specimen mammography in assessing margin status of breast conserving surgery.

Methods

Our study was conducted following guidelines of the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA)⁸. We searched relevant studies in Pubmed, Cochrane Library, Web of Science and EMBASE to date of May 2020. The search strategy comprised both keywords and MeSH terms for “breast cancer” (MeSH term of Breast Neoplasms, breast cancer*, breast tumour*, breast tumor*, breast neoplasm*, Breast carcinoma*, mammary cancer*, mammary tumour*, mammary tumor*, Mammary Neoplasm*, mammary carcinoma*), “specimen mammography” ((mammograph* OR radiograph* OR X-ray) AND specimen*) and “margin*”. All types of articles were included. Extensive crosschecking of the references in retrieved articles was performed. Two investigators (Chen Lin and Kaiyue Wang) screened the titles and abstracts independently. All relevant citations were selected for further analysis. When there was disagreement between two investigators regarding to article inclusion, they discussed these articles with a senior author (Tao Pan).

Studies were included when they met the following criteria: (1) patients were diagnosed of breast cancer (invasive or in situ) and received BCS; (2) specimen mammography should be performed intraoperatively to assess the margin status; (3) studies provided available data of true positive (TP), true negative (TN), false positive (FP), false negative (FN), sensitivity either directly or indirectly. Studies were excluded if not written in English. Opinions, case studies, reviews, conference abstracts and meta-analysis were also excluded. Full-texts of the eligible studies were reviewed. The following information was extracted: (1) the first author; (2) year of publication; (3) number of patients; (4) number of lesions; (5) study design; (6) mean age of patients; (7) histopathological definition of positive margin distances; (8) positive margin rates; (9) mammography system used in the article; (10) diagnostic accuracy raw data- TP, TN, FP, FN; (11) percentages of sensitivity, specificity, positive predictive value, negative predictive value.

Quality assessment of diagnosis accuracy study form (QUADAS-2) was used to assess methodological quality of the eligible studies⁹. QUADAS-2 checklist was independently completed by the two investigators (Hailang Chen and Yuhua Xu).

The relationship between sensitivity and specificity was assessed using a hierarchical summary receiver operating characteristic (SROC) model. The area under the curve (AUC) of the SROC was calculated to measure the diagnostic performance of specimen mammography. An AUC between 0.9-1.0 was considered very good degree of diagnostic accuracy, between 0.7-0.9 represents a moderate degree and close to 0.5 AUC implies a poor degree¹⁰. The Youden index (*Q), which is used in conjunction with SROC analysis and recognized as a preferred statistic to reflect the diagnostic value, were also assessed. A *Q index of 1 indicates a perfect test result.

Heterogeneity was assessed using I^2 . 25-49% was considered a low level, 50-74% was moderate, and >75% was high. A random effects model was used when $I^2 < 50\%$, and a fixed effects model was chosen when $I^2 > 50\%$ ¹¹. Threshold effect was one of the important sources of heterogeneity in diagnostic accuracy test. The Spearman correlation coefficients can determine the existence of threshold effect if P value ≤ 0.05 . Publication bias was analyzed using Deeks' funnel plot. The absence of a non-zero slope coefficient ($P < 0.10$) indicates publication

bias exists among the included studies¹². Subgroup analysis was performed. Statistical software package Revman 5.3 and Stata version 16.0 (StataCorp, College Station, Texas) were used.

Results

Search results and study selection:

The systematic search and manual cross-checking of references yielded 1142 articles in total from PubMed, Web of Science, Embase and Cochrane initially. After duplicates were removed, there were 719 unique records remained. After excluding the obviously unrelated articles by reading the titles and abstracts, 74 remained as potential articles. An additional of 56 articles were excluded after careful full-text review. The reasons for exclusion were as follows: (1) sensitivity and/or specificity data were missing; (2) the paper was not focus on specimen mammography for margin assessment; (3) the paper was published in abstract format only; (4) the paper was a literature review; and /or (5) the paper was not written in English. Eventually, 18 studies were enrolled in the analysis^{13–30}.

Study description:

Our meta-analysis included 18 studies consisted a total of 1661 patients and 1678 lesions(Figure 1). The sample size ranged from 22 to 267 patients and 22 to 280 lesions. Mean or median age was available in 12 studies with a range between 50-62 years old. 14 studies mentioned the system used to take specimen mammograph. 10 of the studies used SSM system, 2 used ISM system and 2 used both systems for margin status assessment in BCS. 4 studies did not provide information about the applied system. In 6 studies, radiologists were blinded to the pathological results. The basic information and principal characteristics of the included studies including number of patients and lesions, method of studies, Mean age of patients, positive margin distance, positive margin rates and mammography system were detailed in Table 1. Documented or calculable percentage of sensitivity, specificity, positive predictive value and negative predictive value for each study are listed in Table 2. According to QUADAS-2 items, the quality assessment of 18 studies was moderate. The results of the distribution are shown in Supplementary Fig. S1.

Table 1
Principal characteristics of the included studies

Author	Year	Number of patients	Number of lesions	Method of studies	Mean age	Positive margin distance	positive margin rate	Mammography system
Mariscotti et al. ¹³	2020	267	280	retrospective	NS	0mm	20.71%	Both
Park et al. ¹⁴	2019	98	99	retrospective	60	0mm	14.14%	ISM
Naz, S. et al. ¹⁶	2018	52	52	retrospective	51	0mm	42.31%	NS
Pop et al. ¹⁵	2018	83	83	prospective	57	0mm	10.84%	NS
Miller et al. ¹⁷	2016	44	44	prospective	57	0mm	18.18%	Both
Hisada et al. ¹⁸	2016	141	141	retrospective	55	5mm	20.57%	SSM
Chagpar et al. ¹⁹	2015	90	90	prospective	60	NS	37.78%	SSM
Layfield DM et al. ²⁰	2012	104	104	retrospective	60	2mm for IDC, 5mm for DCIS	29.81%	ISM
Bathla et al. ²¹	2011	99	102	retrospective	59	0mm	40.20%	SSM
Weber et al. ²²	2008	35	35	retrospective	58	1mm	57.14%	SSM
Ciccarelli et al. ²³	2007	102	102	retrospective	NS	NS	37.25%	SSM
Coombs et al. ²⁵	2006	52	52	retrospective	58	5mm	44.23%	NS
Goldfeder, S. et al. ²⁴	2006	112	112	prospective	NS	NS	43.75%	SSM
Łuczyńska, E. et al. ²⁶	2005	70	70	NS	NS	NS	45.71%	NS
McCormick et al. ²⁷	2004	93	93	retrospective	NS	NS	11.83%	SSM
Gombos, E. V. ²⁸	2004	34	34	NS	NS	NS	35.29%	SSM

NS: not shown; IDC: invasive ductal carcinoma; DCIS: ductal carcinoma in situ; ISM: intraoperative specimen mammography; SSM: standard specimen

Author	Year	Number of patients	Number of lesions	Method of studies	Mean age	Positive margin distance	positive margin rate	Mammography system
Saarela et al. ²⁹	2001	66	66	prospective	55	0mm	40.91%	SSM
Graham et al. ³⁰	1994	119	119	NS	NS	1 mm	84.03%	SSM
NS: not shown; IDC: invasive ductal carcinoma; DCIS: ductal carcinoma in situ; ISM: intraoperative specimen mammography; SSM: standard specimen								

Table 2
Included studies containing raw diagnostic accuracy data for meta-analysis

Author	Year	Number of Lesions	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Mariscotti et al.	2020	280	27	65	31	157	46.55%	70.72%	29.35%	83.51%
Park et al.	2019	99	14	61	0	24	100.00%	28.24%	18.67%	100.00%
Naz et al.	2018	52	16	5	6	25	72.73%	83.33%	76.19%	80.65%
Pop et al	2018	83	4	11	5	63	44.44%	85.14%	26.67%	92.65%
Miller et al.	2016	3	3	6	32	3	33.33%	91.43%	50.00%	84.21%
Hisada et al.	2016	141	6	6	23	106	20.69%	94.64%	50.00%	82.17%
Chagpar et al.	2015	90	14	12	20	44	41.18%	78.57%	53.85%	68.75%
Layfield DM et al	2012	104	18	14	13	59	58.06%	80.82%	56.25%	81.94%
Bathla et al	2011	102	24	5	17	56	58.54%	91.80%	82.76%	76.71%
Weber et al	2008	35	12	6	8	9	60.00%	60.00%	66.67%	52.94%
Ciccarelli et al.	2007	102	25	9	13	55	65.79%	85.94%	73.53%	80.88%
Coombs et al.	2006	52	12	4	11	25	52.17%	86.21%	75.00%	69.44%
Goldfeder et al.	2006	112	24	17	25	46	48.98%	73.02%	58.54%	64.79%
Łuczyńska et al.	2005	70	13	0	19	38	40.63%	100.00%	100.00%	66.67%
McCormick et al.	2004	93	6	10	5	72	54.55%	87.80%	37.50%	93.51%
Gombos et al.	2004	34	11	0	1	22	91.67%	100.00%	100.00%	95.65%
Saarela et al	2001	66	9	8	18	31	33.33%	79.49%	52.94%	63.27%
Graham et al.	1994	119	62	1	38	18	62.00%	94.74%	98.41%	32.14%
TP: true positive; FP: false positive; FN: false negative; TN: true negative; PPV: positive predictive value; NPV: negative predictive value.										

Meta-analysis:

The statistical results confirmed that there was moderate and high heterogeneity of specimen radiography for sensitivity ($I^2 = 68.03\%$) and in specificity ($I^2 = 93.06\%$) respectively. A random-effects coefficient binary regression model was used. The pooled estimate of 18 studies demonstrated a sensitivity of 0.55 (95% CI, 0.45–0.64), a specificity of 0.85 (95% CI, 0.77–0.90) (see Supplementary Fig. S2 online), and a DOR of 7 (95% CI, 4–11). The pooled positive likelihood ratio was 3.6 (95% CI 2.4-5.3) and the pooled negative likelihood ratio was 0.53 (95% CI 0.44-0.65). The AUC value, which represented the overall diagnostic accuracy of specimen radiography, was 0.75 (95% CI 0.71-0.78). The $*Q$ index was 0.6884 ± 0.0373 . The bivariate summary receiver operating characteristic (SROC) graph with the 95% confidence region and 95% prediction region were shown in Supplementary Fig. S3.

The Spearman correlation coefficients' P values (0.630, $P > 0.05$) disclosed the absence of threshold effect. Deeks' Funnel Plot Asymmetry test was performed and no significant publication bias ($P = 0.103$) existed in the enrolled studies (see Supplementary Fig. S4 online).

The results of the subgroup analysis were presented in Table 3 and Supplementary Fig. S5. In the subgroup analysis of different definition of positive margin, the performance of the positive margin defined as tumor at margin subgroup was equivalent to that of other positive margin definition subgroup in assessing the margin status with comparable pooled sensitivity (0.57 [95% CI: 0.42, 0.72] vs. 0.53 [95% CI: 0.42, 0.65], $p = 0.96$), but the pooled specificity was lower (0.79 [95% CI: 0.66, 0.91] vs. 0.88 [95% CI: 0.81, 0.95], $p = 0.01$).

Table 3
Univariable Meta-regression and Subgroup Analysis

subgroup	category	number of studies	Sensitivity with 95% CI	p-value of Sensitivity	Specificity with 95% CI	p-value of Specificity
Positive margin rate >40%	Yes	8	0.54 (0.41 - 0.67)	0.70	0.87 (0.78 - 0.96)	0.21
	No	10	0.55 (0.42 - 0.68)		0.83 (0.74 - 0.92)	
Only standard specimen mammography	Yes	10	0.53 [0.41 - 0.65]	0.51	0.87 [0.79 - 0.94]	0.25
	No	8	0.57 [0.43 - 0.71]		0.82 [0.71 - 0.93]	
Number of lesions > 100	Yes	7	0.52 [0.38 - 0.66]	0.50	0.86 [0.77 - 0.95]	0.17
	No	11	0.57 [0.45 - 0.70]		0.84 [0.75 - 0.93]	
Prospective study	Yes	5	0.39 [0.24 - 0.55]	0.16	0.83 [0.70 - 0.96]	0.11
	No	13	0.59 [0.50 - 0.69]		0.85 [0.78 - 0.93]	
blind	Yes	6	0.53 [0.37 - 0.69]	0.67	0.87 [0.77 - 0.97]	0.28
	No	12	0.56 [0.44 - 0.67]		0.83 [0.75 - 0.92]	
Positive margin defined as tumor at margin	Yes	7	0.57 [0.42 - 0.72]	0.96	0.79 [0.66 - 0.91]	0.01
	No	11	0.53 [0.42 - 0.65]		0.88 [0.81 - 0.95]	

Discussion

Histopathological result of margin status occupies a particularly important place in breast conserving surgery. To assess the diagnostic accuracy of intraoperative methods, in recent years, numerous studies have compared the ability of various techniques of detecting positive margins to the results of final histopathological results.

Intraoperative pathological and intraoperative imaging methods are two main methods for intraoperative margin assessment in breast conserving surgery. Intraoperative pathological methods mainly include frozen section, touch smear and imprint cytology, which all have high sensitivity, specificity and accuracy. Despite the high level of accuracy, intraoperative pathological techniques are infrequently employed and depend a heavily on the experience of pathologists. Pathological methods are also time-consuming. They often add an average of 20 to 30 additional minutes to the operating time. Intraoperative imaging methods, such as intraoperative ultrasound and specimen mammography, can quickly assess margin status and reduce operating time.

Various studies are available in the literature to evaluate the mammography of the excised specimen. Specimen mammography is a sensitive tool to assess both complete excision and positive margin in breast conserving surgery. However, some studies indicate that intraoperative specimen mammography hold a relatively low sensitivity with high specificity. Despite some limitations, the findings of our meta-analysis indicated that the diagnostic accuracy of specimen mammography was promising, with an AUC of 0.75.

In our meta-analysis, there was moderate and high heterogeneity for sensitivity and specificity respectively. There may be some factors leading to the heterogeneity among studies. One of the factors is the study design. We performed subgroup analysis between prospective and retrospective studies, blind and non-blind studies, studies with large and small sample numbers. No significant differences were observed between those subgroups.

Another factor may be the different specimen mammography systems used in the included studies. There are mainly two kinds of systems used to take specimen mammography, standard and intraoperative specimen systems. Two-dimensional standard specimen mammography is a technique used routinely in many cancer institutions. Despite labor intensive and increasing operating time, the disadvantages of standard specimen mammography also include lower specificity, as it often recommended excision of additional tissue unnecessarily. Kyle Ota thought that the high false positive rate may be caused by “pancake phenomenon”. Standard specimen mammography compresses the surgical specimen. This manipulation causes a “pancake phenomenon” which refers to a reduction in the mean volume and height of the breast specimens which may increase false-positive margins³¹. The other newly developed system is intraoperative specimen mammography. It is performed directly near the operating room by intraoperative specimen mammography, without transporting the specimen to the radiology department which usually located in a different unit within the hospital. Intraoperative specimen mammography provides results that are interpretable by the surgeon and as such avoids the need for additional personnel. However, it acquires additional skills by learning to interpret images. Intraoperative specimen mammography system significantly reduced the operative time for BCS compared to standard specimen mammography, which decreased anesthesia time and operating room cost. Aside from the reduced time, some studies have found a reduction in re-operation rates after the introduction of intraoperative mammography^{13,23}. The subgroup analysis result of our study showed that the use of intraoperative specimen mammography revealed comparable diagnostic accuracy as standard specimen mammography.

Histopathological results of the positive margin rate vary among studies, between 11.83–84.03%, which may lead to heterogeneity. Higher positive pathological margin rate means more positive margins to be detected by specimen mammography which may have effect on its diagnostic accuracy. The difference of positive margin rate is probably associated with the great variation of the surgical procedure, doctors’ experience in different centers and pathological characteristics of lesions such as large pathologic size and multifocality lesion. Larger lesions are understandably more difficult to excise completely than smaller ones. Multifocality lesions not only increase positive margin rates, but may also be mammographically undetectable. We performed a subgroup analysis between studies with high and low positive margin rate. No difference of specimen mammography diagnostic accuracy between these two subgroups was observed in our studies (p-value of Sensitivity = 0.70, p-value of Specificity = 0.21).

The appropriate negative margin width for breast conserving surgery remains controversial. The margin status is one of the factors affecting specimen mammography diagnostic accuracy. Among the included studies, negative

margin width differs from no tumor at margin to no tumor within 5mm from margin. Wider negative margin distance defines those cases with close margins as pathological positive. “Pancake phenomenon” causes the reduction in mean volume and height of the breast specimens, which also tends to define close margin cases as radiological positive. Our study showed a significant difference of specificity between two subgroups with a higher specificity in group of wider negative margins.

Besides all the factors mentioned above, there might be other factors affecting the diagnostic accuracy of specimen mammography, such as views of taking mammograph, manifestation of lesions on mammograph, pathological subtypes of breast cancer and so on. Goldfeder found that 1 view had a higher specimen radiography and histopathology concordance rate. Mammographs of specimens were effective in evaluating the surgical margins of mammographic lesions with microcalcifications than other manifestations³². In some subtypes of breast cancer such as medullary carcinoma, the positive margin signs on specimen mammograph might not represent actual tumor but only a nonneoplastic infiltrate of lymphocytes³³. Large scale and well-designed clinical trials are still needed to further assess its diagnostic value.

Declarations

Data availability

All data generated or analyzed in this study is included in this published article and its Supplementary Files.

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Author contributions

The manuscript was drafted by LC. LC and PT developed the search strategies. LC and WKY independently screened eligible studies, extracted data from included studies. When there was disagreement between LC and WKY, they discussed these articles with a senior author PT. QUADAS-2 checklist was independently completed by CHL and XYH. All authors participated in the data synthesis. PT and CYD supervised all phases of this study. Authors all approved its final version.

Conflict of interest statement

The authors declared no conflict of interest.

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Figures

Figure 1
Flowchart illustrating the selection of the studies.

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