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Intraoperative Imprint Cytology and Frozen Section Pathology for Margin Assessment in Breast Conservation Surgery: A Systematic Review

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Abstract

Background—Achieving negative surgical margins is critical to minimizing the risk of tumor recurrence in patients undergoing breast conservation surgery (BCS) for a breast malignancy. Our objective was to perform a systematic review comparing reexcision rates, sensitivity and specificity of the intraoperative use of the margin assessment techniques of imprint cytology (IC) and frozen section analysis (FSA), against permanent histopathologic section (PS).

Methods—The databases PubMed, Web of Knowledge, Cochrane Library and CINAHL Plus were searched for literature published from 1997 to 2011. Original investigations of patients who underwent BCS for breast cancer that evaluated margin assessment with PS and/or IC or FSA were included. Of 182 titles identified, 41 patient cohorts from 37 articles met inclusion criteria: PS (n = 19), IC (n = 7) and FSA (n = 15). Studies were summarized qualitatively using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort studies and the Strength of Recommendation Taxonomy (SORT) numerical scale for diagnostic studies.

Results—The final reexcision rates after primary BCS were 35 % for PS, 11 % for IC (p = 0.001 vs. PS) and 10 % for FSA (p < 0.0001 vs. PS). For IC, reexcision rates decreased from 26 to 4 % (p = 0.18) and for FSA, reexcision rates decreased from 27 to 6 % (p < 0.0001). The pooled sensitivity of IC and FSA were 72 and 83 %. The pooled specificity of IC and FSA were 97 and 95 %. The average length of each technique was 13 min for IC and 27 min for FSA.

Conclusions—Patients who underwent BCS with intraop-erative IC or FSA to assess negative surgical margins had significantly fewer secondary surgical procedures for excision of their breast malignancies.

Breast conservation surgery (BCS) with radiation has become the preferred method of treatment for patients with Stage I and II breast cancer after the 1990 Consensus Conference on Breast Cancer from the National Institutes of Health.[1] To achieve an oncologically and

cosmetically successful BCS, performance by the surgeon and an accurate assessment of the surgical margins by the pathologist are critical. Several studies have clearly defined that achieving a negative surgical margin on patients undergoing BCS is imperative.[2] Despite this, there is no consensus on what constitutes a negative margin; it varies from cancer not touching the ink in the specimen to 3 cm of normal tissue around the tumor.[3] Local recurrence rates increase in patients who have persistent positive surgical margins compared to patients with negative margins.[4–7]

The best cosmetic results are obtained during the primary BCS procedure. Reexcision of the breast results in a greater volume of resected tissue than with a single primary excision, which ultimately may affect cosmesis. In addition to the added costs of revision surgery, reexcision BCS leads to increased patient anxiety and a higher likelihood of infection.[8] Consequently, it is important to identify intra-operative margin assessment methods that would decrease reexcision rates.

Two intraoperative margin assessment methods are frequently reported in the literature: frozen section analysis (FSA) and touch preparation or imprint cytology (IC). FSA is the intraoperative technique that has been most widely used to analyze breast tumor excisions. It consists of freezing and sectioning the sample followed by thawing, fixation and staining. Reports indicate that FSA may cause artifacts in the fatty tissue as a result of the process of freezing and thawing, resulting in loss of tissue. This technique takes approximately 30 min.[9] Because of the disadvantages of FSA, IC has been proposed as an alternative intraoperative method. IC is a simple and rapid method where the excised mass is oriented and pressed onto glass slides making an imprint of all 6 margins. Slides are then fixed and stained. The principle is based on the cellular surface characteristics where only malignant cells will adhere to the slides and adipose cells will not. This method has been reported to take only an average of 15 min to provide a diagnosis.[2] Variability in the sensitivity of the method has been reported and is related to the size of the tumor and the cytological skills of the pathologist.[9] Errors of interpretation are linked to specimen surface irregularity, dryness and presence of atypical cells.[10]

Currently, there exists no systematic review that addresses the impact of these two intraoperative surgical margin assessment techniques in patients undergoing BCS. The primary objective of this work was to systematically review data published in primary studies of IC and FSA and to compare surgical reexcision rates, sensitivity and specificity of these techniques after library BCS against, permanent histopathologic section (PS).

METHODS

Literature Search

The databases PubMed, Web of Knowledge, Cochrane Library and CINAHL Plus were searched from 1997 to July 1, 2011, using the strategy shown in Fig. 1. The study period from 1997 was chosen, as important cohort studies with intraoperative IC and FSA occurred after 1997. References of included articles were also searched. The overall search strategy included terms for breast cancer (e.g., *breast neoplasm, breast cancer*), imprint cytology (e.g., *Touch prep* cytology, TPC, imprint cytology, intraoperative imprint cytology*), frozen

section analysis (e.g., *frozen section or FS*), surgical margin (e.g., *surgical margin*, margin assess*, margin evaluat**), conserving surgery (e.g., *conserving surger*, lumpectomy, partial mastectom*, segmental mastectom *, quadrantectomy*) and reexcision rate (e.g., *reexcision rate, reexcision rate*) and was limited to peer-reviewed human studies. No language restrictions were applied.

Selection Criteria

Articles for inclusion and exclusion were screened by a single reviewer blinding for journal, authors, institution, and country of origin. The inclusion criteria for the overall search targeted articles with the following: (1) individuals with cancer undergoing BCS; (2) surgical margin assessment technique (IC, FSA, PS, or some combination), reexcision rates, and/or specificity and sensitivity values for both intraoperative techniques; (3) study sampling and methods stated and; (4) publication was peer-reviewed. Articles that included sufficient data for cross-tabulation of the results of PS, IC and FSA were included. Articles were excluded if they analyzed or mixed data of lymph nodes, they used other intraoperative margin assessment techniques, or if studies were case reports or meeting abstracts.

Assessment of Methodologic Quality

Articles were extracted and assessed for quality following the same blinding criteria as above. Abstracted data included patient demographics, type of breast cancer, surgical margin assessment techniques, reexcision rates during and after primary BCS, sensitivity and specificity of IC and FSA, false-positive and false-negative cases for IC and FSA, and study quality and type. Quality was assessed by using components of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort studies and the Strength of Recommendation Taxonomy (SORT) numerical scale for diagnostic studies.[11,12] To judge quality, information was abstracted on population source, whether the study had institutional approval, statistical methods and publication bias.

Data Synthesis and Statistical Analysis

Data were used on a per-tumor basis rather than per-patient basis to calculate reexcision rates, sensitivity and specificity. Some patients had more than one tumor extracted and analyzed and each tumor was considered as an independent specimen. If sensitivity and specificity data were missing, they were calculated from the available data. To avoid overlapping patient populations, data on recruitment years, data source and geographic location were compared. If there were multiple publications of the same author with the same patient population, only the most comprehensive and relevant study was included. This resulted in the exclusion of one article.[13]

Nine authors were contacted for unreported secondary information to complete the data tables, and one author replied. From the studies selected, only nine had a SORT/ STROBE score of 2 and the rest had a score of 1, suggesting the findings of this study are reliable.

The final reexcision rates among three groups (FSA, IC and PS) were compared by a general linear model with a *t* test. The *t* test was also used to compare the intraoperative reexcision rate and final reexcision rate within IC and FSA pairs during and after primary surgery.

Finally, the sensitivity and specificity between FSA and IC groups was compared by *t* test. All analyses were conducted by SAS software (SAS Institute, Cary, NC).

RESULTS

Our literature search yielded 182 potentially relevant articles, of which 67 were evaluated in full text. Most excluded studies did not report reexcision rates or mixed intraoperative methods. Of the 67 articles, 37 primary studies were eligible for inclusion in the systematic review. The number of publications doesn't match the number of patient cohort data sets included in the analysis. Four of 37 publications contained two different sets of data within the same publication, resulting in 41 patient cohort data sets for analysis.[14–17] Nineteen publications were included for the analysis of permanent section, seven for IC and 15 for FSA.

Description of Studies

The 37 articles included in this systematic review were homogeneous in their primary goal. The articles measured reexcision rates or recurrence rates on patients undergoing BCS either with intraoperative IC, FSA and/or PS. All studies were conducted in medical institution-based surgical and pathology units. Nine studies used prospective cohorts of breast cancer patients and the remaining utilized retrospective cohorts. Most studies analyzed the use of intraoperative FSA and IC in all types of breast cancer. Five studies analyzed data from patients exclusively with invasive carcinoma; three studies analyzed data from patients with in situ carcinoma, and one included phyllodes tumors.

The studies were conducted in the United States ($n = 21$), Canada ($n = 1$), Brazil ($n = 2$), Europe ($n = 9$), Turkey ($n = 1$), Asia ($n = 4$), and Australia ($n = 1$). Sample sizes ranged from 44 to 2,770 for PS studies (Table 1), from 12 to 1,193 for IC studies (Table 2) and from 54 to 1,016 for FSA studies (Table 3) with a median of 351, 328 and 259, respectively.

Permanent sections and frozen sections were stained with hematoxylin and eosin in all but one study in which methylene blue was used.[18] The majority of IC studies used the Diff-Quik (Baxter Diagnostics, McGaw Park, IL), rapid Papanicolaou and hematoxylin and eosin techniques. The surgical margin results of IC and FSA were categorized as positive, suspicious/close or negative in all studies. Six articles reported the time taken to perform intraoperative IC (mean, 13 min; Table 2) and four articles reported the duration of FSA (mean, 27 min; Table 3). One FSA study reported a mean of 53 min as they performed a total circumference sampling of the specimen which required more slides to analyze.[19] From the IC and FSA analysis publications, cross-tabulation of results against permanent section was either reported or could be inferred from the data provided.

Reexcision Rates

The total number of tumors analyzed across the studies of permanent section was 10,489 with a mean of 542. For IC, a total of 2,296 tumors were analyzed with an average of 300 specimens. Finally, 3,621 tumors were analyzed in FSA publications and 259 tumors were studied on average.

By means of the general linear model, we found significant differences in final reexcision rates among the three groups with an overall *p*-value of <0.0001. Subsequently, we performed a detailed examination with the *t* test. The final reexcision rates of FSA (10 ± 6 %) was significantly lower than PS (35 ± 3 %) ($p < 0.0001$). The final reexcision rate of IC (11 ± 4 %) was also significantly lower than PS (35 ± 3 %) ($p = 0.001$) (Fig. 2a). The final reexcision rates for FSA versus IC were not significantly different ($p = 0.92$).

To further analyze the effects of intraoperative IC and FSA during primary BCS, we compared intraoperative reexcision rates and postoperative reexcision rates within FSA and IC. For FSA, the intraoperative reexcision rate of 27 ± 9 % was significantly reduced to a final rate of 6 ± 6 % ($p < 0.0001$). Similarly, the intraoperative reex-cision rate for IC (26 ± 21 %) was reduced to a final reexcision rate of 4 ± 7 %. However, it was not significantly different ($p = 0.18$) as a result of the variation in the IC group (Fig. 2b). We found that the intraoperative re-excision rate for FSA was not statistically different from the IC group ($p = 0.86$).

Sensitivity and Specificity

Five IC studies and nine FSA studies were used to analyze pooled intraoperative sensitivity and specificity. The sensitivity of FSA (83 ± 13 %) versus IC (72 ± 38 %) was not significantly different ($p = 0.53$). Similarly, the specificity of FSA (95 ± 8 %) versus IC (97 ± 3 %) was not significantly different ($p = 0.58$). In IC studies, the occurrence of false-positive cases was primarily the result of the observation of atypical cells with characteristics of invasive components. False-negative cases were due to patients presenting with ductal carci-noma-in-situ, then invasive lobular carcinoma and lobular carcinoma-in-situ (Table 2). With the intraoperative use of FSA, false-positive cases were linked to atypical cells and sclerosing adenosis. Conversely, false-negative cases were due to all types of malignancy (Table 3). Overall, there were more false-negative cases when using intraoperative FSA in comparison with IC. In one study of FSA, false-negative findings correlated with younger patients and with larger tumors.[20] In other FSA publications, a correlation was found between false negative cases and patients with small volume of lesions, microcalcifications and neoadju-vant therapy.[18,21]

DISCUSSION

The intraoperative use of margin assessment techniques in breast cancer patients undergoing BCS has proven to be sufficiently rapid to be used in a clinically relevant time period during the original surgical procedure. In addition, this approach can efficiently reduce but not eliminate the need for additional surgeries to attain negative margins in these patient populations. Both FSA and IC had a final pooled reexcision rate of approximately 10 %, which is meaningful for surgical outcomes. During surgery, IC took less than 15 min and FSA took less than 30 min to perform. The sensitivity and specificity for IC was found to be comparable to FSA. However, there was a greater degree of variation present in the sensitivity of IC among studies. Overall, for IC and FSA, most false-negative cases were observed in tumors diagnosed with in-situ disease. In addition, false-negative cases for FSA occurred on specimens from invasive ductal carcinoma. These false-negative cases could be

related to sampling errors, size of tumor, size of lesions and the nonpalpable state of the tumor.

Results of this systematic review are limited by the quality of the reporting of the studies analyzed. Both prospective and retrospective patient cohorts were reviewed; however, no randomized clinical trial data were available on this topic. On the basis of SORT and STROBE criteria, the quality of the studies selected was high; even though it is difficult to make comparisons when there are variations in the IC method, histopathological staining techniques and FSA specimen sectioning. The experience of the patholo-gists with each technique, especially cytopathological proficiency, was seldom mentioned and bias was unlikely to occur because most patients had the intraoperative and histological tests performed as part of a protocol.

Increased utilization of intraoperative IC and FSA is likely to lead to declines in reexcision surgery, surgical costs, patient anxiety and surgical complications and increases in cosmetic results, patient safety and patient satisfaction. Indeed, Uecker et al., have demonstrated the cost savings associated with intraoperative assessment of surgical margins through reduced surgical reoperations from two hospitals in Austin, TX.[22] In the hospital that performed routine PS, 60 % of cases required reoperation with average costs of $22,013 per patient. Whereas in the hospital that performed intraoperative assessment, 24 % of cases needed reoperation with average costs of $15,341. Likewise, a recent cost-effectiveness analysis of FSA by Osborn et al. compared patients who underwent lumpec-tomy with and without intraoperative margin assessment.[23] Patients who had lumpectomy without FSA, underwent a reoperation 15–50 % of the time, while patients who had FSA executed during BCS, had a reoperation 3 % of the time and the costs to provider and payor were significantly reduced.

The results of this review suggest that it is worthwhile for clinicians to consider adopting the use of IC and FSA if their current reexcision rates exceed 10 %. The use of IC and FSA as intraoperative margin assessment tools requires a multidisciplinary team effort among the surgeons, pathologists and radiologists. The presence of an on-site pathologist would be a requirement for performance of these procedures and may not be available at institutions where the pathology is performed at a separate location or there is limited experience with cytopathologic outcomes. In considering FSA and IC, the multidisciplinary breast team should evaluate their current reexcision rates and if in the 10 % rate range because of current practices of specimen imaging or use of intraoperative ultrasound, a change in practice may not be indicated. As new technology such as those using radiofrequency ablation and intraoperative optical imaging are refined, their performance against FSA and IC should be considered on the basis of this systematic review.

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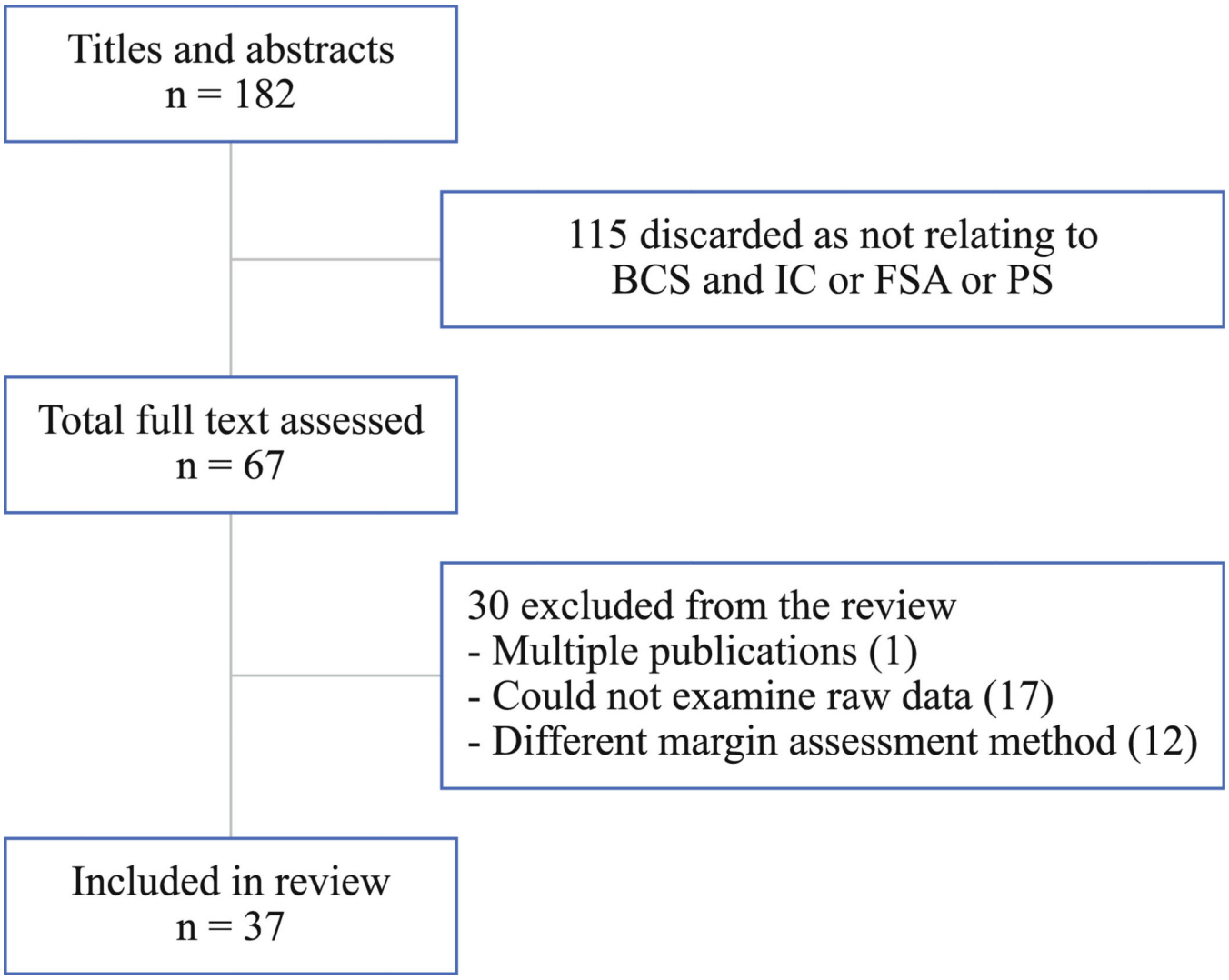

FIG. 1.

Flow diagram of the literature search and study selection. The number of publications does not match the number of patient cohort data sets included in the analysis, which add to 41

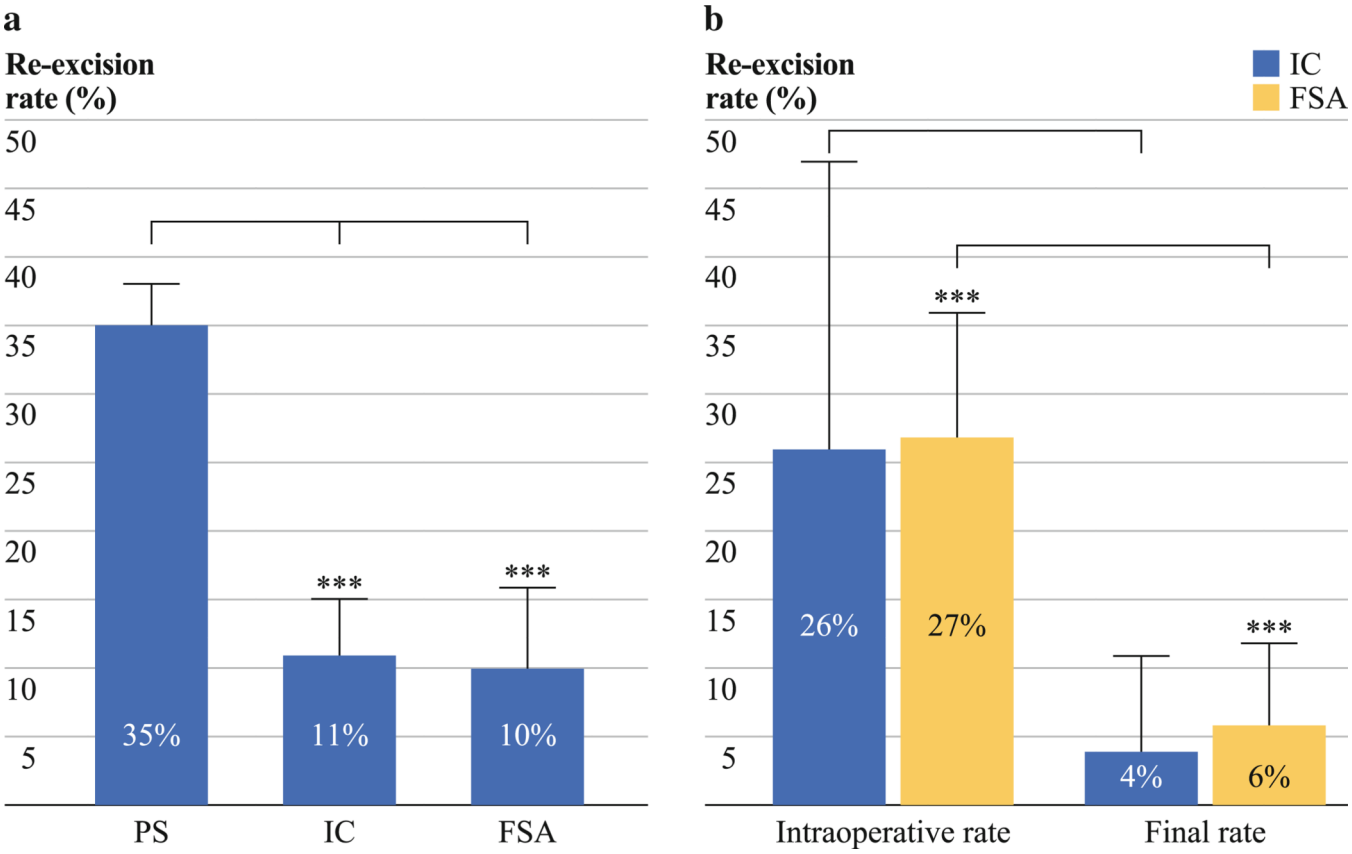

FIG. 2.

Graphs of reexcision rates of permanent section, IC and FSA. **a** Pooled estimates of final reexcision rates after primary BCS. PS (n = 19), IC (n = 7) and FSA (n = 15). IC versus PS (p = 0.001) and FSA versus PS (p<0.0001). **b** Pooled estimates of intraoperative reexcision rates during primary BCS versus final reexcision rates after primary BCS when using intraoperative IC and FSA as surgical margin assessment techniques. IC (n = 3) and FSA (n = 10). IC reexcision rates decreased from 26 to 4 % (p = 0.18) and FSA reexcision rates decreased from 27 to 6 % (p<0.0001)

TABLE 1

Characteristics of permanent section studies

Study	Year	Country	Carcinoma type	BCS	Age range (y)	*n*	Reexcision rate[a]	LOE	Study type
Arora et al.[24]	2007	USA	ADH, DCIS	Lumpectomy	42–87	44	55.0 % (24)	1	Retrospective cohort
Aziz et al.[5]	2006	Canada	IC, DCIS	Lumpectomy	55[b]	1,172	13.0 % (152)	1	Retrospective cohort
Cabioglu et al.[14]	2007	USA	IC, DCIS	Wide local excision, segmental mastectom	27–95	261	44.0% (116)	1	Retrospective cohort
Camp et al.[15] (personal communication)	2005	USA	IC, DCIS	Lumpectomy	26–78	78	33.3 % (26)	1	Retrospective cohort
Huston et al.[25]	2006	USA	DCIS, LCIS, IDC, ILC	Lumpectomy	30–91	171	29.2 % (50)	2	Retrospective cohort
Landercasper et al.[26]	2010	USA	Breast cancer	Lumpectomy	–	568	19.0 % (108)	1	Retrospective cohort hospital report
Loibl et al.[16]	2006	Germany	ILC, IDC	Lumpectomy	26–78	248	27.0 % (67)	1	Retrospective cohort RCT–GEPARDUO
McCahill et al.[27]	2010	USA	DCIS, IDC, ILC	Partial mastectom	–	712	13.0 % (95)	2	Retrospective cohort
Menes et al.[28]	2005	USA	DCIS, ILC, IDC	Lumpectomy	27–87	459	49.9 % (229)	1	Retrospective cohort Prospective database
Miller et al.[29]	2004	USA	DCIS, ILC, IDC	BCS	38–64	143	18.2 % (26)	1	Retrospective cohort
Moorthy et al.[30]	2004	UK	IDC, ILC	Lumpectomy, wide local excision, quadrantectomy	47–73	505	27.1 % (137)	1	Prospective cohort
Mullenix et al.[31]	2004	USA	IDC, ILC	BCS	48–73	150	51.0 % (90)	1	Retrospective cohort, prospective database
Ooi et al.[32]	2003	Australia	DCIS, ILC, IDC, IC, medullary	BCS	28–80	742	3.9 % (29)	2	Retrospective cohort
O'Sullivan et al.[33]	2007	USA	IDC, DCIS, ILC	Lumpectomy	20–91	2,770	59.6 % (1,651)	1	Retrospective cohort, prospective database
Perez[34]	2003	USA	ILC, IDC	Quadrantectomy, wide local excision, local excision	–	1,347	52.3 % (704)	1	Retrospective cohort
Ramanah et al.[35]	2008	France	ILC, IDC	Lumpectomy, wide local excision	44–68	206	41.0 % (84)	1	Retrospective cohort
Sanchez et al.[36]	2010	USA	IDC, ILC, DCIS, atypia	BCS	22–88	351	34.0% (118)	2	Retrospective cohort
van den Broek et al.[37]	2007	Netherlands	ILC	BCS	–	416	14.4 % (60)	2	Retrospective cohort
Vicini et al.[38]	2001	USA	DCIS	Excisional biopsy	–	146	64.0 % (95)	2	Retrospective cohort
Results						351[b]	35 % (±3 %)[c]		

BCS breast conservation surgery, *LOE* level of evidence (SORT), *ADH* atypical ductal hyperplasia, *IC* invasive carcinoma, *DCIS* ductal carcinoma-in-situ, *LCIS* lobular carcinoma-in-situ, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma

[a] After first BCS

[b] Sample median

[c] Pooled estimates

TABLE 2

Characteristics of imprint cytology studies

Study	Year	Country	Carcinoma type	BCS	Age range	*n*	Intraoperative reexcision rate[a]	Reexcision rate final[b]	Sensitivity	Specificity	Time (min)	False-positive cases	False-negative cases	LOE	Study type
Barros et al.[39]	2004	Brazil	IC	Quadrantectomy	28–79	102	37 % (38)	0 % (0)	–	–	15–20	13: Atypical cells present	10: Focal for DCIS (6), IC (3) and presence of carcinoma at margin in a single lymphatic space (1)	2	Prospective cohort
Cox et al[40]	1997	USA	DCIS	Lumpectomy	30–82	104	–	0 % (1)	99 %	98 %		2	1: Focal for DCIS	1	Prospective database
D'Haulluin et al.[41],[c]	2009	France	IDC, DCIS, ILC, LCIS	Lumpectomy	29–88	396	38.63 % (153)	12.6 % (50)	88.6 %	92.2 %	7–17	25: ILC (10.2 %), IDC histological grade 3 (5.6 %), fibricystic mastopathy lesions	9: Contact with 1 margin (4), 2 mm away from margin (5). DCIS, size ≥30 mm, histological grade of 1 or 2.	1	Retrospective cohort
Klimberg et al[42]	1998	USA	DCIS, ILC	Lumpectomy	22–86	428	1.4 % (6)	0 % (0)	96.4 %	100%	2–3	None	3: Focal for DCIS (2), LCIS (1). Thought to be missed by sampling error.	1	Prospective cohort
Valdes et al.[17],[d]	2007	USA	ILC	Lumpectomy		12		33 % (4)	8.3 %	98.3 %	15	1: Atypical lobular hyperplasia	8: Focal for ILC (7) and ILC plus LCIS (1)	2	Prospective cohort
Valdes et al.[17],[d]	2007	USA	IDC	Lumpectomy	–	61	–	23 % (14)	65.7 %	95.5 %	15	4.10 %	3.3 %, DCIS	2	Prospective cohort
Weinberg et al.[10]	2004	USA	DCIS, ILC, IDC	Lumpectomy	–	1,193	–	6.2 % (74)	–	–	15	–	–	1	Retrospective cohort
Results						104[e]	26% (±21 %)[f]	11 % (±4 %)[f]	72 % (±38 %)[f]	97 % (±3 %)[f]	13				

BCS breast conservation surgery, *LOE* level of evidence (SORT), *IC* invasive carcinoma, *DCIS* ductal carcinoma-in-situ, *LCIS* lobular carcinoma-in-situ, *IDC* invasive ductal carcinoma, *ILC* Invasive lobular carcinoma

[a] During first BCS

[b] After first BCS

[c] Cross-publication

[d] Publication used twice in analysis because of different study cohorts in same publication

[e] Sample median

[f] Pooled estimates

TABLE 3

Characteristics of frozen section analysis studies

Study	Year	Country	Carcinoma type	BCS	Age range (y)	*n*	Intraoperative reexcision rate[a]
Cabioglu et al.[14]	2007	USA	IC, DCIS	Wide local excision, segmental mastectom	27–95	110	20.0 % (22)
Camp et al.[15] (personal communication)	2005	USA	IC, DCIS	Lumpectomy	26–78	189	27.0 % (51)
Cendan et al.[43]	2005	USA	DCIS, LCIS, ILC, IDC, MC	BCS	48–71	97	44.0 % (43)
Chen et al.[44]	2005	Taiwan	PT	Local and wide excision	11–73	113	
Dener et al.[45]	2009	Turkey	IC	Lumpectomy	18–94	186	16.0 % (30)
Fukamachi et al.[19]	2010	Japan	IDC, DCIS, ILC, MC, AC	Wide excision, quadrantectomy	32–87	122	27.0 % (33)
Ikeda et al.[46]	1997	Japan	DCIS, IC	Quadrantectomy	33–66	54	37 % (20)
Loibl et al.[16]	2006	Germany	ILC, IDC	Lumpectomy	25–78	240	–
Munhoz et al.[20]	2009	Brazil	DCIS, ILC, IDC	Lumpectomy	23–71	218	28.8 % (63)
Olson et al.[47]	2007	USA	IC, DCIS	Lumpectomy	27–89	290	24.0 % (70)
Park et al.[48]	2011	Korea	ILC, IDC, MC, TC, PC, medullary	BCS	20–78	705	–
Riedl et al.[21]	2009	Austria	DCIS, ILC, IDC	Lumpectomy	24–92*	1,016	–
Rusby et al.[18]	2008	UK	DCIS, ILC, IDC, MC, TC, PC	Partial mastectom	40–59	115	33.0 % (38)
Weber et al.[49]	1997	USA	DCIS	Lumpectomy	–	140	15 % (21)
Weber et al.[50]	2008	Switzerland	IC, DCIS, ADH	Lumpectomy	34–86	80	–
Results						163[c]	27 % (±9 %)[d]

Reexcision rate final[b]	Sensitivity	Specificity	Time (min)	False-positive cases	False-negative cases	LOE	Study type
8.8 % (10)	91.7 %	77.8 %		–	–	1	Retrospective cohort
5.8 % (11)	–	–	13	–	–	1	Retrospective cohort
19.6 % (19)[c]	58.1 %	100.0 %	13	None	22: DCIS (20), LCIS (2)	1	Retrospective cohort
41.6 % (47)	–	–		–	–	2	Retrospective cohort
0 % (0)	100.0 %	100.0 %		None	None	1	Retrospective cohort

Study	Year	Country	Carcinoma type		BCS	Age range (y)	*n*	Intraoperative reexcision rate[a]
9.8 % (12)	78.6 %	100.0 %	53#	None	–	1	Retrospective cohort	
0 % (0)	94%	90%		4: Atypical	1	1	Retrospective cohort	
13.3 % (32)	–	–		–	–	1	Retrospective cohort RCT-GEPARDUO	
5.5 % (12)	–	–		–	12: IDC (7), IDC plus DCIS (2), DCIS (2). Younger age and larger tumors.	1	Retrospective cohort	
5.5 % (16)	73.1 %	99.6 %		27	17	1	Retrospective cohort	
13.5 % (95)	–	–		–	28: Focal intraductal carcinoma	1	Retrospective cohort	
9 % (91)	–	–	30	–	91: IDC (88), ILC (3); Small lessions, microcalcifications, neoadjuvant therapy	1	Retrospective cohort	
7 % (8)	83.0 %	97.0 %		8: Atypia, sclerosing adenosis (3); in situ or IC (4)	9: Sampling error, small volume of tissue	1	Retrospective cohort, prospective database	
0 % (1)	91 %	100%		None	3: DCIS (2), LCIS (1)	1	Retrospective cohort	
12.5 % (10)	80.0 %	87.5 %		–	–	1	Retrospective cohort	
10 % (±6 %)[d]	83 % (±13 %)[d]	95 % (±8 %)[d]	27.25[c]					

BCS breast conservation surgery, *LOE* level of evidence (SORT), *IC* invasive carcinoma, *MC* mucinous carcinoma, *AC* apocrine carcinoma, *TC* tubular carcinoma, *PC* papillary carcinoma, *DCIS* ductal carcinoma-in-situ, *LCIS* lobular carcinoma-in-situ, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *PT* phyllodes tumors, *ADH* atypical ductal hyperplasia

[a] During first BCS

[b] After first BCS

[c] Sample median

[d] Pooled estimates

[*] Personal communication