



Extensive intraductal component as a factor determining local recurrence of breast cancer: a systematic review and meta-analysis

Nuanphan Polchai[^], Sarun Thongvitokomarn[^]

Queen Sirikit Centre for Breast Cancer, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Contributions: (I) Conception and design: Both authors; (II) Administrative support: S Thongvitokomarn; (III) Provision of study materials or patients: N Polchai; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Sarun Thongvitokomarn, MD. Queen Sirikit Centre for Breast Cancer, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, 1873, Rama 4 Road, Pathumwan Sub-district, Pathumwan District, Bangkok 10330, Thailand. Email: toph@hotmail.com.

Background: Breast-conserving surgery and mastectomy are standard surgical options for breast cancer. However, some patients experience a local recurrence after the operation. Many factors have been identified as a risk of local recurrence. Extensive intraductal component (EIC) was found as one of the major risks of the recurrence. Nevertheless, there were neither any systematic reviews nor controlled trials focused on EIC. This study aims to identify the impact of EIC on the local recurrence of breast cancer.

Methods: We searched all relevant studies published between the inception to December 2020. All electronic data from PubMed and Scopus databases were extracted for evaluation of EIC as a factor of the recurrence. Local recurrence was a primary outcome between EIC-positive group and EIC-negative group. Margin status and adjuvant radiation were focused as a subgroup analysis. The Newcastle Ottawa Scale was applied for quality assessment of included studies and RevMan 5.3 program was used to estimate the effect of the results. The odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

Results: A total of 32 studies, comprising 4,290 and 15,143 patients in the EIC-positive and EIC-negative groups respectively, were retrieved and met selection criteria. All included studies were at low to intermediate risk of bias. There was a statistically significant difference in local recurrence between EIC-positive patients and EIC-negative patients (OR =2.73; 95% CI: 2.42–3.07; P<0.00001). However, there was not any significant difference in patients who had negative margin (OR =1.97; 95% CI: 0.92–4.19; P=0.36) or received any adjuvant irradiation (OR =1.58; 95% CI: 0.55–4.54; P=0.24).

Conclusions: EIC increases the risk of local recurrence, especially in breast-conserving surgery patients. However, there are a limited number of populations to analyze in subgroup analysis, the rate of local recurrence between two groups is not different in patients who had negative margin or received postoperative irradiation.

Keywords: Extensive intraductal component (EIC); local recurrence; meta-analysis; systematic review

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[^] ORCID: Nuanphan Polchai, 0000-0002-5496-3844; Sarun Thongvitokomarn, 0000-0002-3519-3290.

Introduction

Multimodality treatment is essential for the improvement in breast cancer survival, however, surgery remains the mainstay option in early breast cancer patients. Multiple prospective randomized trials have demonstrated that breast-conserving therapy and mastectomy showed no significant difference in disease-free survival, distant disease-free survival, and overall survival (1-3). Ipsilateral breast tumor recurrence (IBTR) correlated with systemic recurrence in several studies but the impact of IBTR on overall survival was still controversial. Several studies demonstrated that IBTR cannot translate into decreased survival, but it resulted in a higher risk for distant metastases. Many researchers hypothesized that IBTR might be the cause of systemic recurrence, however, others suggested that IBTR was an indicator of aggressive disease coexisting with micrometastasis (4-6). Thus, locoregional control remained an important goal of treatment for early-stage breast carcinoma. An increased risk of local recurrence was associated with younger patients, involved resection margin, non-luminal biological subtype, lymphovascular invasion (LVI), and an extensive intraductal component (EIC) (5,7,8).

EIC is defined as tumors that are composed of ductal carcinoma in situ (DCIS) component comprising at least 25% and extending to surrounding normal breast tissue. Many studies suggested that the presence of EIC is associated with the amount of residual disease after breast-conserving surgery. However, the correlation of EIC and local recurrence was unclear (9-11). A study

showed that local recurrence rates for EIC-negative tumors and EIC-positive tumors were 2% to 9% and 10% to 30%, respectively (12). Nevertheless, further studies have been reported that there was no association between EIC and local recurrence when resection margin is negative (10,13,14). Additionally, there were neither any systematic reviews nor controlled trials that demonstrated the relationship between EIC and local failure. The purpose of this study is to determine the effect of EIC on local recurrence risk, focusing on margin and adjuvant radiation status. We present this article in accordance with the MOOSE reporting checklist (available at <https://gs.amegroups.com/article/view/10.21037/gS-23-137/rc>).

Methods

Study sources and searches

A systematic literature search was performed using PubMed and Scopus databases. All relevant studies were published from the inception to December 31st, 2020. The Medial Subject Heading (MESH) terms “Extensive intraductal component”, and “Breast” were used. The search was conducted in August 2021. Search strategy was shown in [Appendix 1](#).

Our inclusion criteria were as follows: (I) breast cancer with EIC as a factor of local recurrence; (II) local recurrence was reported as a major focus.

Studies were excluded on the basis of following criteria: (I) reviews, meta-analyses, abstracts, letters, case report, case series, commentaries, or duplicated publications; (II) overlapping articles; (III) unavailable local recurrence rate; (IV) studies of other cancers and (V) non-English published studies.

The primary objective of this study was to report the local recurrence rate in EIC-positive patients comparing to EIC-negative patients. We focused on the patients who received breast-conserving surgery, however, there was one study that included only mastectomy patients. Prespecified subgroup analysis included margin status in pathological report and adjuvant radiation, either whole breast irradiation or any partial breast irradiation.

Data extraction and quality assessment

Two researchers (Polchai N and Thongvitokomarn S) independently reviewed titles and abstracts of all studies. Disagreement on each study was solved by discussion

Highlight box

Key findings

- This meta-analysis suggests that breast cancer patients with extensive intraductal component (EIC) positive tumor have higher rates of local recurrence in overall population, but this cannot be generalized to patients who achieve negative margin or receive irradiation.

What is known and what is new?

- EIC is not a contraindication for breast-conserving surgery. The challenging point is how to obtain negative margin for EIC-containing lesions during breast-conserving surgery.

What is the implication, and what should change now?

- To improve treatment outcomes, accurate predictive tools for EIC-positive tumor, precise estimation in the extent of EIC and proper localization techniques remain the issues for further studies.

between two authors. Next, they screened full-text articles for inclusion. Data from eligible studies were extracted and checked by two researchers. For each study, the following data were considered: first author, year of publication, sample size, local recurrence rate, EIC status, adjuvant radiation and margin status of the specimen. The primary outcome of the meta-analysis was a local recurrence rate in EIC-positive patients compared with EIC-negative patients. The following results allowed for meta-analysis: (I) local recurrence in all studies; (II) local recurrence in margin negative studies and received any type of irradiation; and (III) local recurrence in margin negative studies and received whole breast irradiation. All discrepancies were discussed and resolved by consensus of the researchers.

According to non-randomized studies, the quality of all studies was evaluated with the Newcastle Ottawa Scale (15) (Tables S1,S2).

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were used to estimate the effect of categorical outcomes. If such data were not provided, we had to calculate these. Meta-analysis of each outcome was analyzed by RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and forest plots were used to present the analysis results. The statistical heterogeneity among studies was calculated using I^2 statistics and P values. The heterogeneity was considered significant where $I^2 > 50\%$ or $P < 0.05$. The Inverse Variance fixed effects and random effects model were used to analyze the OR in each study. Publication bias of all included studies was exhibited in funnel plot. Sensitivity analyses were conducted by using an alternative meta-analysis model and by excluding studies which included mastectomy. Additionally, we performed subgroup analysis to investigate the heterogeneity.

Results

We initially identified 346 potentially eligible studies from PubMed and 393 studies from Scopus. Duplicated studies were removed and a total of 434 studies were included for abstract screening. Of these relevant studies, 378 were excluded basing on their titles or abstracts, i.e., not report local recurrence rate, not report EIC as a factor of local recurrence or not in English language.

Among the remaining 56 studies which could be retrieved in full text, 24 studies were excluded from the

following basis: no comparative outcome between EIC positive and EIC negative patients (8 studies); unavailable full text (6 studies); no local recurrence as an outcome (4 studies); publications in languages other than English (4 studies); duplicated studies (2 studies). The PRISMA scheme was shown in *Figure 1*. All included studies were observational studies and classified as low to intermediate risk of bias according to Newcastle Ottawa Scale (Tables S1,S2).

Consequently, there were 32 studies for data extraction and meta-analysis, comprising 4,290 and 15,143 patients in the EIC-positive and EIC-negative groups respectively. A total of 12 studies demonstrated the margin status (14,16-26) but the others did not present this information (8,10,27-44). Among these 32 studies, there were four studies, which reported the local recurrence in margin negative patients who received breast-conserving surgery with any types of irradiation (17,21,24,26). Three out of four studies reported the local recurrence in margin negative patients and received adjuvant whole breast irradiation (17,21,24). Irradiation treatments in those four studies included whole breast irradiation (two studies), whole breast and intra-operative irradiation (one study) and intra-operative irradiation only (one study). Baseline characteristic of all 32 studies was summarized in *Table 1*.

For meta-analysis, local recurrence rate in EIC-positive and EIC-negative groups were analyzed. From all 32 studies, there was a statistically significant difference in local recurrence between EIC-positive patients and EIC-negative patients with respect to both fixed effects model (OR =2.73; 95% CI: 2.42–3.07) and random effects model (OR =2.85; 95% CI: 2.28–3.57). There was a heterogeneity among these 32 studies (I^2 : 68%; $P < 0.00001$) (*Figure 2*).

Regarding the margin status, the meta-analysis was done in patients who had negative margin status. From the four studies which reported local recurrence rate in patients who had negative margin, all patients received irradiation. Meta-analysis in these four studies demonstrated a non-statistically significant difference in local recurrence between EIC-positive patients and EIC-negative patients with respect to both fixed effects model (OR =1.97; 95% CI: 0.92–4.19) and random effects model (OR =1.95; 95% CI: 0.88–4.34). There was not a heterogeneity among these four studies (I^2 : 7%; $P = 0.36$) (*Figure 3*).

Turning to the margin status and whole breast irradiation, the meta-analysis was done in patients who had negative margin status and received adjuvant whole breast irradiation. Meta-analysis in these three studies demonstrated a non-statistically significant difference

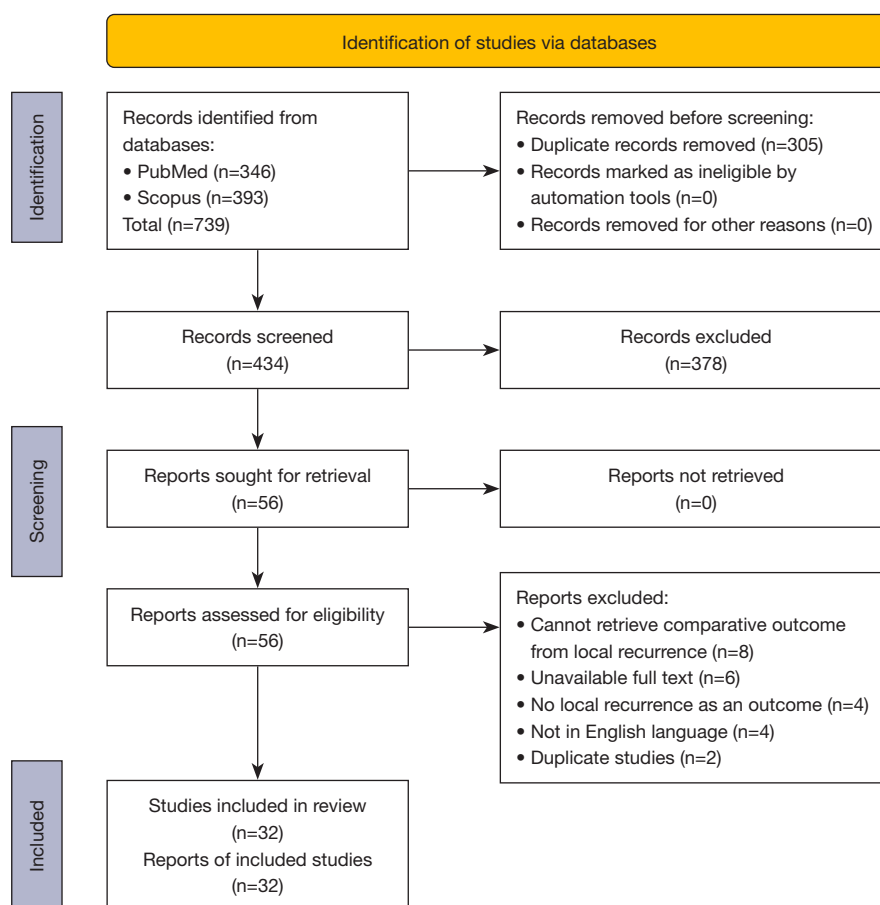


Figure 1 Diagram for selection of the included studies (PRISMA Schema).

in local recurrence between EIC-positive patients and EIC-negative patients with respect to both fixed effects model (OR =1.58; 95% CI: 0.55–4.54) and random effects model (OR =1.55; 95% CI: 0.40–6.00). There was not a heterogeneity among these three studies (I^2 : 31%; $P=0.24$) (Figure 4).

In terms of the type of operation, there was one study which included only mastectomy patients (39). Additionally, there were two studies which included both breast-conserving surgery and mastectomy (40,42). However, 60% and 70% of patients from these two studies underwent breast-conserving surgery. Furthermore, there was one study which did not report the type of operation (27).

The meta-analysis was performed with the exclusion of those four studies. There was still a statistically significant difference in local recurrence between EIC-positive and EIC-negative patients [fixed effects model (OR =3.20; 95% CI: 2.81–3.64) and random effects model (OR =3.27; 95%

CI: 2.72–3.93), heterogeneity (I^2 : 44%; $P<0.00001$)].

Additionally, the meta-analysis was performed with the exclusion of the study that included only mastectomy. Again, there was still a statistically significant difference in local recurrence between EIC-positive patients and EIC-negative patients [fixed effects model (OR =2.71; 95% CI: 2.41–3.06) and random effects model (OR =2.83; 95% CI: 2.25–3.56), heterogeneity (I^2 : 69%; $P<0.00001$)].

Discussion

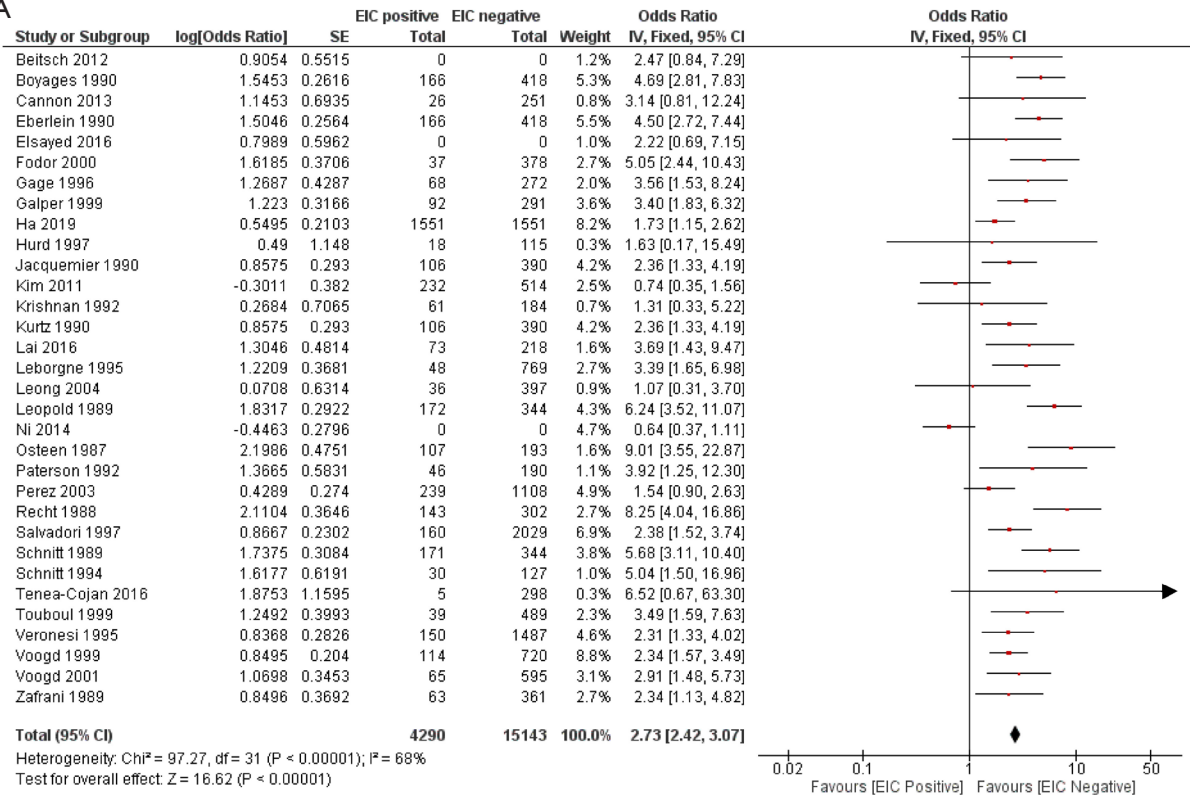
An effective treatment strategy for breast cancer requires both the optimal local control and appropriate systemic therapies. One of the surveillance goals in early-stage breast cancer, which is mostly operated by breast-conserving surgery, is the local recurrence. Positive resection margin was strongly considered as a risk factor for increased local relapse (45), and the presence of EIC seemed to be an

Table 1 Characteristics of 32 included studies

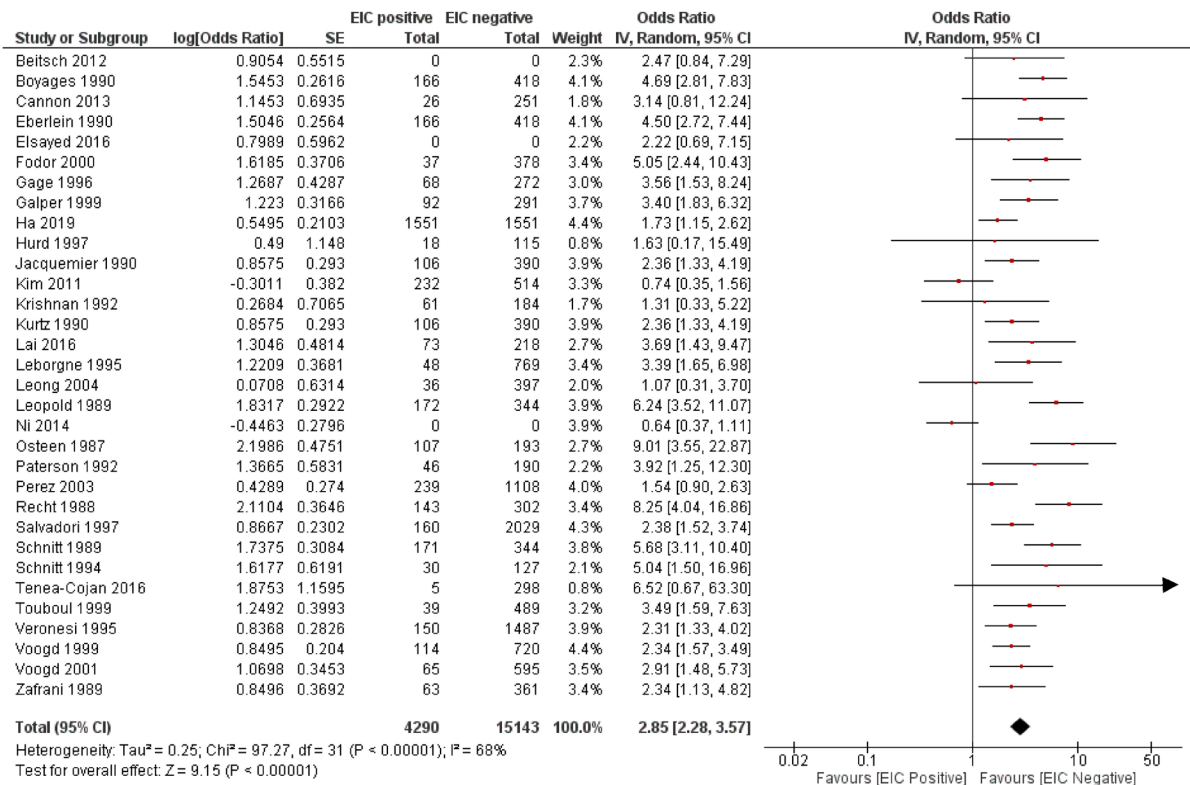
First author	Year	Follow-up (months), median (range)/median/ mean (range)	N	Adjuvant radiation	Report margin status	Negative margin	Definition of EIC	Type of local surgery		Remarks
								BCS	Mastectomy	
Ni (27)	2014	75 (0.23–133.8)	633	n/a	n/a	n/a	n/a	n/a		
Jacquemier (16)	1990	71 (n/a)	496	Yes	Yes	98.4%	>25%	100%		
Elsayed (28)	2016	60 (12–120)	238	Yes	n/a	n/a	n/a	100%		
Krishnan (17)	1992	58 (14–110)	245	Yes	Yes	100%	>25%	100%		
Leborgne (18)	1995	75 (31–248)	817	Yes	Yes	97%	>25%	100%		
Perez (19)	2003	79 (48–360)	1,345	Yes	Yes	71.4%	>25%	100%		
Salvadori (20)	1997	133.5 (n/a)	2,189	Yes	Yes	95.4%	>25%	100%		
Zafrani (29)	1989	103 (52–301)	424	Yes	n/a	n/a	>25%	100%		
Voogd (30)	2001	117 (n/a)	660	Yes	n/a	n/a	>10%	100%		
Boyages (31)	1990	80 (50–202)	600	Yes	n/a	n/a	>25%	100%		
Leong (21)	2004	80 (n/a)	452	Yes	Yes	77.8%	n/a	100%		Report negative margin
Galper (32)	1999	125 (3–217)	383	Yes	n/a	n/a	n/a	100%		
Voogd (22)	1999	n/a	834	Yes	Yes	48.4%	10 ducts involvement	100%		
Tenea-Cojan (33)	2016	120 (n/a)	303	n/a	n/a	n/a	n/a	100%		
Osteen (34)	1987	60 (n/a)	300	Yes	n/a	n/a	>25%	100%		
Hurd (10)	1997	84 (48–180)	133	Yes	n/a	n/a	>25%	100%		
Fodor (35)	2000	120 (11–120)	415	No	n/a	n/a	>25%	100%		
Recht (36)	1988	63 (3–181)	597	Yes	n/a	n/a	>25%	100%		
Schnitt (37)	1989	75 (49–183)	515	Yes	n/a	n/a	>25%	100%		
Touboul (38)	1999	47 (6–217)	528	Yes	n/a	n/a	>25%	100%		
Veronesi (8)	1995	102 (n/a)	1,637	Yes	n/a	n/a	n/a	100%		
Cannon (23)	2013	61 (n/a)	277	Yes	Yes	94%	n/a	100%		
Lai (39)	2016	82.8 (n/a)	293	No	n/a	n/a	n/a	0%	100%	
Ha (40)	2019	79.9 (7–133)	6,136	n/a	n/a	n/a	>25%	70%		
Gage (24)	1996	109 (n/a)	340	Yes	Yes	61.4%	n/a	100%		Report negative margin
Paterson (25)	1992	44.4 (24–84)	236	Yes	Yes	40%	>25%	100%		
Eberlein (41)	1990	91 (51–212)	783	Yes	n/a	n/a	>25%	100%		
Kim (42)	2011	61 (6–144)	762	n/a	n/a	n/a	n/a	60%		
Schnitt (14)	1994	n/a	157	Yes	Yes	60%	n/a	100%		
Leopold (43)	1989	75 (4–192)	516	Yes	n/a	n/a	>25%	100%		
Kurtz (44)	1990	71 (n/a)	496	Yes	n/a	n/a	>25%	100%		90.3% of patients received adjuvant radiation
Beitsch (26)	2012	60 (0–109)	1,449	Yes	Yes	100%	n/a	100%		

EIC, extensive intraductal component; BCS, breast-conserving surgery; n/a, not applicable.

A



B



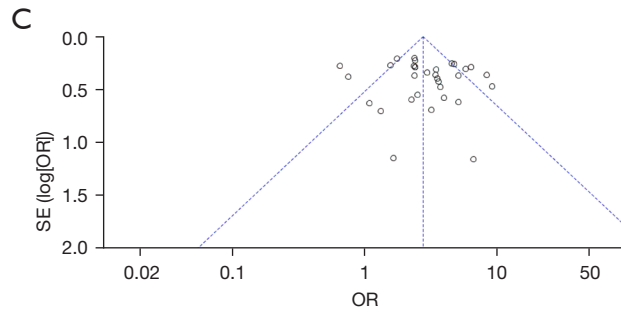


Figure 2 Local recurrence rate in all studies: (A) fixed effects model; (B) random effects model; (C) funnel plot. EIC, extensive intraductal component; SE, standard error; IV, inverse variance; CI, confidence interval; OR, odds ratio.

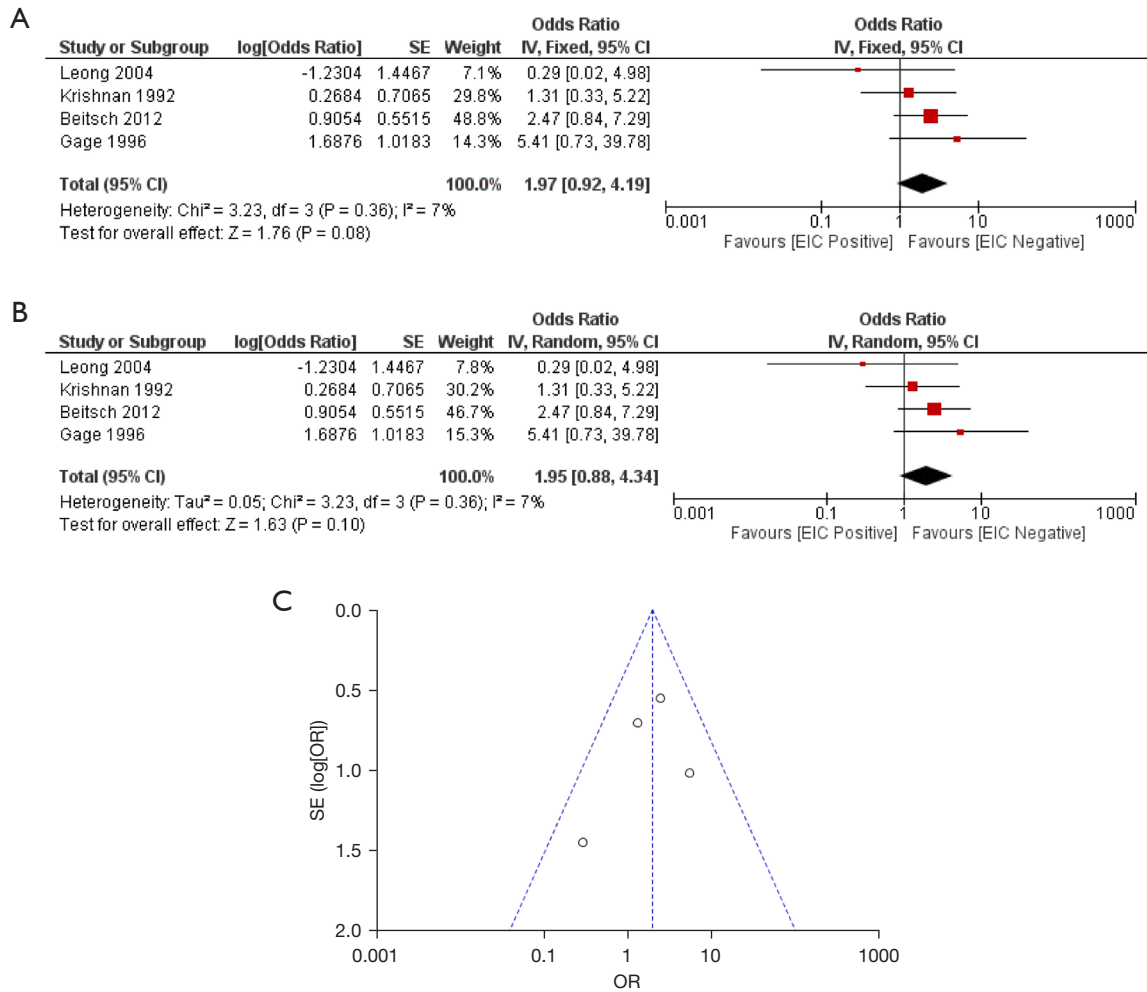


Figure 3 Local recurrence rate in margin negative studies and received adjuvant irradiation: (A) fixed effects model; (B) random effects model; (C) funnel plot. SE, standard error; IV, inverse variance; CI, confidence interval; EIC, extensive intraductal component; OR, odds ratio.

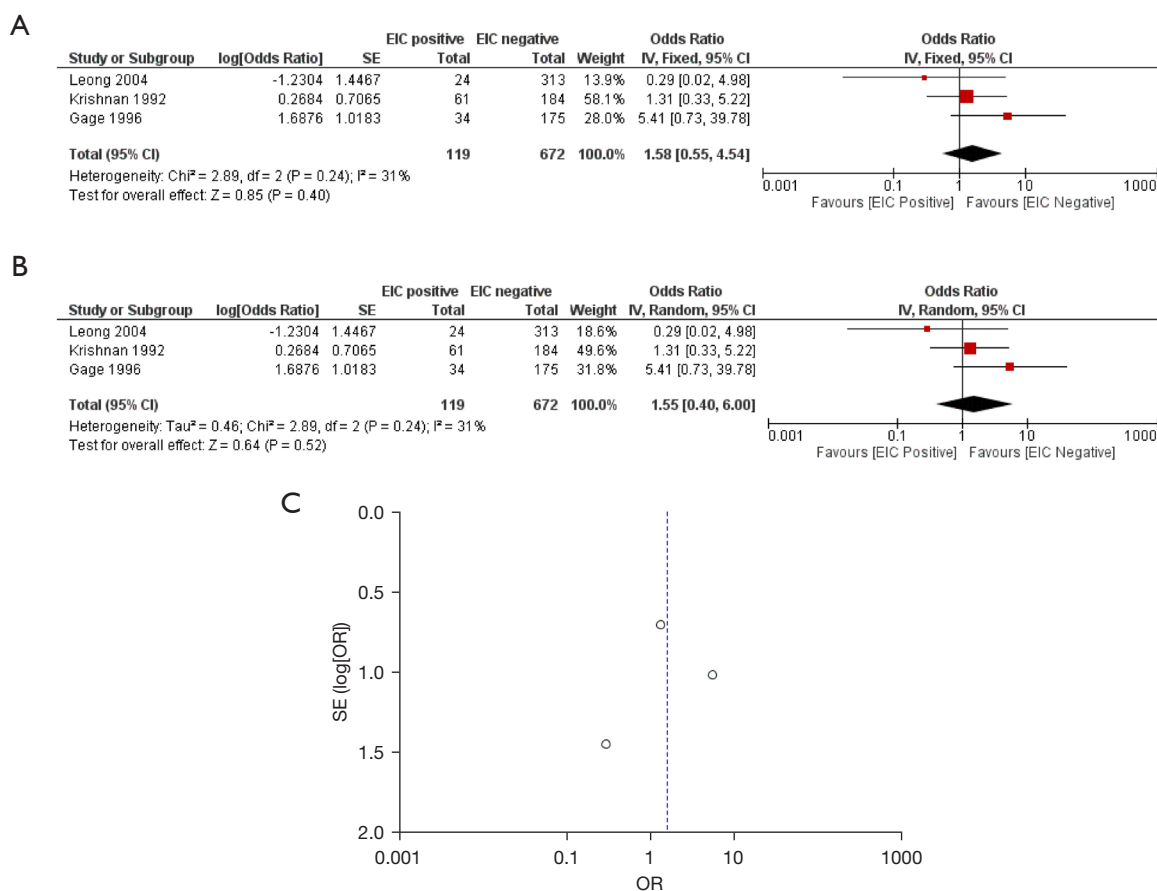


Figure 4 Local recurrence rate in margin negative studies and received whole breast irradiation: (A) fixed effects model; (B) random effects model; (C) funnel plot. EIC, extensive intraductal component; SE, standard error; IV, inverse variance; CI, confidence interval; OR, odds ratio.

additional risk for local relapse apart from negative margin. Thus, we gathered result from current evidence and performed systematic review with meta-analysis to evaluate the impact of EIC on local recurrence

EIC was approximately found in 24–35% of breast cancer patients (46-48). Many studies reported that EIC was a predictor for residual disease after breast-conserving surgery. EIC-positive primary tumors had 38–100% probability of residual disease at re-excision specimens compared to 10–50% probability of carcinoma in the remainder breast in EIC-negative tumors (13,48). Despite the fact that the presence of EIC associated with residual cancer, risk of local recurrence in EIC positive tumor was controversial. Several studies showed that higher local failure rate was higher in patients with EIC (16,44,48). The studies from Kurtz *et al.* and Freedman *et al.* found that breast cancer with EIC increased recurrence rates

regardless of margin status (44,49). Conversely, further studies demonstrated that IBTR rates in the presence of EIC were not greater if negative margins were achieved (10,14). Moreover, the other study showed that recurrence rates in EIC-positive tumor ranged from 21% to 66% in those with close or positive margin and remarkably decreased to 0% to 6% in those with negative margins (12). As aforementioned data, the presence of EIC was currently not a contraindication for breast-conserving therapy with satisfied margin status.

This study is the first meta-analysis which aimed to define the magnitude of EIC impacted on local recurrence of breast cancer. In our study, local recurrence of breast cancer in EIC-positive and EIC-negative tumor was analyzed from all retrospective 32 studies with follow-up period ranged from 44.4 to 133.5 months. The result demonstrated that EIC-positive patients have significantly

higher local recurrence rate than EIC-negative patients according to both fixed and random effect models. However, a heterogeneity was observed among these data, hence we analyzed additional factors that might be specific in increased risk of local recurrence for EIC-positive patients.

Considering margin status, our study demonstrated no statistical difference in local recurrence between EIC-negative and EIC-positive groups who had negative resection margin. Additionally, regarding the studies that reported local relapse in patients who had negative margin and received adjuvant whole breast irradiation, the meta-analysis also showed no statistical difference in local recurrence between EIC-negative and EIC-positive group. A heterogeneity was not detected among these studies. Thus, we could imply that the presence of an EIC did not affect local recurrence of breast cancer if breast-conserving therapy with negative margin can be achieved. Our results were concordant with Society of Surgical Oncology (SSO) and American Society for Radiation Oncology (ASTRO) consensus which recommended no ink on tumor margin was adequate for decrease the rate of IBTR in patients with unfavorable biology, lobular carcinoma or EIC-positive tumors (50). Due to this result, the approaches for obtaining negative margin in EIC-positive patients are necessary and should be recognized in both preoperative and intraoperative assessment.

In terms of preoperative assessment, awareness of EIC-containing lesions is important, and these could be discovered from breast imaging and tissue biopsy. Imaging modalities, which could predict EIC-positive lesions, may guide the extent of resection. Many studies demonstrated that 57.9–65% of lesions, presented with the calcification on mammography with or without a mass, were associated with an EIC, especially when the calcification was greater than 3 cm. Van Goethem *et al.* showed that intraductal spreading in EIC positive carcinoma was predicted 68%, 48.5% and 34.2% by magnetic resonance (MR), mammogram and ultrasound, respectively and pattern of ductal spreading in EIC containing tumors mostly presented as ductal or linear enhancement around a mass from MR. Moreover, a wider excision after MR gained benefit for 86% of patients with invasive carcinoma and EIC (47). Therefore, MR combined with mammogram and ultrasound should be considered for suspicious EIC-coexisting tumors to make the precise surgical planning.

An essential role of core needle biopsy (CNB) is to identify the probability of EIC in surgical specimens.

Several retrospective studies suggested that identification of DCIS with invasive carcinoma on CNB significantly increased the risk of EIC in surgical specimens especially core biopsy tissue comprising more than 45% of the DCIS (51-53). Consequently, this knowledge of DCIS with invasive carcinoma from CNB tissue might facilitate surgeons to increase awareness of EIC during breast-conserving surgery.

Turning to intraoperative period, margin assessment is a critical step to decrease positive margin events. Various types of intraoperative margin assessment including gross evaluation only or microscopic evaluation of the margins have been used, but there were no randomized trials evaluating their efficacy. A meta-analysis of 35 studies demonstrated that frozen section and cytology have the greatest diagnostic accuracy. The sensitivity and specificity were 86% and 96% in frozen section while cytology provided 91% sensitivity and 95% specificity (54). However, these methods have not been generally adopted because they were resource intensive and time consuming. Specimen mammography seemed to be more accessible in some areas. Urano *et al.* showed that digital breast tomosynthesis (DBT) was superior to digital mammography (DM) in terms of EIC detection from breast specimens. In anteroposterior view, 55% and 65% of EIC positive tumors were detected by DM and DBT, respectively (55).

There were several limitations in our study. First, all included studies were retrospective studies which may lead to selection bias. Second, most of the studies did not clarify margin status as well as definition of EIC, resulting in small number of populations to analyze in subgroup analysis. Third, although this study focused on the margin status, adjuvant radiation and type of surgery, the wide range of study periods (1987–2014) might have influenced the efficacy of surgery, radiotherapy and systemic treatment which brought about a great impact on breast cancer recurrence.

Conclusions

This meta-analysis emphasizes that the presence of an EIC significantly relates to increased risk of local recurrence in breast cancer patients, but this cannot be applied in patients who obtain negative resection margin or receive postoperative irradiation, which are currently the standard treatment. To achieve a clear negative margin, accurately predictive tools for EIC-positive lesions, precise estimation in the extent of EIC and suitable localization techniques

for tumor with EIC remain the challenging issues. Further studies in these aspects are required to improve treatment outcomes.

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Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at <https://gs.amegroups.com/article/view/10.21037/gS-23-137/rc>

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <https://gs.amegroups.com/article/view/10.21037/gS-23-137/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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