Research Article

Can a subgroup at high risk for LRR be identified from T1-2 breast cancer with negative lymph nodes after mastectomy? A meta-analysis

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Purpose: To identify a subgroup at high risk for loco-regional recurrence (LRR) from T1-2 breast cancer with negative lymph nodes (N0) after mastectomy by using a meta-analysis.

Methods and materials: Published studies on the relationship between clinical features and LRR of breast cancer were identified from public databases, including PubMed, EMBASE, and the Cochrane Library. High-risk features for LRR in this patient population were defined based on the pooled results of meta-analysis.

Results: For the meta-analysis, a total of 11244 breast cancers with pT1-2N0 after mastectomy from 20 publications were included for analysis. The pooled results indicated that age (hazard ratio (HR) 1.77, \( P = 0.001 \)), lymphovascular invasion (LVI) (HR 2.23, \( P < 0.001 \)), histologic grade (HR 1.66, \( P = 0.001 \)), HER2 status (HR 1.65, \( P = 0.027 \)), menopausal status (HR 1.36, \( P = 0.015 \)), and surgical margins (HR 2.56, \( P = 0.014 \)) were associated with a significantly increased risk of developing LRR in this patient population group, but not for tumor size (HR 1.32, \( P = 0.23 \)), systematic therapy (HR 1.67, \( P = 0.20 \)), and hormonal receptor status (HR 1.04, \( P = 0.73 \)).

Conclusion: In the current study, patients with young age, positive LVI, high histologic grade, HER-2 positive, premenopausal, and positive surgical margins have an increased risk of developing LRR. Further prospective trials are needed to clearly define the role of adjuvant postmastectomy radiotherapy in T1-2N0 breast cancer at high risk of developing LRR.

Introduction

Post-mastectomy radiation therapy (PMRT) has generally not been recommended as a routine part of treatment for T1–T2 breast cancer with negative lymph node (N0) after mastectomy, due to the low loco-regional recurrence (LRR) rates in this patient group as a whole [1,2]. A recent meta-analysis conducted by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) [3] also demonstrated that PMRT did not significantly reduce the 10-year LRR first [3.0% (no RT) versus 1.6% (RT)] in node negative breast patients receiving mastectomy. However, it is becoming increasingly clear that breast cancer represents a heterogeneous group of diseases. And multiple retrospective studies have identified a number of potential risk factors, such as age, tumor size, lymphovascular invasion (LVI), histologic grade, and margin status, for LRR after mastectomy, and patients with certain risk factors might have LRR risks in excess of 20% [4,5]. As a result, patients with multiple risk factors of LRR could derive significant benefit from PMRT in terms of LRR, and a potential survival benefit.

Currently, no consensus has been archived regarding what constitutes ‘high risk’ in the absence of lymph node metastases in this patient group [6,7]. For example, tumor size, histologic grade, and LVI were statistically significant high risk for LRR in T1-2N0 breast cancer after mastectomy in the Truong et al.’s study.
[8,9], while only tumor size, but not for histologic grade and LVI, was regarded as high risk feature for LRR in Mamta
et al.’s study [10]. As a result, we perform the present meta-analysis to pool the controversial results from multiple
included studies, which could increase the statistical power to detect an effect and resolve uncertainty when reports
disagree, and aim to identify risk factors for LRR in T1-2N0 breast cancer after mastectomy by using a meta-analysis.

Materials and methods
We performed the meta-analysis according to the Preferred Reporting Items for Systematic Reviews and
Meta-Analyses (PRISMA) statement guidelines 2009 [11].

Search strategy and study selection
We conducted a comprehensive literature search of public databases including PubMed, EMBASE, and the Cochrane
Library (up to 31 March 2018). Relevant search keywords included the following: 'breast cancer', 'mastectomy',
'loco-regional disease recurrence', and 'lymph node negative'. No language restriction was administered. We also
conducted a manual search of conference proceedings. All results were input into Endnote X8 reference software
(Thomson Reuters, Stamford, CT, U.S.A.) for duplication exclusion and further reference management.

Clinical trials that met the following criteria were included: (1) prospective or retrospective studies involving early
stage (T1-2) breast cancer patients with negative lymph node after mastectomy; (2) available data regarding the re-
relationship between clinical factors and LRR of breast cancer after mastectomy; if multiple publications of the same
trial were retrieved or if there was a case mix between publications, only the most recent publication (and the most
informative) was included.

Data extraction and statistical analysis
Two independent investigators conducted the data abstraction, and any discrepancy between the reviewers was re-
solved by consensus. The following information was extracted for each study: first author’s name, year of publication,
number of enrolled subjects, surgical types, median follow-up, LRR definitions, and LRR rate.

A formal meta-analysis was conducted using Comprehensive Meta Analysis software (Version 2.0). The outcome
data were pooled and reported as hazard ratio (HR). The primary outcome of interest was the relationship between
clinical factors and LRR of breast cancer after mastectomy.

All statistical analyses were performed by using Version 2 of the Comprehensive MetaAnalysis program (Biostat,
Englewood, NJ). Between-study heterogeneity was estimated using the χ²-based Q statistic [12]. The I² statistic was
also calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials. A statistical
test with a P-value less than 0.05 was considered significant. To assess the stability of results, sensitivity analysis was
carried out by sequential omission of individual studies.

Results
We initially found 360 relevant citations in early stage breast cancer. After excluding review articles, Phase I studies,
case reports, editorial, letters, commentaries, meta-analyses, and systematic review (Figure 1), a total of 20 retro-
spective studies were finally included for analysis in the present studies. In all, 11244 breast cancer with pT1-2N0
breast cancers after mastectomy from 20 published studies were included for analysis [4,8–10,13–28]. Table 1 listed
the baseline characteristics of the patients and studies. The incidence of 10-year local recurrence after mastectomy in
pT1-2N0M0 breast cancer ranged from 2.1 to 12.8%, and the high-risk factors of pT1-2N0 breast cancer are listed in
Table 2.

Age
Ten included trials reported the association between age and LRR among pT1-2N0 breast cancer after mastectomy.
The pooled results showed that young breast cancer patients had a significantly increased risk of developing LRR in
comparison with elder patients (HR 1.77, 95% CI: 1.27–2.45, \(P=0.001\), Figure 2). We also did sensitivity analysis to
examine the stability and reliability of pooled HRs by sequential omission of individual studies. The results indicated
that the significance estimate of pooled HRs was not significantly influenced by omitting any single study. Similar
results were observed in subgroup analysis according to median follow-up time (long follow-up: HR 1.45, 95% CI:
1.04–2.00, \(P=0.027\); short follow-up: HR 1.69, 95% CI: 1.43–2.64, \(P<0.001\), Supplementary Figure S1).
Table 1 Baseline characteristics of 20 included studies

| Author/year | Series type | Center | Years | T stage | n   | Age | Surgical type | Chemotherapy, % | Hormone therapy, % | LRR definition | Median follow-up, years | LRR, % |
|-------------|-------------|--------|-------|---------|-----|-----|---------------|-----------------|-------------------|-----------------|------------------------|--------|
| Ahlborn/1988 | R           | Columbia University College | 1975–1985 | T1-2 | 346 | 28–90 | MRM | 0 | 0 | Recurrence on CW | 3.9 | 4-y, 4% |
| Janni et al./2000 | R          | Ludwig-Maximilians-Universitaet | 1963–1996 | T1-2 | 114 | <75 | MRM and AC+PMRT | 0 | NR | Isolated LRR, LRR with or without DF | 6 | 10-y, 14% |
| Voogd/2001 | R           | EORTC and DBCG | 1980–1989 | T1-2 | 804 | <75 | MRM and AC I/II | 0 | NR | Isolated LRR, LRR with or without DF | 9.8 | 10-y, 9% |
| Wallgren et al./2003 | R         | IBCSG trials | 1981–1985 | T1-3 (T3 2.1%) | 1275 | NR | MRM | 66 | NR | Isolated LRR, LRR with or without DF | 14.5 | 10-y, 12.8% |
| Coletti et al./2005 | R          | IBCSG trials | 1978–1999 | T1-3 | 2588 | Median: 54 | M and AC | 67 | 0 | Isolated LRR, LRR with or without DF | 11 | 10-y, 10% |
| Truong et al./2005 | R          | BCCA | 1989–1999 | T1-2 | 1505 | 24–95 | M | 14.1 | 29.9 | LRR with or without DF | 7 | 10-y, 7.8% |
| Jaggi et al./2005 | R          | MGH | 1980–2000 | T1-3 (T3 2.85%) | 874 | Any | MRM and AC | 8.4 | 16.9 | Isolated LRR, LRR with or without DF | 8.3 | 10-y, 6% |
| Truong et al./2005 | R          | BCCA | 1989–1999 | T1-2 | 763 | 24–89 | M | 27.8 | 59 | LRR with or without DF | 7 | NR |
| Buchanan/2006 | P           | MSCC | 1995–1999 | T1 | 325 | Any | M and AC I/II | NR | NR | Isolated LRR, LRR with or without DF | 6 | 5-y, 4% |
| Yildirim et al./2007 | R          | Ankara Oncology Training and Research Hospital | 1990–2004 | T1-2 | 502 | <70 | MRM and AC I/III | 56 | 43 | Isolated LRR | 6.4 | 10-y, 3% |
| Karlsson et al./2007 | R          | IBCSG trials | 1978–1999 | T1-3 | 2588 | NR | M and AC, adjuvant systematic therapy | NR | NR | Isolated LRR, LRR with or without DF | 14 | 10-y, 10% |

Continued over
Table 1 Baseline characteristics of 20 included studies (Continued)

| Author/year | Series type | Center | Years | T stage | n | Age | Surgical type | Chemotherapy, % | Hormone therapy, % | LRR definition | Median follow-up, years | LRR, % |
|-------------|-------------|--------|-------|---------|---|-----|---------------|-----------------|------------------|----------------|----------------------|-------|
| Mamouna et al./2010 | R | B-14-B-20 | 1982–1993 | T1-3 (T3 5%) | 505 | NR | M | 0 | 100 | Isolated LRR | 12.5 | 10-y; 6.1% |
| Sharma et al./2010 | R | M.D. Anderson Cancer Center | 1997–2002 | T1-2 | 753 | NR | M | NR | NR | Isolated LRR, LRR with or without DF | 7.47 | 10-y; 2.1% |
| Abi-Raad et al./2011 | R | MGH | 1980–2004 | T1-2 | 1136 | Any | MRM and AC | 6.8 | 23.8 | Isolated LRR, LRR with or without DF | 9 | 10-y; 5.2% |
| Selz et al./2012 | R | Hopital Rene Huguenin | 2001–2006 | T1-3 (3.5% T3) | 191 | Median: 56 | MRM and AC I/II+PMRT | 68.1 | 73.3 | LRRFS | 4.7 | 5-y; 2.1% |
| | | | | | | | | | | | | |
| Truong et al./2014 | R | BCCA and MGH | 1998–2009 | T1-2 | 1994 | 22-97 | M | 11.5 | 48.2 | Isolated LRRFS (excluded if DF within 4 months of LRR) | 4.3 | 5-y; 1.75% |
| Jwa et al./2015 | R | Soonchunhyang University College of Medicine | 2002–2011 | T1-2 | 390 | 37-87 | MRM and AC | 47.60% | NR | Isolated LRR, LRR with or without DF | 5.6 | 5-y; 2.6% |
| Li et al./2017 | R | Fujian Medical University Cancer Hospital | 2001–2006 | T1-2 | 353 | NR | MRM and AC | NR | NR | Isolated LRR, LRR with or without DF | 9.6 | 5-y; 11% |
| Mamtani et al./2017 | R | MSKCC | 2006–2011 | T1-2 | 657 | 33-86 | M | 14% | 32% | Isolated LRR, LRR with or without DF | 5.6 | 5-y; 4.7% |
| Frandsen et al./2017 | R | Huntsman Cancer Hospital | 1978–2014 | T1-2 | 38 | 25–40 | MRM and AC+PMRT | 55.30% | 2.60% | Isolated LRR, LRR with or without DF | 6 | 10-y 0% |
| | | | | | | | | | | | | |

Abbreviations: AC, axillary clearance (followed by levels cleared); BCCA, British Columbia Cancer Agency; DF, distant failure; IBCSG, International Breast Cancer Study Group; LRRFS, LRR-free survival; M, mastectomy; MGH, Massachusetts General Hospital; MRM, modified radical mastectomy; MSKCC, Memorial Sloan Cancer Center; NR, not reported; P, prospective; R, retrospective.
LVI

Twelve studies contributed to the pooled analysis. Breast cancer patients with positive LVI were associated with a significantly increased risk of developing LRR compared with negative LVI (HR 2.23, 95% CI: 1.87–2.65, \( P < 0.001 \), Figure 3). No significant heterogeneity across the studies was detected (\( I^2 = 0; P = 0.37 \)). Sensitivity analysis indicated...
Table 2 LRR after mastectomy in T1-2 N0 breast cancer

| Author/year          | Overall: LRR | High-risk: 10-year LRR | Low risk: 10-year LRR | High-risk definition | Low-risk definition |
|----------------------|--------------|------------------------|-----------------------|----------------------|---------------------|
| Ahlborn/1998         | 4-year, 4%   | NR                     | NR                    | NR                   | NR                  |
| Janni et al./2000    | 5-year, 8.8% | NR                     | NR                    | NR                   | NR                  |
| Voogd/2001           | 10-year, 9%  | 15%                    | 8%                    | LVI, no LVI          | No LVI              |
| Wallgren et al./2003 (premenopausal) | 10-year, 12.8% | 16%                   | 8%                    | LVI, T ≥ 2 cm        | No LVI, T < 2 cm    |
| Wallgren et al./2003 (postmenopausal) | 10-year, 10% | 19%                   | 8%                    | LVI                  | No LVI              |
| Colleoni et al./2005 | 10-year, 10% | NR                     | NR                    | NR                   | NR                  |
| Truong et al./2005   | 10-year, 7.8% | 21.20%                 | 4.50%                 | LVI, grade 3         | grade 1–2, age ≥ 50 |
| Truong et al./2005   | NR           | 7-year, 19.5%          | 7 year, 3.4%          | LVI, age < 50        | No LVI, age ≥ 50    |
| Jagisi et al./2005   | 10-year, 6%  | 10.0%, 17.9%, 40.6%   | 1.20%                 | close margins, T > 2 cm, premenopausal, and LVI | No risk factor |
| Buchanan/2006        | 5-year, 4%   | NR                     | NR                    | age ≤ 35, LVI, and multi-centrity | No risk |
| Karlsson et al./2007 (premenopausal) | 14-year, 12.5% | 14.70%                 | 10.90%                | 1–10 uninvolved nodes | ≥ 19 uninvolved nodes |
| Karlsson et al./2007 (postmenopausal) | 14-year, 8.2% | 11.60%                | 6.20%                 | 1–10 uninvolved nodes | ≥ 19 uninvolved nodes |
| Yildirim et al./2007 (≤ 40 years) | 10-year, 3% | NR                     | NR                    | T ≥ 2 cm and LVI     | 0–1 risk factor |
| Yildirim et al./2007 (> 40) | NR | NR | NR | T ≥ 3 cm, high grade, and LVI | 0–2 risk factors |
| Mamouna et al./2010  | 10-year, 6.1% | 16.80%                 | 2.30%                 | high 21-gene recurrence score | Low 21-gene recurrence score |
| Sharma et al./2010   | 10-year, 2.1% | 18.60%                 | 1.00%                 | T2, ≤ 40 years       | T1-2, > 40 years |
| Abi-Raad et al./2011 | 10-year, 5.2% | 19.70%                 | 3.30%                 | LVI, positive margins, T ≥ 2 cm, age ≤ 50 years | Low LVI, age ≥ 50, negative margins, size < 2 cm, systemic therapy |
| Selz et al./2012     | 5-year, 2.6% | 5-year, 15.1%          | 5-year, 2.6%          | Ki67 > 20%           | Ki67 ≤ 20%          |
| Truong et al./2014   | 5-year, 1.75% | 5-year, 12.5%         | 5-year, 1.1%          | TNBC, close or positive margins | Negative margin, luminal; |
| Jwa et al./2015      | 5-year, 2.6% | 5-year, 14%           | 5-year, 0%, 5% for 0 and 1 risk factors | age ≥ 50, systematic chemotherapy (2 risk factors) | 0–1 risk factors |
| Li et al./2017       | 5-year 11%    | 5-year, 24.3%        | 5-year, 8.4%          | Age ≥ 40 years, T ≥ 4.5 cm, number of resected nodes ≤ 10 | 0–1 risk factor |
| Mamtani et al./2017  | 5-year 4.7%, 5.3% | 5-year, 9.4% for ≥ 4 risk factors | 3.80%            | age ≥ 40 years, multifocal or multicentric tumor, LVI, central or medial tumor location, and high nuclear grade (≥ 2 risk factors) | 0–2 risk factor |
| Frandsen et al./2017 | 10-year 10% | 28.00%                | 6.70%                 | LVI                  | No LVI              |

Abbreviations: AC, axillary clearance (followed by levels cleared); BCCA, British Columbia Cancer Agency; DF, distant failure; IBCSG, International Breast Cancer Study Group; LRRFS, LRR-free survival; MGH, Massachusetts General Hospital; M, mastectomy; MRM, modified radical mastectomy; MSKCC, Memorial Sloan Cancer Center; NR, not reported; P, prospective; R, retrospective.

that the significance estimate of pooled HRs was not significantly influenced by omitting any single study. Similar results were observed in subgroup analysis according to median follow-up time (long follow-up: HR 2.21, 95% CI: 1.76–2.77, P < 0.001; short follow-up: HR 2.25, 95% CI: 1.71–2.96, P < 0.001, Supplementary Figure S2).

**Histologic grade**

Nine studies contributed to the pooled analysis. Breast cancer patients with Grade 3 histologic type were associated with a significantly increased risk of developing LRR when compared with Grades 1–2 histologic type (HR 1.66, 95% CI: 1.26–2.19, P < 0.001, Figure 4). No heterogeneity across the studies was detected. Sensitivity analysis indicated...
that the significance estimate of pooled HRs was not significantly influenced by omitting any single study. Similar results were observed in subgroup analysis according to median follow-up time (long follow-up: HR 1.63, 95% CI: 1.35–1.98, \(P<0.001\); short follow-up: HR 1.45, 95% CI: 1.02–2.09, \(P=0.041\), Supplementary Figure S3).

**HER-2 status**

In five studies, data about HER-2 status and LRR risk were available. Breast cancer with positive HER-2 status was associated with an increased risk of developing LRR in comparison with negative HER-2 status (HR 1.65, 95% CI: 1.06–2.58, \(P=0.027\), Figure 5). Significant heterogeneity was observed. Sensitivity analysis indicated that the significance estimate of pooled HRs was significantly influenced by omitting any single study.

**Menopausal status**

Five studies contributed to the pooled analysis. Our results showed that menopausal status was significantly associated with LRR in T1-2N0 breast cancer patients. Premenopausal breast cancer was associated with an increased risk of developing LRR in comparison with postmenopausal breast cancer patients (HR 1.36, 95% CI: 1.06–1.74, \(P=0.015\),
Figure 5. Meta-analysis of LRR rate in HER2 positive versus HER2 negative 

Supplementary Figure S4). Significant heterogeneity was observed. Sensitivity analysis indicated that the significance estimate of pooled HRs was significantly influenced by omitting any single study.

**Surgical margins**

In three studies with surgical data available, breast cancer with positive/close surgical margins was associated with an increased risk of developing LRR in comparison with negative surgical margins (HR 2.56, 95% CI: 1.21–5.41, \(P = 0.014\), Supplementary Figure S5). Significant heterogeneity was observed. Sensitivity analysis indicated that the significance estimate of pooled HRs was significantly influenced by omitting any single study.

**Systematic therapy**

Eight studies contributed to the pooled analysis. There was no significant risk difference of LRR in breast cancer receiving systematic therapy (chemotherapy/hormonal therapy) or not (HR 1.67, 95% CI: 0.77–3.50, \(P = 0.20\), Supplementary Figure S6). Significant heterogeneity was observed.

**Tumor size**

Thirteen studies contributed to the pooled analysis. Tumor size was not a significant risk factor for LRR in T1-2 breast cancer with negative lymph node after mastectomy (HR 1.32, 95% CI: 0.85–2.05, \(P = 0.23\), Supplementary Figure S7). No significant heterogeneity was observed.

**Hormonal receptor status**

Thirteen studies contributed to the pooled analysis. Hormonal receptor status was not a significant risk factor for LRR in T1-2 breast cancer with negative lymph node after mastectomy (HR 1.04, 95% CI: 0.76–1.44, \(p = 0.73\), Supplementary Figure S8). No significant heterogeneity was observed.

**Discussion**

Of note, the management of early-stage women with breast cancer after mastectomy is a heterogeneous disease because different subgroups demonstrate significant variation in the risk for recurrence and survival, and in selected women with high risks; the 5-year LRR can be as high as 20% [29,30]. It has been reported that effective local control is associated with improved overall survival, especially for early-stage breast cancer patients [31]. As a result, accurately predicting the women who are at highest risk for recurrence after mastectomy will identify those who might benefit from more aggressive locally adjuvant treatment. During the past decades, although multiples studies have been conducted to investigate the risk factors associated with local recurrence in T1-2 N0 breast cancer after mastectomy, but the results are controversial. In 2005, the ninth St Gallen expert panel agreed that radiation therapy could reduce replacement in the early breast cancer after breast conserving surgery, and the balance between beneficial and harmful effects of PMRT depends on the risk of local recurrence [32], the age of the patient, the efficacy of systemic therapies (especially endocrine agents) and competing causes of morbidity and mortality. However, no quantitative evaluations of clinic-pathological risk features of LRR have been previously investigated. As a result, we conduct the
present meta-analysis to comprehensively evaluate the risk factors for local recurrence in early-stage breast cancer after mastectomy.

To the best of our knowledge, our meta-analysis is the largest and most comprehensive systematic review to specifically investigate risk factors for local recurrence in pT1-2 N0 breast cancer after mastectomy. A total of 11244 pT1-2 breast cancers with negative lymph nodes after mastectomy from 15 publications were included for analysis. The pooled results have demonstrated that T1-2 breast cancer with positive LVI (HR 2.23, \( P < 0.001 \)) or surgical margins (HR 2.56, \( P = 0.014 \)) has increased twice the risk of developing LRR. Consistent with our findings, previous research even found that the LRR of patients with negative lymph node disease and LVI who do not receive PMRT is worse than that of patients with node-positive disease receiving adjuvant radiotherapy [33]. Additionally, the ninth St Gallen expert panel also accepted LVI as a discriminatory feature of increased risk for T1-2 breast cancer with negative lymph node. As for the risk of patients with a close or positive surgical margin after mastectomy, most of published data identified a close or positive surgical margin would increase the risk of chest wall failure [34,35]. In clinical practice today, patients with a close or positive surgical margin after mastectomy are likely to be treated with chest wall irradiation. Our study also suggests that age (HR 1.77, \( P = 0.001 \)), histologic grade (HR 1.66, \( P < 0.001 \)), HER2 status (HR 1.65, \( P = 0.027 \)), menopausal status (HR 1.36, \( P = 0.015 \)) are risk predictors for LRR in this patient population group.

Several previous research have reported different results in terms of systemic chemotherapy as a risk factor for LRR. Truong et al. [8] found that no systemic therapy was associated with increased risk of LRR compared with systemic therapy (14.1% chemotherapy alone, 29.9% hormone therapy alone, 6.7% both) in patients with pT1-2N0 cancer (HR 1.87; \( P = 0.01 \)), while Wallgren et al. [25] analyzed 1275 patients with node-negative disease and found that the LRR risk increased significantly without adjuvant chemotherapy. In the present study, the pooled results showed that systematic therapy (HR 1.67, \( P = 0.20 \)) is not a significant risk factor for LRR. The implications of tumor size and hormonal receptor status on recurrence remain controversial. For example, Abi-Raad et al. [15] reported tumor size is associated with increased LRR risk, while it is not a significant risk factor in Iwa et al. study [27]. In the present study, both tumor size (HR 1.32, \( P = 0.23 \)) and hormonal receptor status (HR 1.04, \( P = 0.73 \)) are not significantly associated with LRR in breast cancer after mastectomy. Consistent with our pooled results, the ninth St Gallen expert panel also regarding age, histologic grade, LVI, and HER2 status as risk factors to identify node negative early breast cancer patients at high risk for LRR [32]. Based on these findings, for early-stage breast cancer with high risk for local recurrence, such as young age, high histologic grade, positive LVI positive, premenopausal and/or positive surgical margins, additional adjuvant local therapy might be warranted for this patient population group in order to reduce the LRR risk.

There are several limitations that need to be mentioned. First, this is a meta-analysis at study level, thus individual patient information is not available from the publication. Second, the application of formal meta-analytic methods to observational studies has been controversial. One of the most important reasons for this is that the designs and populations of the studies are diverse, and that these differences may influence the pooled estimates. However, when no head-to-head comparison data are available for combination therapy versus mono-therapy, a meta-analysis of observational studies is one of the few methods for assessing risk factors for local recurrence. Third, all included studies are retrospective clinical studies, treatment regimen and follow-up time of included patients are significantly different, thus all of these would increase the heterogeneity among included studies.

**Conclusion**

Despite these limitations, the result of this meta-analysis for the first time clearly demonstrates that early breast patients after mastectomy with young age, positive LVI, high histologic grade, HER-2 positive, premenopausal, and/or surgical margins positive have an increased risk of developing LRR, and additional local radiotherapy might be warranted for this subset group population. Further prospective trials are needed to clearly define the role of adjuvant postmastectomy radiotherapy in pT1-2N0 breast cancer with high risk for developing LRR.

**Author Contribution**

F.Y. and G.P. were responsible for study design. Z.Z. and M.J. were responsible for literature search. F.Y. and Z.Z. were responsible for data extraction. G.P. and M.J. were responsible for data analysis. F.Y. was responsible for drafting the manuscript. All authors approved the final version of the manuscript.

**Competing Interests**

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Abbreviations
HR, hazard ratio; LRR, loco-regional recurrence; LVI, lymphovascular invasion; PMRT, post-mastectomy radiation therapy; RT, radiation therapy; 95% CI, 95% confidence interval.

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