

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

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[8,9], while only tumor size, but not for histologic grade and LVI, was regarded as high risk feature for LRR in Mamtani 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 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 resolved 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 χ^2 -based Q statistic [12]. The I^2 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 retrospective 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	1963–1998	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	0	NR	Isolated LRR, LRR with or without DF	9.8	10-y, 4%
Wallgren et al./2003	R	IBCSG trials	1981–1985	T1-3 (T3 2.1%)	535	<70	MRM and AC I/II	NR	NR	Isolated LRR, LRR with or without DF	14.5	10-y, 9%
Colleoni et al./2005	R	IBCSG trials	1978–1999	T1-3	1275	NR	MRM	66	NR	Isolated LRR, LRR with or without DF, DF	11	10-y, 12.8%
Truong et al./2005	R	BCCA	1989–1999	T1-2	2588	Median: 54	M and AC	67	0	Isolated LRR, LRR with or without DF	7	10-y, 10%
Jagsi et al./2005	R	MGH	1989–1999	T1-2	1505	24–95	M	14.1	29.9	LRR with or without DF	8.3	10-y, 7.8%
Jagsi et al./2005	R	MGH	1980–2000	T1-3 (T3 2.85%)	877	Any	MRM and AC	8.4	16.9	Isolated LRR, LRR with or without DF	7	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	6	NR
Buchanan/2006	P	MSCC	1995–1999	T1	325	Any	M and AC I/II	NR	NR	Isolated LRR, LRR with or without DF	6.4	5-y, 4%
Yildirim et al./2007	R	Ankara Oncology Training and Research Hospital	1990–2004	T1-2	502	<70	MRM and AC I/II/III	56	43	Isolated LRR	14	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	Hoôpital René Huguenin	2001–2008	T1-3 (3.5% T3)	191	Median: 56	MRM and AC /II+PMRT	68.1	73.3	LRRFS	4.7	5-y, 2.1%
					508	Median: 63	MRM and SLNB	20.5	62.6			5-y, 2.6%
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	2001–2008	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%
					181	18–40	MRM and AC	35.90%	12.70%	Isolated LRR, LRR with or without DF	4.6	10-y 10%

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.

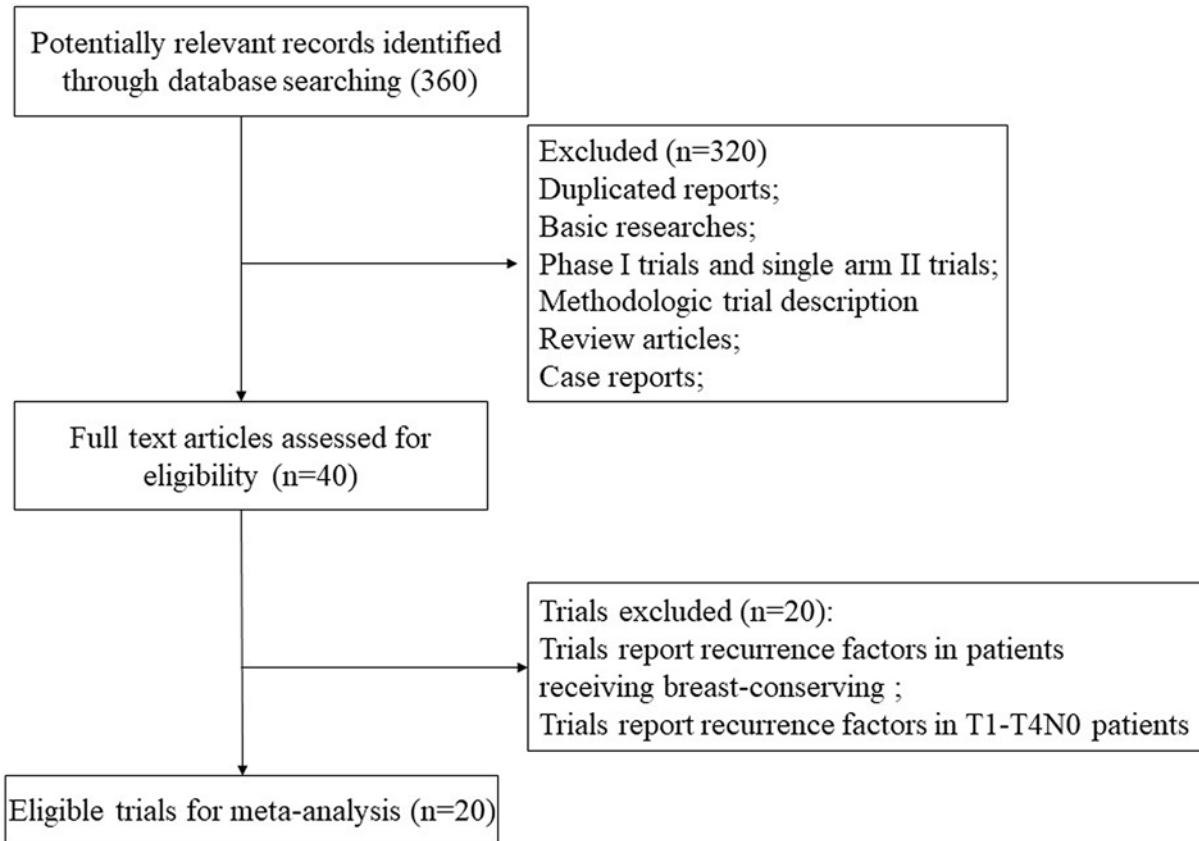


Figure 1. PRISMA flow diagram

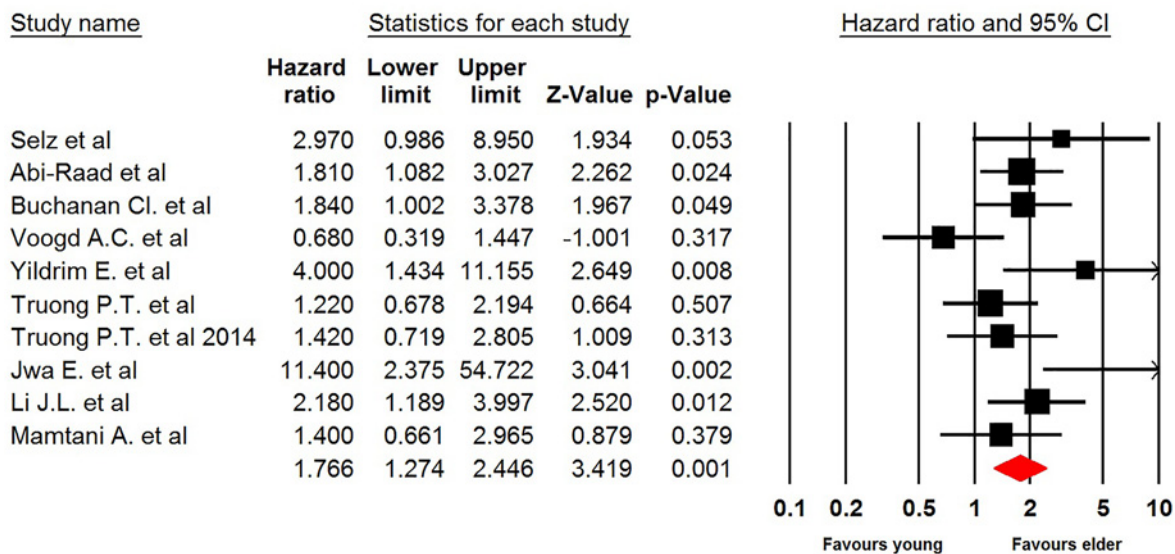


Figure 2. Meta-analysis of LRR rate in young versus elder patients

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	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
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)		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
Jagsi et al./2005	10-year, 6%	10.0%, 17.9%, 40.6% for 1, 2 and 3 risk factors	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-centricity	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	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	No LVI, age >50, negative margins, size <2 cm, systemic therapy
Selz et al./2012	5-year 2.6%	5-year, 15.1% ¹	5-year, 2.6% ¹	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% ¹	5-year, 0%, 5% for 0 and 1 risk ¹ 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.

¹ Actuarial failure rate or calculated from local disease-free survival obtained by Kaplan–Meier method rather than cumulative incidence of LRR.

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

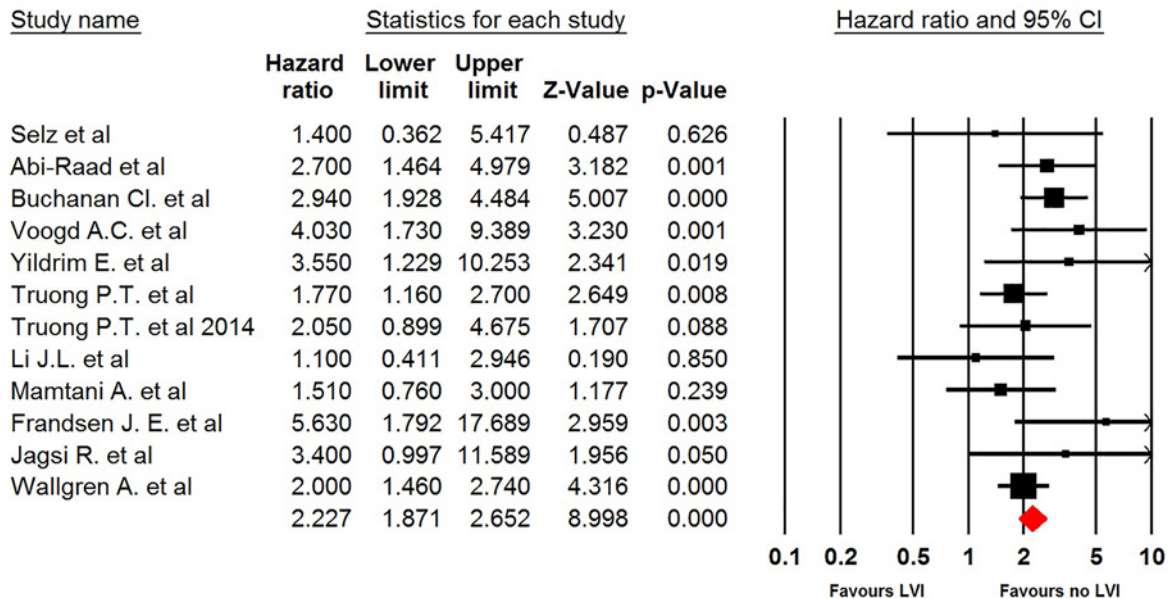


Figure 3. Meta-analysis of LRR rate in LVI versus no LVI

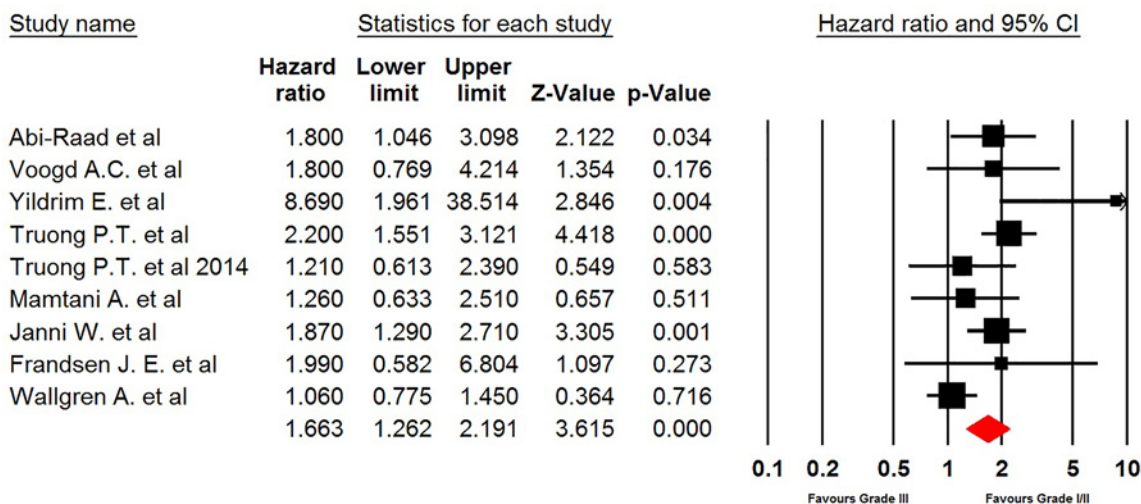


Figure 4. Meta-analysis of LRR rate in Grade III versus Grade I/II

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, $P = 0.015$,

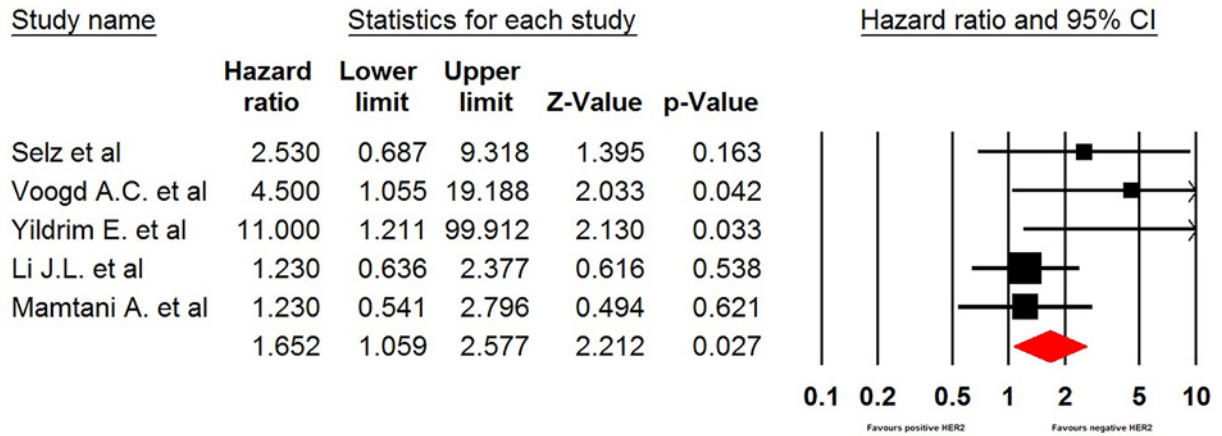


Figure 5. Meta-analysis of LRR rate in HER2 positive versus HER2 negative

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 specially 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 Jwa 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

The authors declare that there are no competing interests associated with the manuscript.

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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.

References

- Schoenfeld, J.D. and Harris, J.R. (2011) Abbreviated course of radiotherapy (RT) for breast cancer. *Breast* **20**, S116–S127, [https://doi.org/10.1016/S0960-9776\(11\)70308-3](https://doi.org/10.1016/S0960-9776(11)70308-3)
- Cheng, S.H., Horng, C.F., Clarke, J.L. et al. (2006) Prognostic index score and clinical prediction model of local regional recurrence after mastectomy in breast cancer patients. *Int. J. Radiat. Oncol. Biol. Phys.* **64**, 1401–1409, <https://doi.org/10.1016/j.ijrobp.2005.11.015>
- McGale, P., Taylor, C., Ebcctg et al. (2014) Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* **383**, 2127–2135, [https://doi.org/10.1016/S0140-6736\(14\)60488-8](https://doi.org/10.1016/S0140-6736(14)60488-8)
- Buchanan, C.L., Dorn, P.L., Fey, J. et al. (2006) Locoregional recurrence after mastectomy: incidence and outcomes. *J. Am. Coll. Surg.* **203**, 469–474, <https://doi.org/10.1016/j.jamcollsurg.2006.06.015>
- Childs, S.K., Chen, Y.H., Duggan, M.M. et al. (2012) Surgical margins and the risk of local-regional recurrence after mastectomy without radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* **84**, 1133–1138, <https://doi.org/10.1016/j.ijrobp.2012.02.048>
- Vila, J., Teshome, M., Tucker, S.L. et al. (2017) Combining clinical and pathologic staging variables has prognostic value in predicting local-regional recurrence following neoadjuvant chemotherapy for breast cancer. *Ann. Surg.* **265**, 574–580, <https://doi.org/10.1097/SLA.0000000000001492>
- Hunt, K.K., Ballman, K.V., McCall, L.M. et al. (2012) Factors associated with local-regional recurrence after a negative sentinel node dissection: results of the ACOSOG Z0010 trial. *Ann. Surg.* **256**, 428–436, <https://doi.org/10.1097/SLA.0b013e3182654494>
- Truong, P.T., Lesperance, M., Culhaci, A., Kader, H.A., Speers, C.H. and Olivotto, I.A. (2005) Patient subsets with T1–T2, node-negative breast cancer at high locoregional recurrence risk after mastectomy. *Int. J. Radiat. Oncol. Biol. Phys.* **62**, 175–182, <https://doi.org/10.1016/j.ijrobp.2004.09.013>
- Truong, P.T., Yong, C.M., Abnoui, F. et al. (2005) Lymphovascular invasion is associated with reduced locoregional control and survival in women with node-negative breast cancer treated with mastectomy and systemic therapy. *J. Am. Coll. Surg.* **200**, 912–921, <https://doi.org/10.1016/j.jamcollsurg.2005.02.010>
- Mamtani, A., Patil, S., Stempel, M.M. and Morrow, M. (2017) Are there patients with T1 to T2, lymph node-negative breast cancer who are “high-risk” for locoregional disease recurrence? *Cancer* **123**, 2626–2633, <https://doi.org/10.1002/cncr.30658>
- Liberati, A., Altman, D.G., Tetzlaff, J. et al. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* **339**, b2700, <https://doi.org/10.1136/bmj.b2700>
- Zintzaras, E. and Ioannidis, J.P. (2005) Heterogeneity testing in meta-analysis of genome searches. *Genet. Epidemiol.* **28**, 123–137, <https://doi.org/10.1002/gepi.20048>
- Sharma, R., Bedrosian, I., Lucci, A. et al. (2010) Present-day locoregional control in patients with t1 or t2 breast cancer with 0 and 1 to 3 positive lymph nodes after mastectomy without radiotherapy. *Ann. Surg. Oncol.* **17**, 2899–2908, <https://doi.org/10.1245/s10434-010-1089-x>
- Frandsen, J.E., Cannon, G., Kokeny, K.E. et al. (2018) Is radiation indicated for young women with early stage, node-negative breast cancer after mastectomy? A multi-institution, retrospective review. *Breast J.* **24**, 7–11, <https://doi.org/10.1111/tbj.12827>
- Abi-Raad, R., Boutrus, R., Wang, R. et al. (2011) Patterns and risk factors of locoregional recurrence in T1–T2 node negative breast cancer patients treated with mastectomy: implications for postmastectomy radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* **81**, e151–e157, <https://doi.org/10.1016/j.ijrobp.2011.01.015>
- Jagsi, R., Raad, R.A., Goldberg, S. et al. (2005) Locoregional recurrence rates and prognostic factors for failure in node-negative patients treated with mastectomy: implications for postmastectomy radiation. *Int. J. Radiat. Oncol. Biol. Phys.* **62**, 1035–1039, <https://doi.org/10.1016/j.ijrobp.2004.12.014>
- Janni, W., Dimpfl, T., Braun, S. et al. (2000) Radiotherapy of the chest wall following mastectomy for early-stage breast cancer: impact on local recurrence and overall survival. *Int. J. Radiat. Oncol. Biol. Phys.* **48**, 967–975, [https://doi.org/10.1016/S0360-3016\(00\)00743-4](https://doi.org/10.1016/S0360-3016(00)00743-4)
- Selz, J., Stevens, D., Jouanneau, L., Labib, A. and Le Scodan, R. (2012) Prognostic value of molecular subtypes, ki67 expression and impact of postmastectomy radiation therapy in breast cancer patients with negative lymph nodes after mastectomy. *Int. J. Radiat. Oncol. Biol. Phys.* **84**, 1123–1132, <https://doi.org/10.1016/j.ijrobp.2012.02.047>
- Truong, P.T., Sadek, B.T., Lesperance, M.F. et al. (2014) Is biological subtype prognostic of locoregional recurrence risk in women with pT1–2N0 breast cancer treated with mastectomy? *Int. J. Radiat. Oncol. Biol. Phys.* **88**, 57–64, <https://doi.org/10.1016/j.ijrobp.2013.09.024>
- Yildirim, E. and Berberoglu, U. (2007) Can a subgroup of node-negative breast carcinoma patients with T1–2 tumor who may benefit from postmastectomy radiotherapy be identified? *Int. J. Radiat. Oncol. Biol. Phys.* **68**, 1024–1029, <https://doi.org/10.1016/j.ijrobp.2007.01.015>
- Colleoni, M., Zahrieh, D., Gelber, R.D. et al. (2005) Site of primary tumor has a prognostic role in operable breast cancer: the international breast cancer study group experience. *J. Clin. Oncol.* **23**, 1390–1400, <https://doi.org/10.1200/JCO.2005.06.052>
- Karlsson, P., Cole, B.F., Price, K.N. et al. (2007) The role of the number of uninvolved lymph nodes in predicting locoregional recurrence in breast cancer. *J. Clin. Oncol.* **25**, 2019–2026, <https://doi.org/10.1200/JCO.2006.09.8152>
- Mamounas, E.P., Tang, G., Fisher, B. et al. (2010) Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. *J. Clin. Oncol.* **28**, 1677–1683, <https://doi.org/10.1200/JCO.2009.23.7610>

- 24 Voogd, A.C., Nielsen, M., Peterse, J.L. et al. (2001) Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. *J. Clin. Oncol.* **19**, 1688–1697, <https://doi.org/10.1200/JCO.2001.19.6.1688>
- 25 Wallgren, A., Bonetti, M., Gelber, R.D. et al. (2003) Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. *J. Clin. Oncol.* **21**, 1205–1213, <https://doi.org/10.1200/JCO.2003.03.130>
- 26 Li, J.L., Lin, X.Y., Zhuang, L.J. et al. (2017) Establishment of a risk scoring system for predicting locoregional recurrence in T1 to T2 node-negative breast cancer patients treated with mastectomy: Implications for postoperative radiotherapy. *Medicine (Baltimore)*. **96**, e7343, <https://doi.org/10.1097/MD.00000000000007343>
- 27 Jwa, E., Shin, K.H., Lim, H.W. et al. (2015) Identification of risk factors for locoregional recurrence in breast cancer patients with nodal stage N0 and N1: who could benefit from post-mastectomy radiotherapy? *PLoS ONE* **10**, e0145463, <https://doi.org/10.1371/journal.pone.0145463>
- 28 Ahlborn, T.N., Gump, F.E., Bodian, C., Habif, D.V. and Kister, S. (1988) Tumor to fascia margin as a factor in local recurrence after modified radical mastectomy. *Surg. Gynecol. Obstet.* **166**, 523–526
- 29 Rowell, N.P. (2009) Radiotherapy to the chest wall following mastectomy for node-negative breast cancer: a systematic review. *Radiother. Oncol.* **91**, 23–32, <https://doi.org/10.1016/j.radonc.2008.09.026>
- 30 Overgaard, M., Hansen, P.S., Overgaard, J. et al. (1997) Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N. Engl. J. Med.* **337**, 949–955, <https://doi.org/10.1056/NEJM199710023371401>
- 31 Skinner, H.D., Strom, E.A., Motwani, S.B. et al. (2013) Radiation dose escalation for loco-regional recurrence of breast cancer after mastectomy. *Radiat. Oncol.* **8**, 13, <https://doi.org/10.1186/1748-717X-8-13>
- 32 Goldhirsch, A., Glick, J.H., Gelber, R.D. et al. (2005) Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. *Ann. Oncol.* **16**, 1569–1583, <https://doi.org/10.1093/annonc/mdi326>
- 33 Sundquist, M., Thorstenson, S., Klintonberg, C., Brudin, L. and Nordenskjold, B. (2000) Indicators of loco-regional recurrence in breast cancer. The South East Swedish Breast Cancer Group. *Eur. J. Surg. Oncol.* **26**, 357–362, <https://doi.org/10.1053/ejso.1999.0898>
- 34 Freedman, G.M., Fowble, B.L., Hanlon, A.L. et al. (1998) A close or positive margin after mastectomy is not an indication for chest wall irradiation except in women aged fifty or younger. *Int. J. Radiat. Oncol. Biol. Phys.* **41**, 599–605, [https://doi.org/10.1016/S0360-3016\(98\)00103-5](https://doi.org/10.1016/S0360-3016(98)00103-5)
- 35 Truong, P.T., Olivetto, I.A., Speers, C.H., Wai, E.S., Berthelet, E. and Kader, H.A. (2004) A positive margin is not always an indication for radiotherapy after mastectomy in early breast cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **58**, 797–804, [https://doi.org/10.1016/S0360-3016\(03\)01626-2](https://doi.org/10.1016/S0360-3016(03)01626-2)