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The curative effects of radiotherapy-based therapies for human epidermal growth factor receptor 2-positive breast cancer

A meta-analysis

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Abstract

Aim: This meta-analysis was designed to fully assess the curative effects of radiotherapy-based therapies for human epidermal growth factor receptor 2-positive (HER2+) breast cancer (BC).

Methods: English articles were retrieved through searching Cochrane library, PubMed, and Embase databases updated to February 2017. Studies were selected based on the inclusion and exclusion criteria. The curative effects of radiotherapy-based therapies forHER2+ BC patients were assessed using hazard rates (HRs) or odds ratios (ORs), as well as their 95% confidence intervals (CIs). In addition, Egger test was used to assess publication bias, followed by sensitivity analysis. All statistic methods were conducted using R 3.12 software.

Results: A total of 9 eligible studies were included into this meta-analysis, which involved 2236 HER2+ BC patients. Egger test showed that the eligible studies had no publication bias (t=2.198, P=.05918). Sensitivity analysis demonstrated that the results were stable. HER2+ BC patients in radiotherapy group had lower locoregional recurrences than those in other groups. Moreover, meta-analysis showed that no significant difference was found between HER2+ BC patients in radiotherapy group and other groups on the 1-year overall survival (P=0.5263, I^2=65.4%), 3-year overall survival (P=0.4591, I^2=0), and 5-year overall survival (P=0.06277, I^2=0).

Conclusion: Radiotherapy-based therapies might have certain advantages in treating HER2+ BC patients.

Abbreviations: BC = breast cancer, CIs = confidence intervals, DFS = disease-free survival, DMFS = distant metastasis free survival, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HRs = hazard rates, LC = lapatinib and capecitabine, ORs = odds ratios, PR = progesterone receptor, WBRT = whole-brain radiotherapy.

Keywords: breast cancer, human epidermal growth factor receptor 2, locoregional recurrence, meta-analysis, radiotherapy

1. Introduction

Breast cancer (BC) is characterized by breast shape change, breast lump, nipple fluid, skin dimpling, or even swollen lymph nodes, bone pain, yellow skin, and breath shortness.[1] There are several risk factors for BC, such as lack of exercise, obesity, alcohol use, ionizing radiation,early menarche, later pregnancy or infertility, older age, being female, and family history.[2] BC is responsible for 25% of all tumors in women and is the most common type of female cancer.[3] BC is more common in women in developed countries, which leads to 522,000 death cases in 2012.[4,5] Estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2), and progesterone receptor (PR) are the 3 important receptors of BC cells, and HER2+ BCs are usually more aggressive than HER2− BCs.[6,7] It has been reported that HER2 or its product is approximately overexpreesed in 25% to 30% BCs, and HER2 overexpression has correlation with elevated recurrence and poor prognosis in BC.[8]

BC patients are usually treated by surgery, or surgery combined with chemotherapy and/or radiotherapy.[9] Additional regional radiotherapy to the medial supraclavicular lymph nodes and internal mammary can significantly increase distant metastasis-free survival (DMFS), disease-free survival (DFS), and overall survival of BC patients in stage I to III.[10] Locoregional recurrence and distant metastases might be limited by postmastectomy radiotherapy,[11] and intraoperative radiotherapy with electrons has potential values in early BC treated by breast-conserving surgery.[12] Whole-brain radiotherapy (WBRT) followed by systemic therapy can be used to improve the survival of BC patients with the HER2, luminal A, and

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luminal B subtypes.[13] In patients with high-risk BC, HER2 and the constructed subtypes may play important roles in predicting survival and locoregional recurrence following postmastectomy radiotherapy.[14] Based on clinical data, the sensitive of HER2-postive positive BC cells in radiotherapy remains controversial as compared with other treatment. For example, compared with WBRT, the combination of lapatinib and capecitabine (LC) is well tolerated and active for HER2+ BC patients.[15] However, some other studies did not show any significant benefit for BC patients who underwent radiotherapy.[14,16]

In these studies, the relatively small sample size makes it difficult to discover the actual impact on outcome. Meta-analysis was a statistical approach combining the results from multiple individual studies in an effort to increase power, improve estimates of the size of the effect, and/or to resolve uncertainty when reports disagree. Thus, to provide a certain basis for the clinical treatment of HER2+ BC, we conducted a meta-analysis to summarize all published studies on the curative effect of radiotherapy for the disease.

2. Methods

2.1. Search strategy

We searched Cochrane library (http://www.cochranelibrary.com), Embase (http://www.embase.com), and PubMed (http://www.ncbi.nlm.nih.gov/pubmed) databases updated to February 2017 for English articles, using (radiotherapy OR radiation OR "radio therapy") AND (HER2+ OR HER-2+ OR HER2-Overexpressing) AND ("breast cancer" OR "breast carcinoma") as key searching terms. In addition, literature review was also used to find more clinical researches.

2.2. Inclusion and exclusion criteria

The inclusion criteria for study selection were as follows: the study was publicly published English literature regarding HER2+ BC treated mainly by radiotherapy; the comparison of curative effects of HER2+ BC patients in radiotherapy group (treated mainly by radiotherapy) and other groups were provided or could be calculated; the study was approved by an ethics committee or institutional review board. Reviews, reports, comments, or letters would be excluded.

2.3. Data extraction

Two reviewers selected the eligible studies and then extracted the following data independently: the name of first author, published year, research area, research time, the numbers of patients in radiotherapy group and control group, as well as locoregional recurrence and survival rate indexes. For the disagreements during data extraction, the group discussion with a third reviewer was performed to come to a consensus.

2.4. Statistical analysis

Meta-analysis was conducted using R 3.12 software (R Foundation for Statistical Computing, Beijing, China; http://www.R-project.org) with function metagen, metabin, metabias, etc. (R package: meta). The hazard rates (HRs) or odds ratios (ORs), as well as their 95% confidence intervals (CIs), were selected as the effect indexes for evaluating the curative effects of radiotherapy for HER2+ BC patients in each study. The heterogeneity of the eligible studies was measured using Q test[17] and I^2 statistic.[18] The random-effects model would be utilized when significant heterogeneity was observed ($P < 0.05$, $I^2 > 50\%$). However, the fixed-effects model would be used when homogeneous outcomes were calculated ($P \geq .05$, $I^2 \leq 50\%$).[19] Egger test[20] was used to assess publication bias. Moreover, sensitivity analysis was carried out by neglecting 1 article each time and observing its impact on the pooled results.

3. Results

3.1. Eligible studies

The results and processes of literature screening are shown in Figure 1. According to the predefined search strategy, a total of 1939 relevant studies were screened from Cochrane library, Embase, and PubMed databases. After 438 repeated studies were screened out, a total of 1501 studies were remained. Subsequently, a total of 1431 studies were further removed after browsing title and abstract, including 1361 studies that did not meet the inclusion criteria obviously, 47 reviews or conference papers, and 23 letters, case series, or reports. Additionally, another 61 articles (31 articles did not provide data for locoregional recurrence and overall survival, 30 articles did not provide control group from the remaining 70 articles) were removed through full text reading. At last, a total of 9 eligible studies were included into the present meta-analysis.[14,15,16,21–26]

The characteristics of the 9 eligible studies are listed in Table 1. The eligible studies involved a total of 2236 HER2+ BC patients. The included studies were published from 2008 to 2015, and their research time varied from 1982 to 2013. The research areas included United States, Denmark, Italy, China, and Egypt. The methods of radiotherapy mainly contained postmastectomy radiotherapy (PMRT), quadrantectomy followed by conventional radiotherapy (QUAD + RT), and whole cranial radiotherapy (whole cranial RT).

3.2. Locoregional recurrence

The locoregional recurrences of HER2+ BC patients in radiotherapy group and other groups were analyzed by meta-analysis. There was significant heterogeneity ($P < 0.001$, $I^2 = 82.2\%$); thus, the random-effects model was used to pool the data (HR = 1.84, 95% CI = 1.19–2.84, Fig. 2). Egger test showed that the eligible studies had no publication bias ($t = 2.198$, $P = .05918$). Sensitivity analysis showed that the pooled results did not reverse after neglecting 1 article every time (Fig. 3), suggesting that the results were stable. These indicated that HER2+ BC patients in other groups had higher locoregional recurrences than those in radiotherapy group.

3.3. Overall survival

Meta-analysis showed that the 1-year overall survival ($P = .5263$, $I^2 = 65.4\%$, selecting random-effects model), 3-year overall survival ($P = .4591$, $I^2 = 0$, selecting fixed-effects model), and 5-year overall survival ($P = .06277$, $I^2 = 0$, selecting fixed-effects model) of HER2+ BC patients in radiotherapy group and other groups had no significant difference (Table 2, Fig. 4).

3.4. Subgroup analysis

Moreover, subgroup analysis was performed for the index of locoregional recurrence. The heterogeneity of each subgroup

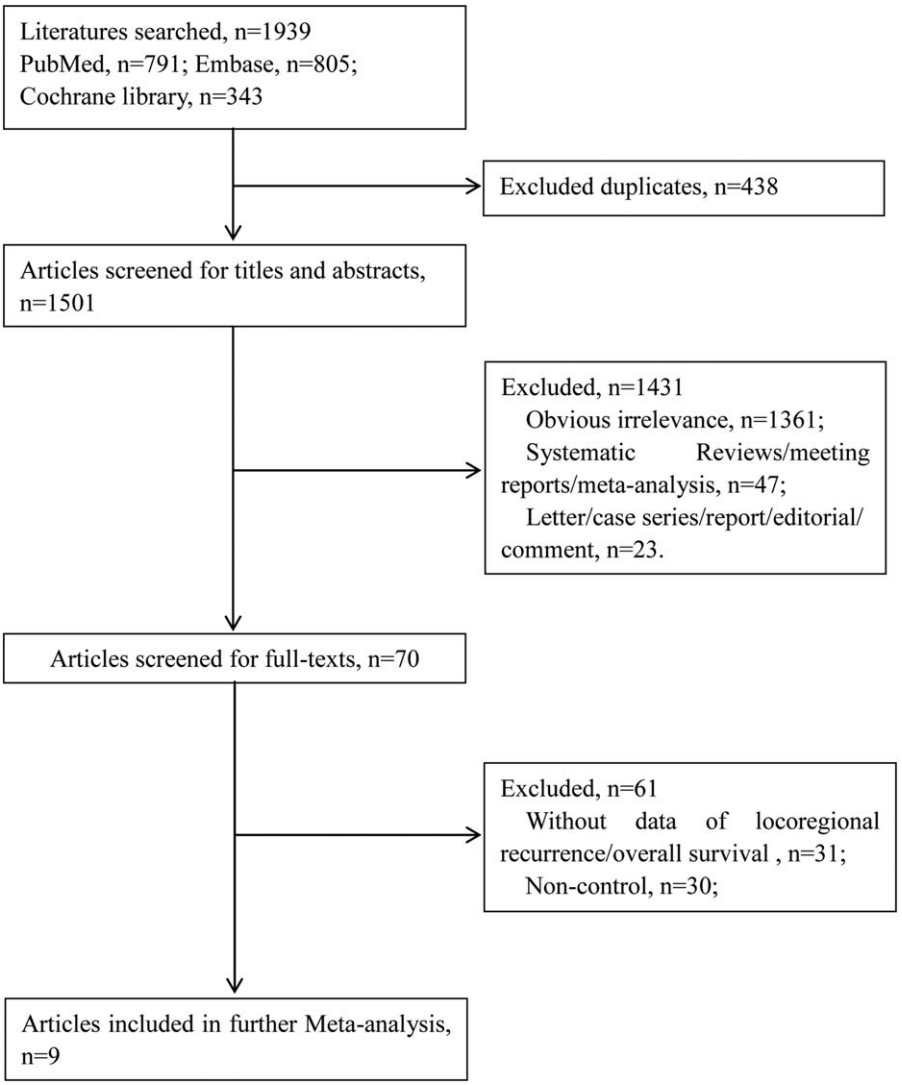

Figure 1. The results and processes of literature screening.

Table 1

The characteristics of the 9 eligible studies.

Author	Public Year	Study design	Study Location	Study Year	Group	N	LRR/n	1 OS	3 OS	5 OS
Arsenault et al[21]	2015	Retrospective	United States	1999.5–2009.12	None vs. any RT	67	4.70 (1.55, 14.22)	NA	NA	NA
Brollo et al[22]	2013	Retrospective	Italy	2005.1–2009.12	MAST no RT	115	2.05 (0.57, 7.40)	115/115	97/103	29/32
					QUAD + RT	270		269/269	243/253	92/97
Kyndi et al[14]	2008	Prospective RCT	Denmark	1982–1990	No RT	46	13	103/106	76/106	45/106
					RT	50	1	108/110	77/110	44/110
Kyndi et al[14]	2008	Prospective RCT	Denmark	1982–1990	No RT	60	16	NA	NA	NA
					RT	60	6	NA	NA	NA
Lanning	2015	Retrospective	United States	1987–2007	No RT	351	1.94 (0.67, 3.51)	NA	NA	NA
					RT	150		NA	NA	NA
Shawky and Tawfik[15]	2015	Prospective RCT	Egypt	2011.1–2013.1	No RT	5	NA	5	NA	NA
					Whole cranial RT	16		4	NA	NA
Su et al[24]	2014	Retrospective	Taiwan	2000.1–2006.12	No PMRT	24	6	NA	NA	14
		Retrospective			PMRT	19	1	NA	NA	15
Tseng et al[25]	2015		United States	2000–2009	No PMRT vs. PMRT	394	2.56 (0.85, 7.69)	NA	NA	NA
Wu et al[16]	2012	Retrospective	China	1999.3–2007.12	No PMRT	63	10	51	40	30
					PMRT	72	15	62	52	36
Wang et al[26]	2011	Retrospective	China	2000.1–2004.12	No PMRT	68	53	NA	NA	NA
					PMRT	87	79	NA	NA	NA
Wang et al[26]	2011	Retrospective	China	2000.1–2004.12	No PMRT	44	35	NA	NA	NA
					PMRT	55	51	NA	NA	NA

1 = Rec+, hormone receptor, 2 = Rec−, hormone receptor, LRR = locoregional recurrence, MAST no RT = mastectomy without radiotherapy, OS = overall survival, PMRT = postmastectomy radiotherapy, QUAD + RT = quadrantectomy followed by conventional radiotherapy, RCT = randomized controlled trail.

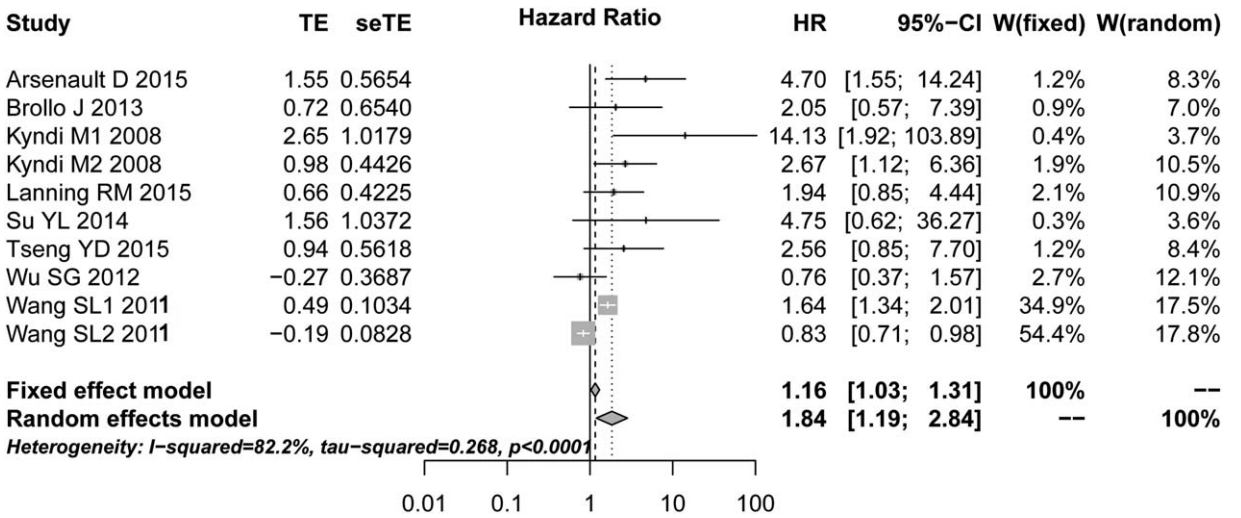

Figure 2. Forest plots of the locoregional recurrences of human epidermal growth factor receptor 2-positive breast cancer patients in radiotherapy group and other groups. HR = hazard rate, OR = odds ratio.

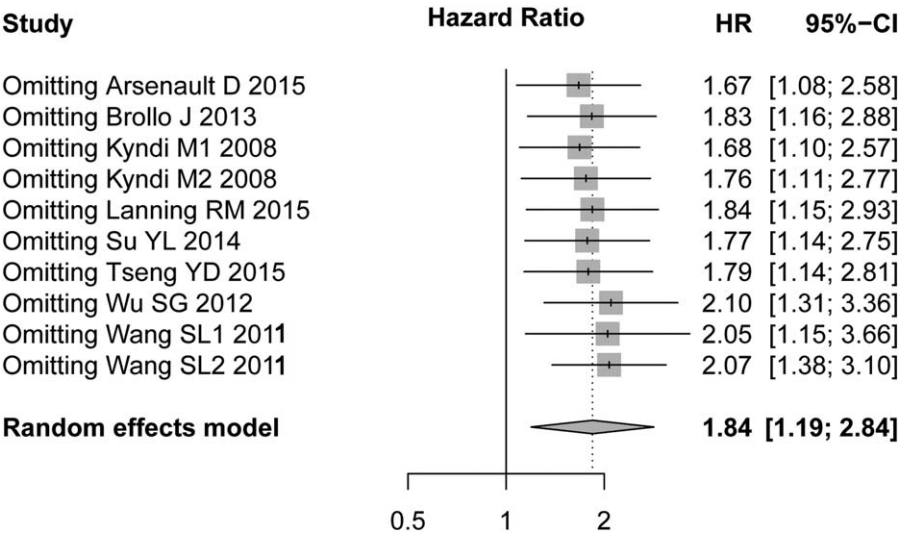

Figure 3. Forest plots of sensitivity analysis showing that the pooled results did not reverse after neglecting one paper every time.

appeared different degree of reduction, whereas the heterogeneity of some subgroups was still obvious. In addition, HER2+ BC patients in surgery type, as well as America and Europe in location subgroups had higher locoregional recurrences than those in radiotherapy group (Table 3).

4. Discussion

HER2+ BC affects living quality and threatens the lives of women in the world, especially in developing countries. The current meta-analysis was designed to fully investigate the curative effect of radiotherapy on HER2+ BC. In this meta-analysis, 9 eligible studies

Table 2

The comparison results of 1-year overall survival, 3-year overall survival, and 5-year overall survival of patients in radiotherapy group and other groups.

Indicator	*k*	OR	95% CI	I^2 (%)	*P*	Model	t*	*P*
1 OS	3	1.4294	(0.2474; 8.2600)	65.4	.0554	Random	0.92047	.5263
3 OS	3	0.8568	(0.5640; 1.3014)	0	.5228	Fixed	1.1375	.4591
5 OS	4	0.9003	(0.6107; 1.3273)	0	.4495	Fixed	3.8011	.06277

CI = confidence interval, OR = odds ratio, OS = overall survival.
* Egger test to evaluate publication bias, $P < .05$ is considered statistically significant.

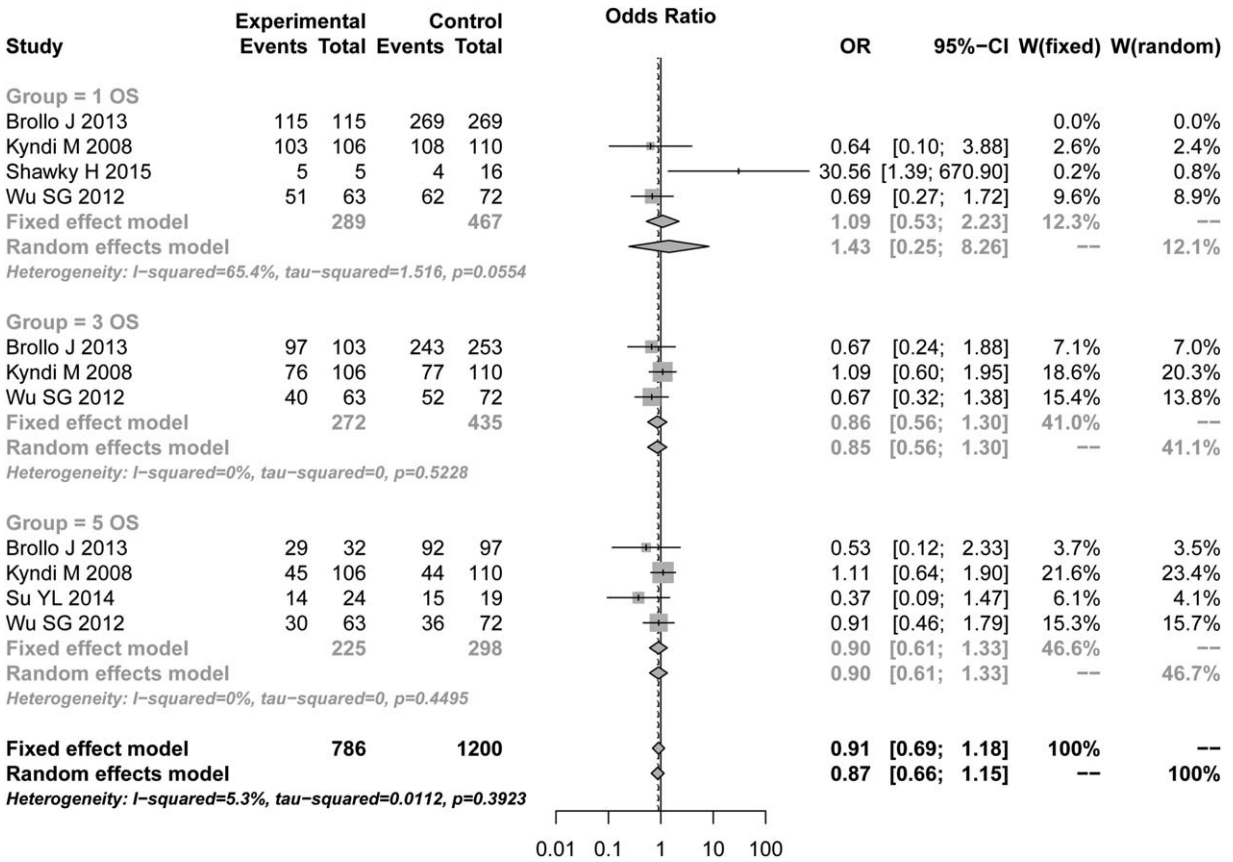

Figure 4. Forest plots showing that the 1-year overall survival, 3-year overall survival, and 5-year overall survival of human epidermal growth factor receptor 2-positive breast cancer patients in radiotherapy group and other groups had no significant difference. CI = confidence interval, OR = odds ratio.

involving a total of 2236 HER2+ BC patients were included. HER2 + BC patients in radiotherapy group had lower locoregional recurrences than those in other groups. Furthermore, subgroup analysis indicated that HER2+ BC patients from America and Europe in location subgroups had higher locoregional recurrences than those in radiotherapy group. However, meta-analysis showed that the 1-year overall survival, 3-year overall survival, and 5-year overall survival of HER2+ BC patients in radiotherapy group and other groups had no significant difference.

Among the eligible studies, a study reports that external radiotherapy combined with trastuzumab may have better curative effect for HER2/neu positive BC.[22] Mastectomy and PMRT reduce the locoregional recurrence in HER2+ BC patients who received trastuzumab, indicating that a higher-risk subset of patients benefit most.[23] For BC patients in T1–2 and N1 stage, PMRT can only reduce locoregional recurrence and improve overall survival of patients with lymphovascular invasion.[24] The patients with triple negative BC are at high risk for locoregional recurrence and benefits least from PMRT.[25] PMRT decreases the rates of distant metastasis-free survival, locoregional recurrence-free survival, and mortality for patients in luminal-A subtypes and reduces locoregional recurrence-free survival for luminal-B subtype, whereas PMRT could not influence the endpoints for the basal-like or HER2-enriched subtypes.[26] These discrepant findings in the included studies might be caused by small sample sizes or ethnic differences. Therefore, the current meta-analysis was important for quantitatively evaluating the eligible studies included into this study.

Radiotherapy after breast-conserving surgery can reduce the recurrence rate of BC by half and decrease the death rate by

Table 3

The results of subgroup analysis.

Item	Group	OR	Model	Q	*P*	I^2 (%)
Rec	Rec+	1.373 (0.4417; 4.2672)	Random	6.73	.0353	77.4
	Rec−	3.794 (0.4844; 29.7163)	Random	4.43	.0095	85.1
Surgery type	Mastectomy	1.6478 (1.0421; 2.6055)	Random	43.61	<.001	83.9
	Other	3.2958 (1.4252; 7.6214)	Fixed	0.92	.3372	0
Location	America	2.6357 (1.4932; 4.6522)	Fixed	1.58	.4549	0
	Asia	1.1507 (0.6663; 1.9874)	Random	29.36	<.001	89.8
	Europe	3.0038 (1.5279; 5.9052)	Fixed	2.73	.2559	26.6

OR = odds ratio.

nearly one-sixth.[27] Radiotherapy followed by mastectomy and axillary dissection reduce both recurrence and mortality of BC patients with 1 to 3 positive lymph nodes.[28] An extra dose of 16 Gy of radiation for BC patients having received breast-conserving surgery and 50 Gy of radiation can decrease local recurrence.[29] Radiotherapy can increase survival and decrease locoregional recurrence in T1–2 N1BC patients with lymphovascular invasion and negative ER status.[30] Omission of radiotherapy can largely increase the recurrent risk of ipsilateral BC and slightly increase the mortality risk of patients.[31] Combinations of some clinical and pathologic factors enlarge the risk of locoregional recurrence, for which PMRT is considered for improving locoregional control and potentially increasing survival of patients with T1-T2 BC.[32] These indicated that radiotherapy could decrease locoregional recurrence in HER2+ BC patients.

There was significant heterogeneity for the indexes of locoregional recurrence and 1-year overall survival; thus, the random-effects model was used to pool the data. These heterogeneities might be resulted from the differences in different countries and ethnic regions, as well as the confounding factors such as sex and age. The present meta-analysis firstly and comprehensively evaluated the curative effects of radiotherapy-based therapeutic schemes for HER2+ BC, making the results more reliable.

However, some limitations should not be neglected. First, the results of meta-analysis might be affected by some unknown sources of heterogeneity. Although no significant publication bias was observed in the study, exaggerated outcomes might be introduced because the studies with negative results or insignificant results are less likely to be published. To avoid false-positive results, more eligible included studies should be widely searched by systematic selection. Second, the demographic data in the included studies were not very complete; thus, subgroup analyses for sex and age could not be performed. In addition, although fixed-effect model and/or random-effects model was chosen in the meta-analysis, result deviation might be introduced by other models such as quality-effect models. Third, HR is traditionally used for survival data, which take the changes in the time of life and the ending into account. Most included studies did not report HR for survival rates. Moreover, OR is close to the relative risk if probabilities of the outcome are small, and we recognized that OR could be on behalf of relative risk. Moreover, relative risk and hazard ratio are more or less equal by most researchers.[33] Therefore, OR was pooled to evaluate the survival rates. Moreover, none of the included studies were designed as randomized controlled study. The above factors might weak the strength of the study. In spite of these limitations, our findings were reliable because of the strict screening of the included studies.

In conclusion, our findings suggested that the therapeutic schemes based on radiotherapy might have certain advantages in treating HER2+ BC patients. However, these results should be further confirmed by including more relevant studies with large samples.

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