Triple Negative Breast Cancer versus Non-Triple Negative Breast Cancer Treated with Breast Conservation Surgery Followed by Radiotherapy: A Systematic Review and Meta-Analysis

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Keywords

Triple negative breast cancer · TNBC ·
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Summary

Background: The aim of this study was to compare the efficacy of breast conservation surgery (BCS) followed by radiotherapy (RT) in triple negative breast cancer (TNBC) versus non-TNBC. **Methods:** We searched the MEDLINE and EMBASE databases from inception through March 31, 2014, using search terms related to TNBC, BCS, and RT. Studies comparing the efficacy of BCS followed by RT in TNBC versus non-TNBC were reviewed. **Results:** 5 studies including 2,922 non-TNBC and 510 TNBC cases were selected. The overall quality of included studies was deemed moderate to high. Compared with non-TNBC, the pooled relative risk of 5-year local relapse-free survival was 1.315 (95% confidence interval (CI) 0.967–1.789; $p = 0.008$) for TNBC, and that of 5-year overall survival, regional relapse-free survival, and distant metastasis-free survival was 1.929 (95% CI 1.392–2.674; $p = 0.000$), 3.052 (95% CI 1.629–5.715; $p = 0.000$), and 2.407 (95% CI 1.910–3.034; $p = 0.000$), respectively. **Conclusion:** The local control rate of TNBC treated with BCS plus RT is similar to that of non-TNBC.

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Introduction

Breast conservation surgery (BCS) followed by radiotherapy (RT) has been considered the standard treatment for early breast cancer patients. Previous studies demonstrated that BCS plus RT signifi-

cantly reduced the risk of local recurrence in breast cancer patients [1–3]. Those studies treated early breast cancer as a whole group and analyzed survival outcomes. However, breast cancer represents a heterogeneous group of tumors characterized by a wide spectrum of clinical, pathological, and molecular features [4–6]. This wide spectrum of factors accounts for variations in response to therapy and outcomes. The subgroup of triple negative breast cancer (TNBC) is associated with a worse prognosis compared to non-TNBC. TNBC is associated with an increased risk of recurrence within the first 3 years and increased mortality during the first 3–5 years after diagnosis because of aggressive clinicopathological features and ineffectiveness of endocrine therapy or trastuzumab [7–10]. Some studies demonstrated that TNBC was worse than non-TNBC in its response to treatment with BCS followed by RT [11–15], while others showed no such difference [16–20]. Identifying the effectiveness of BCS plus RT (especially local control rate) in the treatment of TNBC would allow clinicians to offer better local treatment. Therefore, we conducted a systematic review and meta-analysis to evaluate local relapse-free survival (LFS), overall survival (OS), regional relapse-free survival (RFS), and distant metastasis-free survival (DFS) of patients with TNBC treated with BCS plus RT.

Methods

Data Sources and Searches

From inception to March 31, 2014, MEDLINE and EMBASE were searched by 2 independent investigators. The search strategy used the terms ‘triple negative breast cancer’, ‘breast conservation surgery’, and ‘radiotherapy’. Reference lists of original and review articles were double checked to identify additional relevant studies. No language restrictions were imposed.

Study Selection and Quality Assessment

For inclusion, studies had to fulfil the following criteria: i) cohort design; ii) complete data on estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2); iii) exact reporting of end-

Fig. 1. Flowchart of study selection.

points (relapse-free survival was defined as time from diagnosis to first relapse, local recurrence, regional recurrence, or distant metastasis, and OS as the time until death); and iv) at least 1 outcome report of LFS, OS, RFS and DFS, or sufficient information to calculate them. Study selection and data extraction were conducted independently by 2 investigators. Differences were resolved by discussion with a third investigator. Our systematic review was conducted according to the meta-analysis of observational studies in epidemiology (MOOSE) guidelines [21]. Quality assessment was performed according to the criteria recommended by Hayden et al. [22].

Statistical Analysis

Heterogeneity tests and sensitivity analysis were performed to investigate the sources of heterogeneity in relative risk. Cochran Q test and I^2 statistics were used to assess heterogeneity among studies [23]. For Q test, $p < 0.05$ indicates presence of heterogeneity; for I^2 statistics, $I^2 > 50\%$ indicates severe heterogeneity. Publication bias was evaluated using a funnel plot of a trial's effect size against the standard error [24, 25]. All statistical analyses were performed using STATA version 12.0 (STATA, College Station, TX, USA).

Results

Literature Characteristics

The process of evaluating articles for inclusion is depicted in figure 1. In total, 1,182 titles were reviewed, 5 studies [14, 15, 18–20] including 2,922 non-TNBC and 510 TNBC cases were selected. The characteristics of included studies are summarized in supplemental table 1 A–C (www.karger.com/?DOI=441436). When compared with non-TNBC cases, patients with TNBC were younger at diagnosis and had a larger tumor size. In addition, TNBC cases were more frequently high grade and were more likely to receive chemotherapy. However, lymph node positivity was not significantly different.

Quality Assessment

On methodology and reported data, the overall quality of included studies was deemed moderate to high (supplemental table 2 A–C; www.karger.com/?DOI=441436). ER and PR status were obtained through immunohistochemistry (IHC) in all studies. For ER and PR, receptor positivity was based on more than 10% of cells testing positive according to Haffty et al. [18] and at least 1% of cells testing positive according to Barbieri et al. [19]. The remaining 3 studies did not define clear cutoffs for positivity of ER and PR. HER2 status was obtained through IHC in 2 studies [14, 18], and IHC/fluorescent in situ hybridization (FISH) in 3 studies [15, 19, 20]. During the study period of Solin et al. [14], the currently accepted system of scoring HER2 expression as 0, 1+, 2+, or 3+ was not generally used. Rather HER2 expression was primarily reported as positive or negative. Herceptest™ (Dako, Glostrup, Denmark) scores of 2+ and 3+ were considered to indicate HER2 positivity by Haffty et al. [18] because this was the accepted classification scheme at the time of clinical treatment. HER2 was considered negative when 0 or 1+, or positive when 3+ on IHC. If tests revealed a 2+ value, FISH was conducted. However, no cutoffs were reported by Barbieri et al. [19]. A positive HER2 marker was defined as IHC identification of 3+ and/or amplified (ratio > 2.0) expression of HER2 on FISH for Gangi et al. [20] and Zaky et al. [15]. Classification of ER, PR, and HER2 status in all studies was based on IHC and/or FISH but not on genotype evaluation. Local and regional recurrences were defined as recurrent tumor developing in the ipsilateral breast (local recurrence) or regional lymph nodes (regional recurrence). Distant metastasis was defined as distant relapses. For OS, death from any cause was scored as failure. Local and regional relapses were defined as a histologically documented relapse in the ipsilateral breast or regional nodes in 2 studies [18, 19]. In another 2 studies [14, 15], relapse was defined as a clinically, radiologically, and/or histologically documented relapse. Distant metastasis was clinically and/or radiographically documented relapse, and death was assessed by medical record. Gangi et al. [20] did not report an exact explanation of the end points. Time of follow-up in all studies was longer than 3 years which is sufficient for TNBC due to the increased risk of recurrence within the first 3 years; however, for non-TNBC this period is not sufficient to assess recurrences and metastasis.

Meta-Analysis

Treatment outcomes are shown in table 1. 4 studies directly provided LFS, OS, RFS, and DFS. We calculated LFS and RFS using the information provided by Barbieri et al. [19] who reported local-regional relapse-free survival only. OS could not be calculated for the study of Gangi et al. [20] due to insufficient data. Compared with non-TNBC, the pooled relative risk (RR) of 5-year LFS was 1.315 (95% confidence interval (CI) 0.967–1.789; $p = 0.008$) for TNBC, and that of 5-year OS, RFS, and DFS was 1.929 (95% CI 1.392–2.674; $p = 0.000$), 3.052 (95% CI 1.629–5.715; $p = 0.000$), and 2.407 (95% CI 1.910–3.034; $p = 0.000$), respectively (table 2 and supplemental fig. 1 A–D; www.karger.com/?DOI=441436). Sensitivity analysis indicated that the pooled RR was stable (fig. 2 and supplemental fig. 1; www.karger.com/?DOI=441436).

Table 1. 5-year outcomes of included studies

Study [ref.]	Subgroup	OS, %	LFS, %	RFS, %	DFS, %
Haffty et al. [18]	TNBC	80.00	83.00	94.00	68.00
	non-TNBC	89.00	83.00	99.00	83.00
Solin et al. [14]	TNBC	88.00	95.00	99.00	85.00
	non-TNBC	94.00	98.00	100.00	95.00
Zaky et al. [15]	TNBC	87.90	88.00	85.00	85.00
	non-TNBC	95.00	96.00	96.30	96.00
Barbieri et al. [19]	TNBC	80.60	95.60	100.00	68.40
	non-TNBC	90.30	97.10	100.00	87.30
Gangi et al. [20]	TNBC	NC	95.30	98.70	91.00
	non-TNBC	NC	97.84	98.89	97.22

OS = Overall survival; LFS = local relapse-free survival; RFS = regional relapse-free survival; DFS = distant metastasis-free survival; TNBC = triple negative breast cancer; NC = not clear.

Fig. 2. Sensitivity analysis of included studies.

Heterogeneity Assessment and Publication Bias

According to the L'Abbe plot and Galbraith plot, there was little heterogeneity among the studies. We further detected p (Q) and I^2 , and found a small degree of heterogeneity. In subgroup analysis, slight heterogeneity was found in the IHC subgroup. Heterogeneity might result from potential misclassification of TNBC or non-TNBC by IHC-assessed HER2. Slight asymmetry was found in the funnel plot, suggesting a small publication bias. The p value for Begg's adjusted rank correlation test was 0.221, and that for Egger's regression asymmetry test was 0.067, suggesting a low probability of publication bias.

Discussion

Multiple studies have indicated that TNBC is associated with a poor prognosis. TNBC is more likely than non-TNBC to recur locally [11] and metastasize to lung and brain. The aggressive nature of TNBC may exclude such patients from BCS under the assumption that more extensive treatment would provide better effects. Our systematic review qualitatively assessed the quality of related

Table 2. Pooled relative risks (RRs) and heterogeneity of the meta-analysis

Outcomes (5-year)	Pooled results	Heterogeneity		
	RR (95% CI)	p (RR)	p (Q)	I ² (%)
LFS	1.315 (0.967–1.789)	0.080	0.353	9.400
IHC	1.111 (0.727–1.696)	0.626	0.241	27.400
IHC/FISH	1.600 (1.019–2.511)	0.041	0.444	0.000
OS	1.929 (1.392–2.674)	0.000	0.965	0.000
IHC	1.864 (1.271–2.736)	0.001	0.778	0.000
IHC/FISH	2.133 (1.148–3.965)	0.017	0.785	0.000
RFS	3.052 (1.629–5.715)	0.000	0.231	33.100
IHC	6.179 (2.020–18.895)	0.001	0.584	0.000
IHC/FISH	2.049 (0.924–4.547)	0.078	0.133	55.800
DFS	2.407 (1.910–3.034)	0.000	0.334	12.600
IHC	2.074 (1.526–2.819)	0.000	0.223	32.700
IHC/FISH	2.978 (2.088–4.249)	0.000	0.612	0.000

OS = Overall survival; LFS = local relapse-free survival; RFS = regional relapse-free survival; DFS = distant metastasis-free survival; CI = confidence interval; IHC = immunohistochemistry; FISH = fluorescent in situ hybridization; Q = Cochran Q test; I^2 = I-squared.

studies, and quantitatively assessed the efficacy of BCS plus RT treatment in TNBC versus non-TNBC. Our meta-analysis showed that TNBC was associated with an equal risk with regard to 5-year local control, but worse RFS, DFS, and OS compared with non-TNBC. The pooled RR of LFS indicated that BCS plus RT is a viable option for TNBC. However, the high RR of RFS is an unexpected finding. Lacking the necessary information regarding supraclavicular, axillary, and internal mammary lymph node irradiation,

tion and lymph node dissection, it was difficult to explain this observation. The higher 5-year OS compared to 5-year DFS for TNBC was another unexpected finding. The interpretation remained debatable given the relatively small number of TNBC and the retrospective nature of the included studies.

The current systematic review had some advantages. First, the retrospective cohort studies included were of moderate to high quality with all articles adjusting for key confounding variables. Thus inherent weakness due to potential confounding factors was minimized in all observational studies and meta-analyses. Second, little heterogeneity and only slight publication biases were observed in the studies included in our meta-analysis.

However, possible limitations of our meta-analysis must be considered. First, in retrospective cohort studies, exclusion of potential biases was difficult. Studies included in our systematic review varied in ascertainment of HER2 status, study population, age, and chemotherapy. Hence, confounding factors could be inherent in the included studies. We attempted to manage this heterogeneity with appropriate meta-analytic techniques but failed due to insufficient data. Second, only 5 studies were included in our systematic review, and the sample of TNBC was substantial. These aspects may significantly reduce the statistical power of the analysis. Third, funnel plot and parameters of the Begg's/Egger's test may be inappropriate to estimate publication bias among 5 included studies. The methodologies of publication bias assessment used in the current study may therefore have brought about inaccurate results.

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Conclusion

The current meta-analysis indicates that TNBC treated with BCS followed by RT showed a similar local control rate but worse RFS, DFS, and OS compared to non-TNBC. Hence, TNBC should not be considered for non-conservative surgery. Further large prospective cohort-designed or randomized clinical trials on this issue should be performed to verify the results.

Disclosure Statement

The authors declare that they have no competing interests.

Supplemental Material

Supplemental Table 1. A Basic study characteristics; B Study treatment; C Surgery and radiotherapy in the studies

Supplemental Table 2. A, B Study quality; **C** Quality assessment

Supplemental Fig. 1. A Pooled relative risks (RRs) of 5-year local relapse-free survival (LFS) of triple negative breast cancer (TNBC) versus non-TNBC; B Pooled RRs of 5-year overall survival (OS) of TNBC versus non-TNBC; C Pooled RRs of 5-year regional relapse-free survival (RFS) of TNBC versus non-TNBC; D Pooled RRs of 5-year distant metastasis-free survival (DFS) of TNBC versus non-TNBC.