Systematic Review

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Role of Radiotherapy in Elderly Patients (≥65 Years) With Triple-Negative Breast Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

This is the first meta-analysis evaluating the benefit of adjuvant radiotherapy in older patients (≥65 years) with triple-negative breast cancer (TNBC). The medical literature was searched for all randomized controlled trials, nonrandomized controlled trials, and cohort studies with more than one treatment arm that evaluated radiation therapy for TNBC in patients aged >65 years. The primary outcome was overall survival. Four cohort studies (2015–2019) were eligible for analysis, including a total of 10,710 patients with TNBC of whom 7,209 underwent radiotherapy. Two were large retrospective population-based studies that yielded major findings on adjusted multivariable analysis. Patients who underwent radiotherapy (n = 6283/8526) had a significantly better 5-year overall survival than patients who did not (77% *vs.* 55%, p<0.001). The addition of radiotherapy (n = 815/1957) was associated with better cancer-specific survival. Of the two smaller studies, one prospective study reported similar survivability for treatment with breast-conserving surgery, chemotherapy, and radiotherapy or mastectomy with radiation, or mastectomy alone, and the other retrospective study found that adding radiotherapy had no effect on 5-year overall survival. Multivariate analyses of data from the two large retrospective population-based studies suggested that adding radiotherapy to breast-conserving surgery may improve overall and disease-free survival in elderly patients with TNBC.

Keywords: Breast cancer; triple-negative; radiation; elderly

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Key Points

- Breast cancer
- Triple-negative
- Radiation
- Elderly

Introduction

Breast cancer is the leading cause of cancer-related death in women worldwide. The primary risk factor is advanced age. According to the Surveillance, Epidemiology and End Results (SEER) program, the median age at breast cancer diagnosis in the United States is 68 years (1). The proportion of older women with breast cancer is expected to grow as technology and medical care continue to improve and life expectancy increases accordingly (2).

Triple-negative breast cancer (TNBC) is a subtype of breast cancer in which the tumor cells lack expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2. It accounts for 15% of all breast cancers diagnosed, and is less common in elderly patients than hormone-receptor-positive breast cancer (3). The treatment of breast cancer in general, and TNBC in particular, in elderly patients is controversial. According to the National Comprehensive Cancer Network guidelines of 2015 "… there are limited data to make recommendations for those >70 years of age" (4). The problem may be largely due to under-representation of elderly patients in clinical trials from which they are often excluded because of ageism and comorbidities. Furthermore, as TNBC is unresponsive to endocrine treatment, adjuvant treatment options are limited to chemotherapy and radiotherapy, and chemotherapy is best avoided in the elderly in whom the side effects have a more substantial impact

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relative to younger patients. The SEER database shows that, among patients with node-positive stage I-II TNBC, chemotherapy was administered to 80% of those aged 67-69 years and to less than 10% of those aged more than 85 years (5). Thus, the decision to initiate adjuvant radiotherapy in the older TNBC population is a challenge.

The purpose of this systematic review and meta-analysis was to evaluate the benefit of adjuvant radiotherapy to survival in elderly patients with TNBC.

Materials and Methods

Search Strategy

A systematic review was conducted and reported in accordance with the PRISMA statement. The search was performed without date limits during May 2021 using PubMed. Reference lists from key trials were manually scanned for additional results. The following search criteria were used: ("breast cancer"[MeSH Terms] OR "breast cancer"[All Fields] OR "breast carcinoma"[MeSH Terms] OR "breast carcinoma"[All Fields]) AND ("triple negative"[MeSH Terms] OR "triple negative"[All Fields]) and filters: 65 and over: 65+ years.

Eligibility Criteria

Studies that met the following criteria were included: (1) relevance - randomized controlled trials, nonrandomized controlled trials, and cohort studies with more than one treatment arm that evaluated radiotherapy for the treatment of TNBC; (2) participants - patients of both sexes aged 65 years and older with a histological diagnosis of TNBC. Although there is no clear definition of the term "elderly", we defined it as 65 years and older in accordance with other researchers (6). We excluded (a) studies not reporting our primary or secondary outcomes, and (b) studies not written in English.

Outcome

The primary outcome was overall survival (OS). Secondary outcomes were disease-free survival (DFS) and adverse effects. If the primary and secondary outcomes were not reported, we considered other endpoints with different definitions, such as cancer-specific survival.

Study Selection and Data Extraction

Two reviewers (I.M. and I.S.) independently screened titles and abstracts, followed by the full text of potentially eligible studies. One reviewer (I.S.) extracted the data onto an electronic form, and the other (I.M.) checked the extracted data, including the first author's name, year of publication, number of participants, mean patient age, primary *vs.* recurrent malignancy, stage, chemotherapy status, type of surgery and radiotherapy, length of follow-up, overall survival, disease-free survival, and side effects. Each reviewer independently assessed risk for observational studies using the Newcastle-Ottawa Scale. Any disagreement was resolved by discussion. Further discrepancies were resolved by the first author (E.S.).

Statistical Analysis

The OS rate was pooled using the statistical software package Comprehensive Meta-Analysis, version 3.0 (Meta-Analysis@Meta-Analysis.com, Biostat Inc., Englewood, NJ, USA). Meta-analyses were performed with the random effects model of DerSimonian and Laird because we expected considerable clinical heterogeneity. Heterogeneity was assessed by visually examining the forest plots for non-overlapping confidence intervals and by chi-square test, with $p<0.05$ indicating statistical significance and $I^2 >50\%$ indicating substantial heterogeneity.

Results

Characteristics of Studies

Our search yielded 3167 records (Figure 1). After the exclusion process, four cohort studies were found eligible for analysis (7-10). They included three retrospective studies and one prospective study with a total of 10,710 patients, of whom 7,209 received radiotherapy. All four studies were published in peer-reviewed journals between 2015 and 2019. The largest, by Haque et al. (7) (n = 8526), was based on the U.S. National Cancer Database (NCDB), 2004–2014, and the second largest (n = 1957), by Zhu et al. (8), was based on the SEER database, 2010–2011. The characteristics of the included studies are detailed in Table 1.

In all studies, mean patient age was 65-70 years, and all patients were female. Across all studies, the majority of patients (≥93%) underwent surgery; however, the addition of chemotherapy and radiotherapy and the type of radiotherapy delivered varied significantly between studies. Three studies provided data on our primary outcome of OS, and one study provided data only on cancer-specific survival.

Risk of Bias

All four cohort studies were designated high quality on risk of bias analysis (for further details see Table 1).

Overall Survival

The largest of the three studies that provided OS data was based on the NCDB and included 8526 patients with primary stage I-II TNBC who underwent breast-conserving surgery with (n = 6283) or without (n = 2243) radiotherapy (7). At a median follow-up of 38 months, 5-year OS was significantly higher in the patients who received radiotherapy than in the patients who did not (77% *vs.* 55%, $p<0.001$). A higher proportion of the patients who received radiotherapy also received chemotherapy (68% *vs.* 56%). Nevertheless, the results remained significant regardless of whether or not chemotherapy was

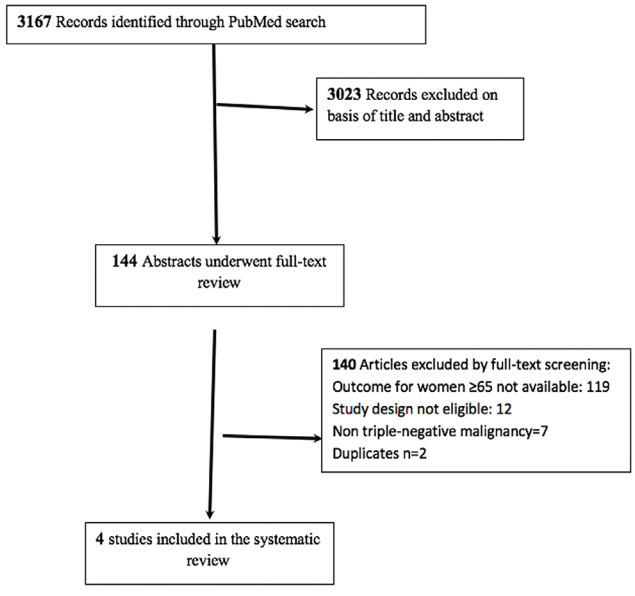

Figure 1. Flow chart of selection of studies for meta-analysis

Table 1. Characteristics of radiotherapy in the four cohort studies included in the systematic review

Reference	Country	*n*	Mean age	Stage (%)*	Chemo-therapy (%)	Surgery (%)	Type of RT (%)	OS (%)	DFS (%)	Median FU (m)
Haque et al. (7) 2019 (retrospective; NCDB 2004–2014)	USA	RT: 6283 No RT: 2243	≥70	I–II (100)	68 *vs.* 56	BCT (100)	Conventional fraction: 59 Hypofraction-ation: 22 Not recorded:10	**5-year OS** 77 *vs.* 55[§] (p<0.001)	NA	38
Qiu et al. (9) 2016 (retrospective)	China	RT: 49 No RT: 17	68	I–II (83); III (17)	Adjuvant: 38 Neo-adjuvant: 6[†]	Mastectomy: 86 BCT:14	NA	**5-year OS** 92 *vs.* 94 (p = 0.28)	86 *vs.* 94 (p = 0.37)	90[a]
Bhoo-Pathy et al. (10) 2015 (prospective)	Malaysia, Hong Kong, Singapore	BCT+chemo+RT: 22 Mastectomy+RT: 40 Mastectomy: 99	≥65	I–III (100)	13[‡]	Mastectomy: 86 BCT: 14	Variable protocols across centers	Similar survivability on crude and multiple variable adjusted analysis	NA	NA
Zhu et al. (8) 2015 (retrospective; SEER 2010–2011)	USA	RT: 815 No RT: 1142	≥70	I–III (100)	NA	Mastectomy or BCT: 93	NA	NA	RT improved cancer-specific survival (HR = 0.4, p<0.001, MVA)	~ 24

BCT: Breast-conserving therapy; DFS: Disease-free survival; FU: Follow-up; MVA: Multivariate analysis; NCDB: National cancer database; OS: Overall survival; RT: Radiotherapy; SEER: Surveillance, Epidemiology and End Results; HR: Hazard ratio; *: All patients in studies by Haque et al. (7), Qui et al. (9), and Zhu et al. (8) had primary tumors; status not mentioned in the study of Bhoo-Pathy et al. (10)

[†]: Type of chemotherapy: Anthra-cycline, cyclophosphamide ± taxanes (*n* = 30); cyclophos-phamide, methotrexate, 5-FU (*n* = 14). Type of chemotherapy unavailable in other studies

[‡]: For the overall cohort which also included patients younger than 60 years

[§]: Results remained significant on propensity-matched analysis (5-year OS, 68% *vs.* 57%); Note: None of the studies discussed side effect

administered and on propensity-matched analysis (68% *vs.* 57%, p<0.001).

By contrast, a smaller retrospective study from China including 66 patients with primary stage I-III TNBC (83% I–II, 17% III) who underwent mostly (86%) breast-conserving surgery (9) found that the addition of radiotherapy had no effect on the 5-year OS or DFS. However, it was unclear if the groups treated or not treated with radiotherapy were balanced in terms of staging, chemotherapy status, and type of surgery.

Meta-analysis of these two studies revealed that the addition of radiotherapy was associated with improved 5-year survival, with borderline significance (odds ratio: 2.26, 95% confidence interval: 0.9–5.71, I^2=27%) (Figure 2).

The third study that evaluated OS prospectively investigated the outcome of breast-conserving surgery, chemotherapy, and radiotherapy (*n* = 22) versus mastectomy (*n* = 99) versus mastectomy and radiotherapy (*n* = 40) in 161 patients with stage I-III TNBC (9). Similar survival was reported in all three groups on crude and adjusted analyses.

Cancer-Specific Survival

The sole study that investigated cancer-specific survival was based on SEER data for 1957 patients with primary stage I–III TNBC (8). The majority (93%) underwent either mastectomy or breast-conserving surgery (Chemotherapy status is unavailable in the SEER database). On multivariate adjusted analysis, the addition of radiotherapy in 815 patients was associated with an increase in cancer-specific survival during a mean follow-up of approximately 24 months.

Discussion and Conclusion

Many studies have recommended omitting adjuvant radiotherapy in older women with early hormone-receptor-positive breast cancer who receive endocrine therapy (11-14). However, in patients with TNBC, especially the 65+ age group, the role of adjuvant radiotherapy is still controversial (15-20). This is the first meta-analysis conducted to date to attempt to answer this question.

The two largest of the four studies evaluated, by Haque et al. (7) and Zhu et al. (8), were based on the NBSD and SEER program data, respectively. In both, patients of different

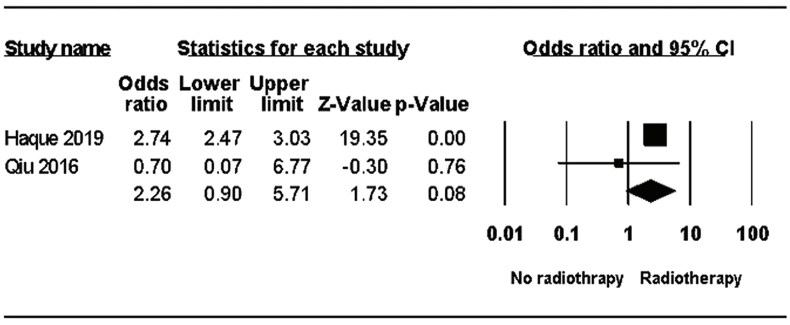

Figure 2. Forest plot comparing 5-year overall survival in patients with triple-negative breast cancer who received or did not receive radiotherapy

CI: Confidence interval

age groups who were treated or not treated with adjuvant radiation were compared for outcome using multivariate analysis. Haque et al. (7) concluded that in elderly women with T1-2N0 TNBC, omitting adjuvant radiotherapy was associated with a statistically poorer OS, regardless of age group, T-stage, or chemotherapy. However, the analysis did not correct for performance status and comorbidities. Likewise, Zhu et al. (8) suggested that the poor prognosis of elderly patients with TNBC might be associated with their lower rate of loco-regional treatment with surgery and radiation.

It is well recognized that adjuvant radiotherapy reduces the loco-regional recurrence rate and risk of breast cancer (21-25). The Early Breast Cancer Trialists' Collaborative Group study (21), including more than 10,000 women from 17 trials, concluded that adjuvant therapy is associated with a nearly 50% reduction in 10-year risk of any first recurrence compared with breast-conserving surgery alone. In addition, the patients given radiotherapy showed a reduction in 15-year risk of death from breast cancer. The improvement in prognosis might be even greater for TNBC owing to its association with the *BRCA1* mutation. Several clinical and experimental studies have suggested that tumors harboring the *BRCA1/BRCA2* mutation are more sensitive to radiotherapy (26-28). These findings prompted Trainer et al. (29) to suggest that in patients with TNBC, the presence of a *BRCA* mutation may impact the benefit of adjuvant radiotherapy.

The two other studies in our meta-analysis were conducted in Asia and included a considerably lower number of patients. Bhoo-Pathy et al. (10) found that adjuvant radiotherapy was associated with a survival gain in patients with locally advanced TNBC. Among those with early TNBC (T1-2, N0-1, and M0), the 5-year relative survival rate was highest in patients who underwent mastectomy only, followed by patients undergoing breast-conserving surgery and mastectomy with radiation. However, we believe conclusions regarding the role of adjuvant radiotherapy in early TNBC cannot be drawn on the basis of these results because patients treated with mastectomy and radiation have a worse prognosis to begin with, regardless of the addition (or not) of adjuvant radiotherapy. Therefore, they should not have been included in the early breast cancer group. Moreover, the survival gain associated with radiotherapy applied only to very young patients with TNBC.

The fourth and smallest study analyzed reached an opposite conclusion from the others. Qiu et al. (9) found that 5-year DFS and OS were significantly higher in the elderly patients even though they received significantly less radiotherapy and chemotherapy than the younger patients. The authors advised that clinicians take a more conservative and cautious approach to the decision to administer postoperative adjuvant treatment (radiotherapy, chemotherapy, or both) to elderly patients with TNBC.

Overall, the two larger studies, which were based on databases in the U.S. and evaluated the data using multivariate analysis, suggested that adjuvant radiotherapy may improve prognosis in elderly patients with TNBC. The sole study leading to a contrary conclusion used a retrospective design and a substantially smaller patient sample.

The present meta-analysis was limited by the small number of studies that met the inclusion criteria and the retrospective design of three of them. Moreover, the study population was heterogeneous in terms of age, adjuvant chemotherapy, and type of surgery.

This is the first meta-analysis to evaluate the role of adjuvant radiotherapy for TNBC in elderly patients (age ≥65 years). The weight of the evidence supports the notion that adjuvant radiotherapy has a survival advantage in this age group.

Footnotes

Authorship Contributions

Concept: R.Y., I.M.; Design: R.Y., I.M.; Data Collection or Processing: E.S., I.S.; Analysis or Interpretation: I.S.; Writing: E.S.

Conflict of Interest: No conflict of interest declared by the authors.

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