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Review Article

Adjuvant locoregional radiation therapy in breast cancer patients with pathologic complete response after neoadjuvant chemotherapy: A systematic review and meta-analysis

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A B S T R A C T

Purpose: The aim of the present meta-analysis was to investigate the impact of adjuvant locoregional radiation therapy (LRRT) in breast cancer patients with clinical lymph node metastatic disease achieving ypN0 after neoadjuvant chemotherapy (NACT).

Materials and methods: A systematic review of studies on PubMed was performed. A meta-analysis was conducted by computing extracted hazard ratios (HRs) and 95% confidence intervals (CIs) into a fixed-effects model.

Results: Thirteen studies were included in the meta-analysis. Adjuvant LRRT significantly reduced the risk of locoregional recurrence (LRR) in patients with N+ at diagnosis and ypN0 (HR 0.59; 95% CI 0.42–0.81). However, no statistically significant difference on disease-free survival (DFS) or overall survival (OS) was found.

Conclusions: LRRT significantly reduced the risk of LRR in patients with ypN0 after NACT whereas no impact on DFS or OS was observed. The low level of evidence should be considered when interpreting the results in clinical practice.

Introduction

Neoadjuvant chemotherapy (NACT), namely the use of chemotherapy before surgery has been shown to be as effective as adjuvant chemotherapy for patients with operable breast cancer in terms of survival [1]. However, NACT has some potential advantages over adjuvant therapy as the higher probability for breast conserving surgery, and the ability for response-guided treatment both preoperatively and postoperatively [2]. Considering these potential advantages, a significant increase in the use of NACT has been noted over the past ten years [3].

Several randomized trials have shown that patients with large tumors or positive lymph nodes undergoing local or locoregional radiation therapy (LRRT) after adjuvant chemotherapy have a lower risk for locoregional recurrence (LRR) and improved breast cancer survival [4–6]. However, the benefit of LRRT for breast cancer patients where pathologic complete response (pCR) has been achieved after NACT is not established. According to the National Cancer Institute (NCI), the suitability of LRRT after NACT should be considered for patients with initial N+ breast cancer or lymph node metastatic disease after surgery [7]. However, the prognostic significance of pCR after NACT and the lack of convincing evidence on the impact of LRRT on patients with pCR after NACT has made the usage of LRRT in this setting questionable [8–12]. In fact, some studies have shown that LRRT in patients with pCR after NACT reduces the risk of LRR, whereas another study have failed to confirm these results [13–15]. Due to the limited evidence and conflicting results from existing research, there is a lack of consensus regarding the use of LRRT in clinical T3 and/or lymph node metastatic breast cancer patients with favorable response after NACT [16]. In addition, two major sources of bias, namely the confounding by indication and the immortal time bias (ITB), are common in existing studies on this topic and should be considered when interpreting the results.

The aim of this meta-analysis was to gather the current evidence and investigate the impact of adjuvant LRRT on breast cancer patients with clinical T3 and/or lymph node metastatic disease and pCR after NACT.

Materials and methods

Literature search and study selection

A systematic review was carried out through a literature search on

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PubMed until November 2020 limited by studies published in English and after 1990. The following searching algorithm was used: “(radiotherapy OR radiation therapy) AND (neoadjuvant OR preoperative OR induction OR primary) AND (postmastectomy OR postoperative) AND breast cancer”.

To be included in this systematic review and meta-analysis, the studies had to include patients with clinically T3 and/or lymph node metastatic disease at diagnosis, present data on adjuvant radiotherapy in relation to pCR after NACT, and present outcome of adjuvant radiotherapy in terms of LRR and/or disease-free survival (DFS) and/or overall survival (OS). Considering the risk for confounding by indication, namely the risk that adjuvant radiotherapy was selected to patients with more aggressive disease, only studies presenting data from multivariate analyses or propensity score matching were eligible.

The concept of adjuvant radiotherapy in the present study included both the local radiation therapy to the chest wall after mastectomy and the LRRT to breast or chest wall and to regional lymph nodes after mastectomy or breast conserving surgery.

The exclusion criteria were studies that only included patients with inflammatory breast cancer or clinically T4 disease, studies without data on whether adjuvant radiation therapy was given or data on response to chemotherapy and studies without presenting relevant outcomes.

Two independent researchers carried out the literature search and data extraction and consensus through discussion was achieved between the researchers in case of discrepancy.

**Data collection process**

The following data were extracted from the studies: first author’s surname, year of publication, journal, country, type of study (prospective, retrospective analysis of prospectively collected data, retrospective), multicentric (yes or no); enrollment years, median follow-up, total number of patients, number of patients for adjuvant radiation therapy / no adjuvant radiation therapy; stage at diagnosis, pCR (defined as ypT0 mastectomy or breast conserving surgery.

The initial search on PubMed yielded 1837 studies. After applying the inclusion and exclusion criteria, 13 studies were included in the meta-analysis [13–16,20–28]. Fig. 1 summarizes the selection process.

**Study characteristics**

Table 1 presents a summary of the characteristics of eligible studies. The median follow-up among the eligible studies ranged between 39 and 91.4 months. All studies were based on breast cancer patients with initial clinical stage T≥N0 whereas no study specifically addressed the impact of adjuvant radiation therapy after pCR in patients with initially clinical T3N0 breast cancer. The latter research question was an additional aim of our meta-analysis that was unable to be investigated using pooled analyses due to the lack of relevant studies in literature.

There were five studies that adjusted for ITB in their analyses [14–16,25,26]. Two of them used suitable statistical methods to minimize ITB [14,25], and three adjusted for the bias in their study design [15,16,26].

**Risk of bias**

The overall risk of bias was judged as serious in 12 out of 13 eligible studies whereas 1 study was judged as moderate overall risk of bias (Table 2).

**Impact of LRRT on LRR, DFS, and OS in patients with axillary pCR**

The analysis on the impact of LRRT on LRR included six studies (Fig. 2A) [15,20–24]. In total, 2388 patients with N+ at diagnosis and ypN0 after NACT were included in the analysis, 859 received LRRT and 1529 did not. The results showed a statistically significant reduced risk of LRR in patients who received LRRT (HR 0.59; 95% CI 0.42–0.81; P = 0.001). The symmetric funnel plot indicated that no publication bias was present (Fig. 2A). The certainty of evidence in the pooled analysis was evaluated as low by GRADE (Table 3).

Five studies investigated the role of LRRT on DFS were eligible (Fig. 2B) [20,22–24,26]. A total of 2019 patients were included in the analysis out of which 626 received LRRT and 1393 did not. The results showed no statistically significant difference between the LRRT and no LRRT groups (HR 1.00; 95% CI 0.75–1.33; P = 0.99). The symmetric funnel plot indicated that no publication bias was present (Fig. 2B). The certainty of evidence in the results from this analysis was evaluated as very low by GRADE (Table 3).

Regarding the impact of LRRT on OS, nine studies were eligible including 14,991 patients out of which 8281 were treated with LRRT and 6710 without LRRT (Fig. 2C) [14,16,22–28]. The pooled HR showed no statistically significant difference between the LRRT and no LRRT groups (HR 0.92; 95% CI 0.82–1.03; P = 0.14). The symmetric funnel plot indicated that no publication bias was present (Fig. 2C).
certainty of evidence in the results from this analysis was evaluated as very low by GRADE (Table 3).

In all three meta-analyses regarding the impact of LRRT on LRR, DFS, and OS, respectively, we performed sensitivity analyses by excluding one study where patients with cN0 were also included in the study cohort [23], and found very similar results (data not shown).

**Subgroup analyses**

A subgroup analysis was performed including three studies with data on the impact of LRRT on LRR in patients with pCR (both ypT0 and ypN0) [13–15]. In total, 390 patients were included in the analysis, 242 received LRRT and 148 did not. The results showed a statistically significant lower risk of LRR in patients who received LRRT (HR 0.24; 95% CI 0.11–0.49; P < 0.0001).

Considering the risk of ITB in studies investigating adjuvant radiotherapy, an additional subgroup analysis was performed including only studies that presented results on OS where ITB was mitigated by study design or suitable statistical analysis. In total, four studies were eligible for this subgroup analysis including 5389 patients, 3426 received LRRT.
| Author (year) [Ref] | Country | Type of study | Multicentric | Enrollment years | Number of patients | Age at diagnosis and molecular subtype in study cohorts | Median follow-up (months) | ITB adjustment | Covariates in multivariate analyses |
|---------------------|---------|---------------|--------------|-----------------|-------------------|--------------------------------------------------|--------------------------|---------------|----------------------------------|
| Cho (2019) [21]     | Korea   | Retrospective | Yes          | 2005–2011       | 189               | >50 yrs old 43.4%; Luminal 45.5%, HER2-positive 25.9%, TNBC 28.6% | 78.0                     | No            | Grade, LVI, endocrine therapy    |
| Fayyazju (2020) [27]| USA     | Retrospective with prospectively collected data | Yes          | 2004–2015       | 6183              | Median age 51 (IQR: 43–60); Luminal 40%, HER2-positive 34.4%, TNBC 21% | 40.1                     | No            | Age, radiation, race/ethnicity, insurance status, grade, cT stage, Charlson/Deyo comorbidity score, facility type, facility location, extent of axillary surgery, histology, tumor subtype |
| Haffty (2019) [26]  | USA     | Retrospective with prospectively collected data | Yes          | 2009–2011       | 248               | Luminal 59.6%, HER2-positive 32.8%, TNBC 26.3% | 70.8                     | Yes           | cT stage, in-breast pCR, tumor biology |
| Huang (2020) [20]   | China   | Retrospective | Yes          | 2000–2014       | 282               | Median age 49 (range: 20–79); Luminal 50.1%, HER2-positive 30.9%, TNBC 19.0% | 72.9                     | No            | Age, cT stage, cN stage, LVI, molecular subtype, ypT, endocrine therapy, adjuvant chemotherapy |
| Kantor (2017) [28]  | USA     | Retrospective with prospectively collected data | Yes          | 2004–2008       | 1937              | <50 yrs old 46.1%, 50–70 yrs old 46.6%, >70 yrs old 7.3% | 69                      | No            | Age, race, insurance, Charlson comorbidity index, histology, grade, ER-status, PR-status, endocrine therapy, cT stage, ypT stage |
| Krug (2019) [15]    | Germany | Retrospective with prospectively collected data | Yes          | 2002–2010       | 402               | Median age 49 (range: 21–78); Luminal 52.1; HER2-positive 15.3%, TNBC 15.7% | 51.5                     | Yes           | cT stage, cN stage, age, ER-status, PR-status, HER2 status, histologic subtype, grading, response to chemotherapy |
| Le Scodan (2012) [23]| France  | Retrospective | No           | 1990–2004       | 134               | Mean age 49.9 (range: 28–71) | 91.4                     | No            | Age, cT stage, cN stage, histologic subtype, inflammatory signs, endocrine therapy, NACT regimen, ER-status, PR-status response to NACT |
| Liu (2016) [16]     | USA     | Retrospective | No           | 1998–2009       | 1046              | Median age 50 (range: 20–88) | 56.0                     | Yes           | Age, cT stage, cN stage, histologic subtype, inflammatory signs, endocrine therapy, NACT regimen, ER-status, PR-status response to NACT |
| Miyashita (2019) [24]| Japan   | Retrospective with prospectively collected data | Yes          | 2004–2009       | 1297              | Median age 53 (range: 23–92) | NR                      | No            | Age, cT stage, cN stage, biological subtype |
| Rusthoven (2016) [25]| USA     | Retrospective with prospectively collected data | Yes          | 2003–2011       | 3040              | Age < 50 yrs old 55.8%, >50 yrs old 44.2% | 39                      | Yes           | Age, race, year of diagnosis, Charlson/Deyo comorbidity score, grade, cT stage, in-breast pCR, ypT, extent of axillary surgery, ER status, endocrine therapy, age, cT stage, cN stage, ypT stage, ypT, ypT, NACT regimen, nodal surgery, ER status, PR status, HER2 status, hospital type |
| Shim (2014) [22]    | Korea   | Retrospective | Yes          | 1998–2009       | 151               | Median age 47 (range: 27–78); Luminal 41.1%, HER2-positive 13.9%, TNBC 24.5% | 59                      | No            | Age, cT stage, cN stage, ypT stage |
| Wang (2020) [13]    | China   | Retrospective | No           | 2004–2016       | 48                | Median age 50 (range: 23–64); Luminal 54.2%, HER2-positive 19.8%, TNBC 19.8% | 72                      | No            | Age, clinical stage |
| Zhang (2020) [14]   | Taiwan  | Retrospective with prospectively collected data | No           | 2007–2015       | 1423              | Median age 51 (IQR: 44–59) | NR                      | Yes           | Age, diagnosis year, Charlson comorbidity index, tumor differentiation, clinical stage, ypT, ypT, ypT, NACT regimen, nodal surgery, ER status, PR status, HER2 status, hospital type |
and 1963 did not [14,16,25,26]. The results showed no statistically significant difference between the LRRT and no LRRT groups in terms of OS (HR 0.86; 95% CI 0.73–1.01; P = 0.06).

Discussion

This meta-analysis showed a statistically significant reduced risk of LRR when receiving LRRT in breast cancer patients with N+ at diagnosis and ypN0 after NACT whereas no survival benefit was observed regarding DFS or OS. However, the certainty of evidence from the pooled analyses ranges from very low to low, thus jeopardizing the implication of the results into daily clinical practice.

The study design of the eligible studies is prone to two major risks of bias that could influence the results, namely confounding by indication and ITB. To mitigate the risk of confounding by indication in our meta-analysis, we included only primary results from multivariate analyses or results after adequate matching method. Although the risk for unmeasured confounding in observational studies remains despite the adequate use of statistical methods, the pooled analyses of multivariate results provide a more reliable approach.

ITB can cause an inaccurate survival benefit among patients that receive adjuvant radiotherapy, because patients must survive until the start of the intervention in order to be included in the adjuvant radiotherapy group, meanwhile patients that die before the start of the intervention are included in the no adjuvant radiotherapy group [29]. To investigate how ITB could impact our meta-analysis, we performed a subgroup analysis including only studies that used methods to mitigate the risk of ITB. Considering the pooled OS results between the main analysis and the subgroup analysis with only studies adjusted for ITB we can hypothesize that ITB does not seem to represent a major drawback in our meta-analysis.

Recently, a meta-analysis by the Italian Association of Radiation therapy and Clinical Oncology investigating the same research question was published [30]. The authors could not find any difference in LRR, DFS, or OS when adjuvant radiation therapy was added in patients with pCR after NACT. However, the later meta-analysis did not consider the potential impact of confounding by indication or immortal-time bias on the primary analyses of the eligible studies and, as a result, the pooled analyses have a high level of uncertainty.

The lack of survival benefit with the addition of LRRT in patients with ypN0 despite the potential benefit in LRR observed in the present meta-analysis is somewhat unexpected and challenging to explain. The inclusion of different study cohorts in the pooled analyses for LRR and OS respectively based on the available results within each study as well as the lack of adequate follow-up to observe survival differences might be some potential explanations. However, an inherent risk of bias in pooled analyses due to the low certainty of evidence, as it clearly observed using the GRADE approach, might also be the driving factor for this discrepancy.

All analyses in this study were based on breast cancer patients with initial lymph node metastatic disease achieving ypN0 and therefore, the impact of adjuvant radiation therapy in breast cancer patients with initial T3N0 breast cancer that achieve pCR after NACT remains unclear. However, in a systematic review of 24 studies, 23 of which were single-institution retrospective cohorts, it was suggested that omitting post-mastectomy radiation therapy (PMRT) can be considered in patients with T3N0 breast cancer with pCR in breast and axilla after NACT. The systematic review proposed some groups of breast cancer patients who were at low risk of LRR if PMRT was omitted after NACT and breast cancer patients with T3N0 breast cancer with pCR in breast and axilla after NACT. The addition of LRRT in patients with T3N0 breast cancer with pCR in breast and axilla after NACT was published [30]. The authors could not find any difference in LRR, DFS, or OS when adjuvant radiotherapy was added in patients with pCR after NACT. However, we observed a benefit with LRRT in terms of LRR that was similar with the benefit on LRR observed in our primary analysis of patients achieving ypN0.

We were unable to conduct further subgroup analyses based on...
different patient- or tumor characteristics due to the lack of adequate data from primary studies. However, a retrospective study from the National Cancer Data Base (NCDB) including 8321 patients with lymph node metastatic breast cancer (cN1-2 stage) showed that LRRT improved OS in patients with hormone-receptor negative disease, and ypN0 after NACT (HR 0.65; 95% CI 0.48–0.88; P < 0.01) whereas no OS benefit was observed in the whole study cohort including patients with different breast cancer subtypes [28].

Two additional limitations of the present meta-analysis that deserve attention is the fact that our pooled analyses were based on study-level results and not on patient-level data that would give the possibility to investigate the research question within different patient subgroups. Furthermore, the lack of relevant information regarding irradiated target volumes within primary studies is a source of clinical heterogeneity among eligible studies that could potentially influence the results.

Considering the high risk of bias of the eligible studies, especially the risk for confounding by indication and ITB, it was expected that the certainty of evidence from the present meta-analysis ranges from very low to low. The most suitable way to overcome these biases and provide high level of evidence is to perform well-designed randomized trials. In fact, the ongoing NSABP B-51/RTOG 1304 randomized trial will be able to answer to the research question on the role of adjuvant radiotherapy after NACT and pCR using randomized evidence [31].

So, how does one interpret the results of the present meta-analysis while anticipating for the results of the ongoing randomized trial? Using well-defined approaches to grade the level of evidence, this meta-analysis provides the current evidence on this research question from studies that tried to mitigate the risk of major biases on their analyses. Our results accompanied with their level of evidence can be used by the clinicians in the discussion with the breast cancer patients for a shared decision making on this complex clinical situation until the evidence from the randomized trial is available.

This meta-analysis including studies that tried to mitigate the risk for confounding by indication bias and ITB showed that receiving LRRT significantly reduced the risk of LRR in patients that achieve ypN0, and pCR in both breast and axilla after NACT whereas no impact was found on DFS or OS. However, the results should be interpreted in clinical practice with caution considering the low certainty of evidence. Results from the ongoing randomized trial are anticipating to provide results with high level of evidence for this complex clinical situation.
Table 3

| Outcomes                  | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) |
|---------------------------|--------------------------|-------------------------------|----------------------------------|
| Locoregional recurrence   | HR 0.59 (0.42 to 0.81)   | 2388 (6 observational studies) | LOW                              |
| Disease-free survival     | HR 1.00 (0.75 to 1.33)   | 2019 (5 observational studies) | VERY LOW                         |
| Overall survival          | HR 0.92 (0.62 to 1.03)   | 14,991 (9 observational studies) | VERY LOW                         |

Abbreviations: CI, confidence interval; HR, hazard ratio; No., number.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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