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Triple-negative breast cancer and radiation therapy

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Abstract

Background: This study aimed to review specific indications of radiation therapy for triple-negative breast cancer (TNBC), and to introduce the hypothesis of TNBC as an independent predictor for postmastectomy radiation therapy (PMRT).

Materials and methods: Two reviewers independently searched two electronic databases (Pubmed and Embase), with the inclusion dates of January 2000 to December 2021, for the following terms: “mastectomy” or “breast conserving surgery” or “lumpectomy”, and “radiation” or “radiotherapy”, and “triple negative” and “recurrence”. All evidence was explored by two reviewers, then organized into a narrative review considering grades of recommendation.

Results: Patients with TNBC are candidates for breast conserving surgery (grade of recommendation B). Postoperative whole-breast irradiation must be offered following breast conserving surgery (grade of recommendation A). Do not omit postoperative radiation therapy in older patients with TNBC (grade of recommendation B). Do not use partial-breast irradiation in patients with TNBC (grade of recommendation B). Postmastectomy radiation therapy should be offered for women with T3–T4 or node-positive TNBC, for any number of positive nodes (grade of recommendation A). Radiation therapy following mastectomy might also benefit patients with T1–T2 node-negative TNBC (grade of recommendation B). For patients treated with neoadjuvant systemic therapy, radiation therapy indication is based on pretreatment features. Retrospective studies suggest that residual TNBC is sensitive to radiation therapy to optimize locoregional control (grade of recommendation C).

Conclusions: Postoperative radiation therapy should be offered for most patients with TNBC. Upcoming studies, preferably prospective randomized trials, should evaluate the indications of radiation therapy, especially in the context of novel systemic treatments.
Key words: triple negative breast neoplasms; radiotherapy; mastectomy; mastectomy, segmental

Introduction

Triple-negative breast cancer (TNBC) is a subset of breast cancer that does not express estrogen, progesterone, or HER-2 receptors, as observed on immunohistochemistry. TNBC has worse outcomes than non-TNBC after either breast-conserving surgery (BCS) or mastectomy [1]. Unlike hormone-receptor-positive and HER-2-positive cancers, TNBC only had modest advances in treatment over the years [2–5].

TNBC is further subdivided into basal and non-basal subtypes. Basal subtypes express cytokeratins 5/6 or epidermal growth factor receptor on immunohistochemistry [6]. Their gene expression patterns matched with those cells that originated in the basal/myoepithelial layer of the ductal epithelium [6]. Basal TNBC has less lymphocyte infiltration, which is associated with better prognosis [7–9].

In contrast, the non-basal subtype contains apocrine tumors that express androgen receptors and claudin-low tumors, with features suggestive of epithelial-to-mesenchymal transition [6]. Compared with patients with non-apocrine TNBC, those with apocrine TNBC are older and have smaller, lower-grade tumors and better survival rates [10]. Historical randomized controlled trials on breast oncology did not consider different molecular subtypes. Yet, uniform treatments for such heterogeneous diseases are no longer suitable in the era of precision, evidence-based medicine.

This study aimed to review specific indications of radiation therapy for TNBC, and to introduce the hypothesis of TNBC as an independent predictor for postmastectomy radiation therapy (PMRT).

Material and methods

Two reviewers independently searched two electronic databases (Pubmed and Embase), with the inclusion dates of January 2000 to November 2021, for the following terms: “mastectomy” or “breast conserving surgery” or “lumpectomy”, and “radiation” or “radiotherapy”, and “triple negative” and “recurrence”. Filters were applied to retrieve only randomized or observational clinical trials and meta-analyses.

Non-comparative studies, reviews, case reports, case series, comments, editorials and studies published in other languages than English were excluded. References from included studies were also considered to construct the narrative review.

All evidence was then organized into a narrative review considering the grades of recommendation as proposed by Hadorn and modified by Harbour and Miller [11, 12].

Results

Our search retrieved 26 studies from Pubmed and 34 studies from Embase (Fig. 1). After excluding duplicated and non-comparative studies (by the prescription of radiotherapy in TNBC), our analysis was limited to 11 studies [13–24]. These are further detailed in the following narrative review.

Breast-conserving surgery

All molecular subtypes, including TNBC, benefit from whole-breast radiation therapy following BCS [14, 15]. In TNBC, age is not determinant of radiation therapy prescription. In older patients (aged more than 65–70 years), randomized trials show that tamoxifen alone, without radiation therapy, provides low rates of recurrence without significant differences in mortality, in luminal breast cancer [25, 26]. For triple-negative, though, large population-based retrospective studies showed that radiation therapy improved survival [27–29].

A meta-analysis suggested that triple-negative tumors benefit from BCS with radiation therapy over mastectomy. However, low-quality trials, retrospective designs, wide confidence intervals (CIs), and high heterogeneity (including patients with T3/T4 and N2/N3 disease) make it unwise to state any conclusions [16].

The MA.20 trial, which addressed the role of nodal (internal mammary, supraclavicular, and axillary) irradiation following BCS for node-negative or high-risk N1 tumors, failed to show significant differences for the overall population, but a subgroup analysis suggests that estrogen-negative and/or progesterone-negative tumors benefit from nodal irradiation [30]. The impact of the molecular subtype was even more important than the number of positive nodes or location of tumor [30].

As for ultrafractionation (5 fractions) whole-breast radiation, the triple negative subtype was included in the FAST-Forward trial but represented less than 10% of the sample [31]. Yet, there is no data indicating that those patients had worse outcomes. The European Society for Radiotherapy and Oncology (ESTRO) Advisory Committee in Radiation Oncology Practice consensus states that ultrafractionation can be offered for non-nodal breast or chest wall (without reconstruction) radiation therapy regardless of the molecular subtype [32].

Patients with TNBC are not candidates for partial-breast radiation therapy. Triple negative subtype was the only independent predictor of recurrence in a prospective trial of accelerated partial-breast irradiation (APBI) using 32 Gy in 8 twice-daily sessions [18].

In ELIOT, a randomized trial, patients with TNBC who received intraoperative radiation therapy had much higher rates of ipsilateral breast tumor recurrence [33] The American with T1 or small (non-high grade, screen-detected) DCIS are suitable for APBI, with Society for Radiation Oncology (ASTRO) and ESTRO consensus states that only patients caution for estrogen-receptor negative tumors [32, 34].

In conclusion, patients with TNBC are candidates for BCS (grade B recommendation). Therefore, postoperative whole-breast irradiation must be offered following BCS (grade A recommendation). Postoperative radiation therapy must not be omitted in older patients with TNBC (grade B recommendation), and partial-breast irradiation must not be administered to patients with TNBC (grade B recommendation).

Postmastectomy radiation therapy

Nearly 20 years ago, PMRT promoted an increase in non-breast cancer deaths, possibly related to cardiac adverse effects [35]. Most expert panels retained recommendations for PMRT in patients with a high risk of recurrence, such as those with T3/T4 disease or 4 positive nodes [36, 37]. In 2014, one large meta-analysis conducted by the EBCTCG group, including individual patient data of 8,135 women, concluded that PMRT significantly affected mortality of patients with node-positive breast cancer, including those with any extent of positive nodes [38]. The authors highlighted the safety of current radiation therapy, with tridimensional planning and better coverage of target areas. Conversely for patients with node-negative breast cancer who underwent axillary dissection, outcomes following mastectomy without radiation therapy were excellent and PMRT provided no additional benefit. As an important limitation, molecular subtype classification, axillary surgery and systemic therapy were outdated in a substantial proportion of studies, thus affecting the external validity.

One of the trialists included in the EBCTCG meta-analysis later presented results stratified by molecular subtype. At first, TNBC seemed markedly radioresistant.(22) The same was observed in a large national retrospective study [17]. However, subsequent analyses showed that resistance was specific for basal TNBC [23]. Non-basal TNBC had a great benefit from PMRT, reducing recurrence from 64% to 22% ($p = 0.03$). Conversely, basal TNBC had no impact at all (20% and 19%, $p = 0.87$).

Tumor-infiltrating lymphocytes (TILs), another feature commonly seen in TNBC, is also predictive of response to PMRT [24].

Recently, a subset analysis of the BEATRICE trial, which randomized patients with operable pT1a–pT3 TNBC to adjuvant bevacizumab, suggested that patients with N1

disease who went through radiation therapy had fewer locoregional recurrences than those with mastectomy alone (4% and 9%, respectively; HR = 0.46) [13].

Only one randomized controlled trial specifically included patients with TNBC as the target population [19]. A total of 681 women with stage I–II TNBC treated with mastectomy and partial axillary dissection were randomized to receive systemic chemotherapy plus radiation therapy or chemotherapy alone. After a median follow-up time of 86.5 months, PMRT improved the overall recurrence (HR = 0.77, 95% CI: 0.72–0.98, p = 0.02) and overall survival (HR = 0.79, 95% CI: 0.74–0.97, p = 0.03). Although this study has important limitations (imbalance in the number of subjects to each arm, lack of sample size calculation, and dropout rates), this result is in accordance with the EBCTCG data for mastectomy with axillary sampling [38].

Skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM) are techniques that allow immediate reconstruction with implants. A meta-analysis of 11 observational studies that included 6,502 patients showed increased rates of local recurrence for NSM and no difference in overall survival among the groups; however, the authors considered that the quality of evidence was very low to make a definite conclusion [39]. Whether SSM and NSM retain the same indications for radiotherapy as simple mastectomy remains unclear. In an international survey that included 298 radiation oncologists and 252 breast surgeons, most responders affirmed that PMRT should be offered to patients with adverse prognostic features, such as young age, lymph node involvement, lymphovascular invasion, histological grade III, and triple-negative subtype [40].

The EORTC 22922 trial, although with outdated chemotherapy regimens, showed that nodal (internal mammary and medial supraclavicular) irradiation improved breast-cancer specific survival and recurrence rates for stage I-III central or medially located tumors [41]. Subgroup analyses were not provided, but recalling the MA.20 trial (following BCS) the benefit of nodal irradiation might be even greater for estrogen-negative and progeteron-negative tumors [30].

In conclusion, PMRT should be offered to women with node-positive TNBC for any number of positive nodes (grade A recommendation). In addition, one randomized controlled trial and consistent observational trials suggested that radiation therapy following mastectomy could benefit patients with T1–T2 node-negative TNBC (grade B recommendation). Following SSM and NSM, radiation therapy should be offered to patients with node-positive (grade B recommendation) and T1–T2 node-negative TNBC (grade D recommendation).

PMRT after neoadjuvant systemic therapy

Long-term results of 10 randomized trials confirm the equivalence of preoperative and postoperative chemotherapy in terms of breast cancer-specific survival and overall survival [42]. Current guidelines state that radiation therapy is based on the maximum disease stage at diagnosis (before chemotherapy) [43].

It is unknown if stage III complete responders could be spared of adjuvant radiation therapy, as well as if stage I/II non-responders, instead, should not [44]. Retrospective studies have suggested that patients with residual HER-2-positive and TNBC are sensitive to radiation therapy to optimize locoregional control [45]. Stage II-III patients, especially with the triple negative subtype, also benefit from internal mammary nodal irradiation, according to a propensity-score matching retrospective study [21].

In conclusion, patients with TNBC are candidates for preoperative chemotherapy (grade A recommendation). Following BCS, all patients should be offered adjuvant radiation therapy (grade A recommendation). Prescription of radiation therapy is based on the maximum disease stage at diagnosis (grade of recommendation D). It is unknown if patients with stage I/II TNBC and complete pathological response may forego adjuvant radiation therapy.

Discussion

Although TNBC foreshadows, in a substantial number of women, poorer prognosis than that observed for other breast cancer subtypes, the current status of available prospective and retrospective data suggests that postoperative radiation therapy has an important role and should be performed in most patients. Figure 2 represents a suggested clinical recommendation for postoperative radiation therapy based on the literature review.

Future studies, preferably prospective randomized trials, should be conducted to evaluate the indications of radiation therapy, especially in the context of novel systemic treatments for patients with TNBC.

Conflict of interest

The authors declare that they do not have any conflict of interest.

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Author contribution

The authors have developed the design of this article, both engaged in article search and data extraction. Bessa made the first draft, Marta revised it critically, and both approved the final version. Both agreed to be accountable for all aspects of the work.

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Figure 1. Search results of comparative studies by prescription of radiation therapy among triple-negative breast cancer (TNBC)

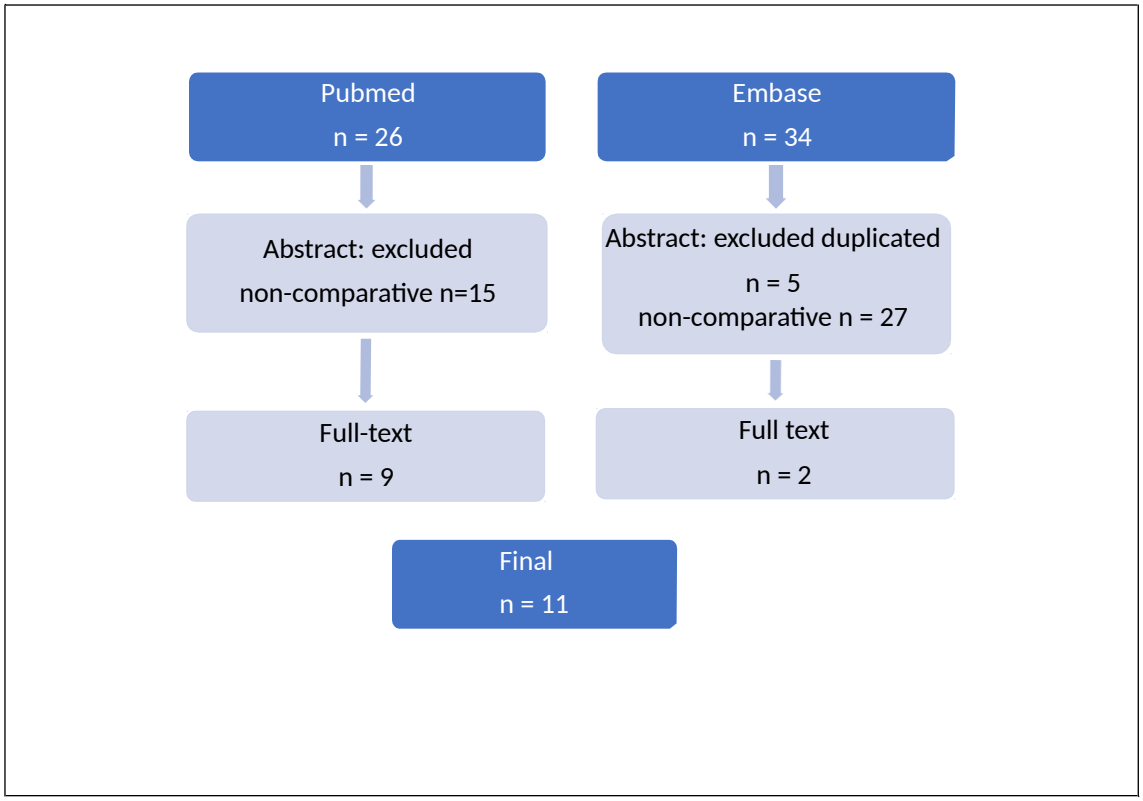

Figure 2. Clinical recommendation. RT — radiation therapy; N+ — positive node