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Original article

Omitting radiation therapy in women with triple-negative breast cancer leads to worse breast cancer-specific survival

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ABSTRACT

Purpose: To examine locoregional recurrence (LRR) and breast cancer-specific survival (BCSS) after breast-conserving therapy (BCT) or mastectomy (ME) with or without radiation therapy (RT) in triple-negative breast cancer (TNBC).
Material & Methods: We identified non-metastatic TNBC cases from a single institution database. BCT, ME with RT (ME + RT) and ME only were compared with respect to LRR and BCSS. Cox regression models were used to analyze the association between prognostic factors and outcome.
Results: 439 patients fulfilled the inclusion criteria. Median follow-up was 10.2 years (interquartile range 7.9; 12.4 years). Patients in the BCT (n = 239), ME + RT (n = 116) and ME only (n = 84) group differed with respect to age, pT, pN, lymphovascular invasion, lymph node dissection and chemotherapy administration. Ten-year LRR rates were seven percent, three percent and eight percent for the BCT, ME + RT and ME only group, respectively. pN was associated with LRR. In multivariable analysis LRR were significantly lower in the ME + RT group compared to the BCT and the ME only group (p 0.037 and 0.020, respectively).
Ten year BCSS was 87%, 84% and 75% for the BCT, ME + RT and ME only group, respectively. pT, pN, lymph node dissection, lymphovascular invasion and the administration of chemotherapy were associated with BCSS. In multivariable analysis BCSS was significantly lower in the ME only group compared to the BCT group and the ME + RT group (p 0.047 and 0.003, respectively).
Conclusion: TNBC patients treated with ME without adjuvant RT showed significant lower BCSS compared to patients treated with BCT or ME + RT and significant more LRR compared to ME + RT when corrected for known clinicopathological prognostic factors.

1. Introduction

Breast cancer is a heterogeneous disease encompassing distinct molecular profiles associated with different clinical outcomes. Based on gene expression profiling a molecular classification system has been proposed characterizing five subtypes: luminal A or B, Human Epidermal growth factor Receptor 2 (HER2)-positive, normal and basal-like [1,2]. The basal-like subtype is characterized by the molecular absence or minimal expression of receptors for estrogen (ER), progesterone (PR), and HER2 in addition to high expression of c-Kit, myoepithelial cytokeratins 5, 6 and 17, and HER1. In clinical routine, these molecular subtypes are approximated using immunohistochemistry (IHC) for ER, PR and HER2. The basal-like subtype is then represented by the lacking of these three markers and entitled Triple Negative Breast Cancer (TNBC) even though there is 25–30% discordance [3].

TNBC comprises 15–20% of breast cancers and has worse outcomes compared to other breast cancer subtypes [4,5]. Studies exploring the importance of molecular subtyping

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suggested that the luminal-A subtype has the lowest risk for locoregional recurrence, while HER2 positive and triple negative subtypes are associated with a substantially higher risks [6,7]. Even though the prognostic and predictive value of breast cancer subtypes are widely recognized and used in the elaboration of systemic treatment, their value for locoregional management needs further clarification [4,5]. There are two main pathways for locoregional therapy. Firstly, there is breast conserving therapy (BCT), including breast conserving surgery (BCS) followed by radiation therapy (RT); and secondly there is mastectomy (ME) with or without adjuvant RT; both with axillary nodal assessment and treatment. Level-I evidence has shown equivalence of these two strategies in terms of survival without taking molecular subtypes into account [8,9]. The poor prognosis of TNBC could suggest the need for an aggressive locoregional approach such as more radical surgery or the addition of radiation therapy. A randomized controlled multi-center trial from Wang et al. included 681 women with stage I-II TNBC treated with mastectomy and chemotherapy of whom 366 patients received radiation therapy. Five-year overall survival significantly improved in the RT group [10]. Limited data also suggest a better locoregional control for TNBC when treated with BCT compared to ME without adjuvant RT [11–13].

With this paper, we want to clarify the following remaining question further: is there a difference in locoregional recurrence (LRR) and breast cancer-specific survival (BCSS) in TNBC patients treated with BCT, ME plus adjuvant RT and ME only?

2. Material & methods

2.1. Patient selection and data collection

A large prospectively collected database, set up in January 2000 and now containing prospectively obtained data of more than 12.200 patients files was used for selection. The database includes data of all patients diagnosed with breast cancer and having at least one of the following treatments, i.e. surgery and/or RT and/or systemic therapy, at University Hospitals Leuven, Belgium. The patient cohort used for this analysis included patients diagnosed with a non-metastasized invasive TNBC between January the first, 2000 and December 31, 2009. TNBC was defined as tumors with negative IHC for the ER (<one percent), PR (<one percent) and low or absent HER2-amplification (IHC zero or one + or negative in situ hybridization). Patients were excluded in case of no local surgery, no adjuvant RT after BCS or in case neo-adjuvant chemotherapy was administered.

All treatment decisions were discussed in multidisciplinary tumor board and were with curative intent. Locoregional therapy consisted of BCT or ME with or without RT, sentinel lymph node procedure or axillary lymph node dissection.

All radiation treatments had to be administered at University Hospitals Leuven. Post ME RT was administered according to the international guidelines. The standard dose for whole breast irradiation (WBI) and chest wall RT was 50 Gy (Gy) in 25 fractions. Standard practice was to boost the tumor bed after WBI (external radiation therapy or brachytherapy). For the selection of the boost technique, an in-house developed flowchart based on the depth of the tumor bed was used [14]. The standard external boost dose was 16 Gy in eight fractions. The standard dose with brachytherapy was 8.5 Gy in high dose rate, prescribed at 85% of the Mean Central Dose. Regional RT was administered according to in-house protocol and included patients participating in the European Organization for Research and Treatment of Cancer trial on the irradiation of the internal mammary nodes [15].

Chemotherapy was given according to standard protocol and involved cyclophosphamide, methotrexate, 5-fluorouracil, epirubicin and taxanes.

Based on the locoregional treatment, patients were divided into three groups: BCT, ME with adjuvant local, regional or locoregional RT (ME + RT) and ME only.

This study was approved by the Clinical Trial Center and the Ethics Committee of our institution.

2.2. Endpoints

LRR was defined as local and or regional (axillar, parasternal or supraclavicular region) recurrence. BCSS was defined as death from breast cancer. Death from other causes, or death from unknown cause was not included, and patients were censored when these events occurred. Patients were also censored at the last date of follow-up. Clinicopathological risk factors (age, grade, pT, pN, lymphovascular invasion, perineural invasion, surgical margins, extensive ductal carcinoma in situ, histology, details on surgery, radiation therapy and chemotherapy) for LRR and BCSS were available in the database. LRR and BCSS were compared for the BCT, ME + RT and ME only group. Subgroup analysis involved patients with an invasive ductal adenocarcinoma not otherwise specified (IDA_NOS) to create a more pathologically homogenous subgroup, this means excluding for example cystic, apocrine and medullary-like tumors [16]. A second subgroup analysis involved all patients who would not receive RT after ME according to the current guidelines: pT1-2N0 tumors with negative surgical margins [17].

2.3. Statistical analysis

Summary statistics were presented as medians and range for continuous variables and as frequencies and percentages for categorical variables.

Summary statistics on time-to-event outcome variables were based on the cumulative incidence function considering death without event as competing event. Summary statistics for follow-up time were based on the Kaplan-Meier estimate of potential follow-up [18]. Group differences were tested by a Chi-square test for categorical variables or one-way ANOVA for continuous variables. Cox regression models were used to analyze the association between prognostic factors and outcome. A non-linear trend for age was tested. Results were presented as hazard ratios with 95% confidence intervals. Outcome variables were defined as the time between diagnosis and the time of event. Patients without the respective event were censored at time of death or last follow-up. Analyzing the association between treatment approach and outcome, correction was performed by including possible confounders as covariates in the multivariable model. Variables corrected for were these clinicopathological factors that were associated with outcome and for which there were differences between treatment approaches. All tests were two-sided, a five % significance level was assumed for all tests. Analyses have been performed using SAS software (version 9.4 for Windows).

3. Results

3.1. Patients, tumor and treatment characteristics

Clinicopathological factors of 439 TNBC patients were assessed. 239 patients were included in the BCT group, 116 in the ME + RT group, 84 in the ME only group. Median follow-up time for the 439 patients was 10.2 years (interquartile range 7.9; 12.4 years, range 0.36; 15.6 years).