The Breast 24 (2015) 175–181

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Overall survival according to type of surgery in young (≤40 years) early breast cancer patients: A systematic meta-analysis comparing breast-conserving surgery versus mastectomy

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ARTICLE INFO

Article history:
Received 24 November 2014
Received in revised form
15 January 2015
Accepted 2 February 2015
Available online 23 February 2015

Keywords:
Meta-analysis
Young women
Breast cancer
Breast-conserving surgery
Mastectomy

ABSTRACT

Objectives: Young age is an independent risk factor for local recurrence after breast conserving surgery (BCS) and whole breast radiotherapy (WBRT) for breast cancer. The aim of this study was to carry out a systematic meta-analysis to address the issue as to whether type of surgery might have an impact on overall survival (OS) of young patients with early breast cancer.
Material and Methods: We summarized six studies comparing OS between BCS + WBRT vs. mastectomy in young patients (≤40 years) with T1-T2 N0–N + M0 breast cancer. Primary endpoint was OS or distant metastasis free survival (DMFS). Only studies with fully adjusted Hazard Ratios (HR) were analyzed. Summary HRs were calculated through random effects models. We investigated publication bias and heterogeneity by means of sensitivity analyses and meta-regression models.
Results: Five population-based studies and a pooled study of two clinical trials, for a total of 22598 patients 40 years old or younger, were considered: 10898 patients underwent BCS and 11700 underwent mastectomy. After all the adjustments, including nodal status and tumor size, no difference in risk of death was found between the two groups (10% not sgnificant risk reduction in patients who underwent BCS compared to mastectomy; summary HR = 0·90; 95%CI: 0·81 to 1·00). Between-study heterogeneity was not statistically significant (I^2 = 34% and Chi-square P = 0·15). Heterogeneity investigation did not find any variable influencing results. No indication for publication bias was found (P-value = 0·37). Excluding the only study presenting DMFS the results did not change (HR = 0·88; 95%CI: 0·78 to 1·01).
Conclusion: Considering all the limitations, from the present meta-analysis carried out on 22598 patients it appears unlikely that mastectomy provides better OS compared to BCS + WBRT in early breast cancer patients aged 40 years or younger.

Introduction

Young patients with breast cancer represent a unique entity as they comprise specific both personal and clinical issues such as the occurrence of more aggressive tumors leading to a worse prognosis [1–6]. Although theoretically arbitrary, a cut-off of 40 years seems to identify a cohort of patients with similar characteristics and demands [4–7].

Breast conserving surgery (BCS) plus whole breast radiotherapy (WBRT) is the first option of surgical treatment in patients with early breast cancer as it provides the same overall survival as mastectomy in mixed age patients [8–13]. The European Society of Breast Cancer Specialists (EUSOMA) working group considered breast-conserving surgery followed by radiation therapy as the first option whenever suitable for young women with breast cancer [14]. The same recommendation was made within the first international consensus conference for breast cancer in young women [15] and the panel of the 2013 St. Gallen Consensus expressed the opinion that young age in itself is not an absolute contraindication for breast conserving-surgery [16].

Abbreviations: BCS, breast conserving surgery; WBRT, whole breast radiation therapy; OS, overall survival; DMFS, distant metastasis free survival; HR, hazard ratio.

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http://dx.doi.org/10.1016/j.breast.2015.02.002
0960-9776/

Nevertheless, the decisions about surgical management of breast cancer in young women represent a challenge in part because it is a relatively uncommon condition, but also because young age is an independent risk factor increasing local recurrence after BCS + WBRT [8–10,12,17,18]. Moreover, the management of these patients might be sometimes emotionally driven leading to more aggressive treatments without a clear demonstration of benefit.

Young patients are in general poorly represented in trials and no randomized trials have been conducted evaluating overall survival in young patients according to type of surgery. A new and dedicated randomized trial specifically evaluating this issue is at best hard to imagine.

Therefore, we performed a comprehensive meta-analysis in order to address the relevant question as to whether BCS is as effective as mastectomy in terms of overall survival (OS) in patients of ≤40 years with early breast cancer.

Methods

Literature search

This review was performed by following MOOSE guidelines regarding meta-analysis of observational studies [19]. The focus of this systematic review and meta-analysis was to specifically report the outcomes of breast cancer in patients ≤40 years with early stage breast cancer (stage I and II) treated with BCS or mastectomy. A selective literature search was performed by two reviewers (JV and OG) using the following databases using validated search strategies: PUBMED (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi), Ovid Medline (Ovid Technologies, Inc., New York, 1950–April 29, 2011), EMBASE (Elsevier, Amsterdam, the Netherlands, 1980–April 29, 2011), ISI Web of Knowledge (Thomson Scientific Technical Support, New York, 1945–May 4, 2011), without restriction of languages and publication dates, until February 1, 2014. We also performed manual searches of references cited in the retrieved articles and preceding reviews on the topic. The following medical subject search headings (MeSH) were used: “surgical management”, “loco-regional therapy”, “breast conservative surgery”, “mastectomy” and, “breast cancer young women”, “breast cancer under 40 years” or “very young women”.

All citations were independently reviewed by two of the authors (JV and OG) and categorized as relevant or not relevant. Studies that were considered as relevant were selected for full-text review and their references manually searched for important citations.

We also reviewed current recommendations of The European Society of Breast Cancer Specialists (EUSOMA) and the National Comprehensive Cancer Network (NCCN 2013) [14,20]. Only those studies comparing mastectomy and BCS that published adjusted HR were included in the meta-analysis. Ecological studies, case reports, reviews and, editorials were not considered eligible.

Eligibility criteria

Studies included in the meta-analysis had to meet the following criteria: (1) They have to publish full adjusted risk estimates (at least for age, tumor size and lymph node status) comparing BCS with mastectomy in patients ≤40 years with stage I or II breast cancer, with no prior evidence of cancer or metastatic disease, (2). They have to be independent and not duplicate results published in another article. In case of overlapping studies, those with the largest sample data were selected. (3) Adjusted hazard ratio estimates for overall survival or distant metastasis free survival, with 95% CIs, should be reported.

We excluded studies that did not contained a comparative group. We did not include or calculate crude HR, from published data, in order to increase reliability of our estimates and achieve more homogeneous summary risk estimates.

Data extraction

Data were carefully and independently extracted by two reviewers (JV and SG) and consensus was reached on all outcomes. Whenever information for outcomes was missing, we contacted the corresponding author to obtain specific data or to clarify further details [18,21]. A standardized data-collection protocol was used for gathering the relevant data from each selected article. We recorded the following information about each eligible study: the name of the first author, year of publication, study characteristics (aim; years of patients accrual; country of single-center or population-based registry; elegibility criteria, median of follow-up; stage of breast cancer; type of adjustments, median age of the patients; local or loco-regional recurrence rates). We also recorded the following information from both arm of each treatment group: the number of patients included in each treatment group (BCS or mastectomy) and the number of patients with T1, T2, node negative and, node positive, separately.

Data analysis and statistical methods

Every HR, adjusted for the maximum number of confounding variables, and corresponding confidence intervals, was retrieved and transformed into log relative risks and the corresponding variance was calculated using the formula proposed by Greenland (1987) [22]. Hazard Ratios from the pooled trials were not found in the publication and they were calculated from the original dataset provided by the authors [18]. A Cox model was adopted to obtain a risk estimate for overall survival adjusted for age, tumor size, lymph node status, vascular invasion, histological grade, microscopic involvement of excision margins, from the original dataset provided by the authors.

The summary hazard ratio (SHR) was estimated by pooling the study-specific estimates with the random effects models as described by van Houwelingen et al., with maximum likelihood estimation [23]. Confidence intervals were computed assuming an underlying t-distribution to be conservative, taking into account correlation between estimates within study.

The homogeneity of the effects across studies was assessed using the large sample test based on the Chi-square statistic. Since the Chi-square test has limited power, we considered statistically significant heterogeneity at the $P = 0.10$ level of association. A further measure of heterogeneity I^2 has been considered in order to compare between heterogeneities for different numbers of pooled studies. It can be interpreted as the percentage of total variation across several studies that is attributable to heterogeneity: larger values of I^2 indicate greater heterogeneity [24]. A threshold of I^2 below 50% is generally considered an acceptable level of variability.

We produced forest plots including both the study specific and the SHR.

To assess the influence of possible sources of bias, we considered the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist proposed for observational epidemiologic studies [25]. According to the STROBE checklist, using meta-regression, we evaluated between-study heterogeneity assessing the influence of different study features. We also examined changes in results after exclusion of specific studies to evaluate the stability of the pooled estimates. Meta-regressions and subgroup analyses were carried out to quantify between-study heterogeneity [22]. Heterogeneity and sensitivity analyses were evaluated looking at all