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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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 significant 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 (I² = 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].
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 ≤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”, “locoregional 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, studies comparing mastectomy and BCS that published adjusted HR 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. 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.

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; eligibility 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 I² 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 I² indicate greater heterogeneity [24]. A threshold of I² 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

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.
the possible factors that could influence the estimates (adjustment for confounding factors, type of endpoints and, features of study designs). Weighted average percentages of frequencies of T2 and nodal status by groups are calculated, weighting for the sample size of each study.

Publication bias was evaluated graphically with a funnel plot; and we conducted the Macaskill test that is more powerful when less than 20 estimates are included in the analysis [26].

All the statistical analyses were performed using SAS software (SAS Institute Inc., Cary, NC; version 9.2) and R software, version 2.12.2 (http://www.r-project.org).

Findings

Results of search strategy

Overall, 631 articles were identified using the aforementioned MeSH. From this, 72 were selected for abstract review and, of those, 19 abstracts were considered relevant for full-text review. Copies of all 19 studies were obtained and carefully read. 9 articles were excluded, 3 of them because a different definition of young patient was used [8,27,28], and the other 6 studies because they did not report on direct comparison between BCS and mastectomy in terms of overall survival or distant metastasis free survival (DMFS) [17,29–33]. Finally, 4 articles were excluded due to the lack of relevant data regarding primary endpoint, given that adjusted HR comparing BCS with mastectomy was not reported [11,34–36].

An article selection flowchart is showed in Fig. 1.

Table 1 summarizes the characteristics of the studies included in the meta-analysis. From the 5 population-based studies and one pooled study of two clinical trials, a total of 22598 patients ≤40 years were enrolled, 10898 patients underwent BCS and 11700 underwent mastectomy [18,21,37–40].

All six studies included patients treated between 1980 and 2007. Inclusion criteria of the six studies was restricted to patients with early stage breast cancer; so approximately 70% of the total of patients had a tumor less than 2 cm (T1) and 65% of patients were
node-negative (N0) as shown in Table 2. The group of patients who underwent mastectomy presented a greater frequency of tumors >2 cm (in two studies) [38,39] and a higher percentage of positive axillary lymph nodes (4 studies) [21,38–40]. One study did not report data from axillary status, but only patients with tumors smaller than 2 cm were included in the analysis [37]. Overall, the weighted average percentages of patients with bigger tumors (37% T2 in mastectomy group vs 25% T2 in BCS group) and positive axillary lymph nodes (40% in mastectomy group and 27% in BCS group) were higher in the mastectomy group. We also recorded all available data about adjuvant therapies administered in both surgical groups [Table 3]. According to 5 of 6 studies [18,21,38–40], all patients treated with BCS received adjuvant radiotherapy whereas that only 37% and 17% patients received radiation therapy after mastectomy [38,39]. In 2 studies the number of patients who received adjuvant chemotherapy and hormonotherapy after mastectomy was statistically higher [21,38] while in one study more adjuvant therapy was administered to the BCS group [40].

Meta-analysis of primary outcome: survival rates (OS or DMFS)

We included in the meta-analysis 6 studies with 9 risk estimates (one study reported two estimates by age and two studies two estimates by lymph-node status) [Table 4]. SHR indicates a borderline significant reduction in risk of 10% for BCS vs mastectomy (SHR = 0.90; 95%CI: 0.81—1.00), as shown in Fig. 2.

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.

Excluding the study presenting only DMFS the summary estimate decrease but it lost statistically significance (HR = 0.88; 95% CI: 0.78—1.01).

No indication for publication bias was found ($P$-value = 0.37).

Discussion

In this meta-analysis of five population-based observational studies and one pooled study of two clinical trials including 22598 patients, mastectomy was not associated with an improved OS or

Table 2

<table>
<thead>
<tr>
<th>Authors (year, ref)</th>
<th>T-Stage</th>
<th>Lymph-node status</th>
<th>T-Stage</th>
<th>Lymph-node status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kroman et al. (2004, 37)</td>
<td>T1: 401 (100)</td>
<td>N0: 581 (65.4)</td>
<td>T1: 401 (100)</td>
<td>N0: 581 (65.4)</td>
</tr>
<tr>
<td>Van der Sangen et al. (2011, 38)</td>
<td>T1: 610 (68.6)</td>
<td>N0: 693 (76.2)</td>
<td>T1: 610 (68.6)</td>
<td>N0: 693 (76.2)</td>
</tr>
<tr>
<td>Banterma-Joppe et al. (2011, 21)</td>
<td>T1: 909 (100)</td>
<td>N0: 693 (76.2)</td>
<td>T1: 909 (100)</td>
<td>N0: 693 (76.2)</td>
</tr>
</tbody>
</table>

ref: reference, n: number of patients, BCS: breast conserving surgery, N0: negative nodal status, N+: positive nodal status.
Table 3
Number of patients according to adjuvant therapies in both surgical groups.

<table>
<thead>
<tr>
<th>Authors (year, ref)</th>
<th>Adjuvant therapies</th>
<th>BCS n (%)</th>
<th>Masteectomy n (%)</th>
<th>p (&lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voogd et al. (2001, 18)</td>
<td>Chemotherapy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kroman et al. (2004, 37)</td>
<td>Hormonotherapy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Van der Sangen et al. (2011, 38)</td>
<td>Radiotherapy</td>
<td>108 (100)</td>
<td>108 (100)</td>
<td>NA</td>
</tr>
<tr>
<td>Bantema-Joppe et al. (2011, 21)</td>
<td>Hormonotherapy</td>
<td>331 (36.4)</td>
<td>242 (44.5)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Mahmood et al. (2012, 39)</td>
<td>Radiotherapy</td>
<td>118 (13)</td>
<td>100 (18.4)</td>
<td>0.05*</td>
</tr>
<tr>
<td>Won Jeon et al. (2013, 40)</td>
<td>Hormonotherapy</td>
<td>1289 (66.1)</td>
<td>985 (63.1)</td>
<td>0.067</td>
</tr>
</tbody>
</table>

ref: reference, n: number of patients, BCS: breast conserving surgery.
*Bold print indicates a p value <0.05.

DDFS compared to BCS + WBRT in early stage breast cancer patients ≤40 years. Despite the limitations related to the analysis, these results achieved on a large population of patients, with long follow-up (from 6 to 10 years), support BCS as the first option in young patients as well as demonstrated in older counterparts within prospective randomized trials with long follow-up. Prospective randomized trials comparing BCS vs mastectomy in young patients do not exist. Therefore, the present analysis represents the most powerful available statistical method to provide an answer to the relevant question as to whether BCS offers the same OS or mastectomy in the cohort of young patients with breast cancer.

SHR indicates a not significant risk reduction of 10% favoring BCS vs mastectomy (SHR = 0.90; 95%CI: 0.80–1.00). We acknowledge that selection bias might be taken into account to justify the not significantly better outcome of patients who received BCS + WBRT due to the non-randomized design of all but one included papers. In order to reduce as much as possible the potential impact of a selection bias concerning tumor size we included in the analysis only papers which reported on patients with T1-T2 breast cancer.

Our study has a further limitation since three of the six studies included in our analysis are population-based database retrospective studies [21,37,40].

Four comparative studies between BCS and M in patients younger than 40 years were not included in the meta-analysis due to the lack of an adjusted HR for OS. The aim of these studies was the impact that both BCS and mastectomy have on local or loco-regional recurrence for young patients [11,34,36]. All but one study found that BCS was associated with a higher rate of LR or LRR when compared with mastectomy [11,35,36]. Conversely, in a subset analysis of 101 patients ≤35 years with stage I breast cancer, no significant difference was observed in the 10-year LRR rate (18% BCS vs 19.8% Mastectomy), distant metastasis and overall survival when comparing BCS versus mastectomy [34]. Interestingly, a better local control was achieved when radiation therapy is delivered after mastectomy [34,35].

It is also of note that patients with T1 breast cancer and 1–3 positive nodes had a better OS after BCS compared to mastectomy in two of the papers included in the meta-analysis [21,30]. The beneficial effect of radiotherapy on outcome seems a logical reason to explain the results of this analysis and previous reports. The recent data coming from the update of the meta-analysis of the EBCTCG on the effect of post-mastectomy radiotherapy support this argument. The authors concluded that after mastectomy and axillary dissection, radiotherapy reduced both recurrence and breast cancer mortality among women with one to three positive lymph nodes, even when systemic therapy was given [41].

While we want to be cautious in the interpretation of the borderline significantly improved OS after BCS, on the other hand data of the present analysis make extremely unlikely that mastectomy can actually provide young patients with a better OS compared to BCS. The large number of patients, the strict definition of age and the very recent included papers are the strengths of our analysis, apart from the severe statistical methods which have been carried out.

Mastectomy has traditionally been the standard treatment of breast cancer, until publication of multiple randomized clinical trials demonstrating an equivalent overall survival of BCS in patients with early-stage breast cancer [8–13]. However, BCS still remains debated in patients younger than 40 years because young age has been demonstrated as an independent risk factor for local recurrence after conservative treatment and more aggressive tumours are associated with this age-group of patients [1–6].

The results of this meta-analysis support the concept that combining wide local excision plus modern radiotherapy seems to be at least equivalent to the total removal of the breast gland in young patients as well as shown in older counterparts. This observation appears to be even more evident in the subset of node positive patients. Therefore, the increasing use of mastectomy in young patients may no longer be justified with the assumption of a better survival, whenever a conservative procedure can be technically and cosmetically pursued.

Table 4
Summary of Hazard Ratios and 95% confidence interval for overall survival, comparing breast conserving surgery and mastectomy.

<table>
<thead>
<tr>
<th>Authors [ref]</th>
<th>Category</th>
<th>HR for OS</th>
<th>95% CI</th>
<th>Variables used for adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voogd et al. [18]</td>
<td>&lt;40 y</td>
<td>1.11</td>
<td>0.62 – 1.99</td>
<td>Age, tumor size, lymph node status, vascular invasion, histological grade, Microscopic involvement of excision margins</td>
</tr>
<tr>
<td>Kroman et al. [37]</td>
<td>&lt;35 y</td>
<td>1.05</td>
<td>0.71 – 1.54</td>
<td>Tumor size, lymph node status, histological grade, estrogen receptor status, year of treatment and protocol allocation.</td>
</tr>
<tr>
<td>Bantema-Joppe et al. [21]</td>
<td>35–39 y</td>
<td>0.77</td>
<td>0.53 – 1.12</td>
<td>Age at diagnosis, pathological tumor size, adjuvant chemotherapy, adjuvant hormonal therapy and period of diagnosis</td>
</tr>
<tr>
<td>Van der Sangen et al. [38a]</td>
<td>N+</td>
<td>0.52</td>
<td>0.35 – 0.78</td>
<td>Age and period of diagnosis, tumor size, axillary nodal status and use of adjuvant systemic treatment</td>
</tr>
<tr>
<td>Mahmood et al. [39]</td>
<td>N0</td>
<td>0.93</td>
<td>0.83 – 1.04</td>
<td>Age, year of diagnosis, race, grade, progesterone receptor status, tumor size, number of positive and examined lymph nodes</td>
</tr>
<tr>
<td>Won Jeon et al. [40]</td>
<td>N+</td>
<td>0.93</td>
<td>0.65 – 1.33</td>
<td>Age, tumor size, hormone receptor status, adjuvant chemotherapy and hormonal therapy</td>
</tr>
</tbody>
</table>

OS: Overall survival, HR: hazard ratio, CI: confidence interval, y-years, N0: negative nodal status, N+: positive nodal status.

*a HR for Distant metastasis free survival.
In addition, the overall cumulative incidence of local reappear-
ance of the tumor after BCS + WBRT dramatically decreased in the
recent years and it is now below 1% at 5 years in the general popu-
lation being to date much lower than the historical 1% per year
[42].

Advances in diagnostic pre-operative work-up, should lead to a
better selection of patients for conservative surgery. The intro-
duction of more tailored and effective medical and radiotherapy
treatments have probably already reduced the incidence of local
recurrence in young women as well as pointed out in older women.
More recent series evaluating local control after breast conserva-
tion in young patients are requested to support this hypothesis.
For the time being, young patients (<40 years) should be reassured
that a more aggressive surgical attitude does not translate into an
increased likelihood of surviving breast cancer.

Conflict of interest statement

The authors indicated no potential conflict of interest.

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