



Oncological Safety of Breast Conserving Surgery in Breast Cancer

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Abstract

Background/Aim: Breast-conserving surgery is a type of surgery used as a treatment option for breast cancer. It was introduced at the end of the 20th century following and in accordance with relevant clinical studies. With heightened public awareness of breast cancer and the introduction of new diagnostic procedures, despite the proven oncological safety of this type of surgery, a growing number of women choose to undergo total mastectomy. The aim of this study was to confirm the oncological safety of breast-conserving surgery performed on breast cancer patients at the University Clinical Centre of the Republic of Srpska.

Methods: This study analysed 305 female patients with I and II stage of breast cancer, operated on between March 2009 and December 2013. One group of patients underwent breast-conserving surgery (BCS), followed by adjuvant radiation therapy and the other total mastectomy (MX). The patients were followed up for 5 years after the surgery. Analysed herein were the local-regional recurrence, distant metastases, disease-free survival and overall survival rates.

Results: After a five-year follow-up, the local-regional recurrence rate for patients in the BCS group was 4.3 %, while for the MX group it was 4.2 %. The overall survival rate of patients in the BCS group was 90.9 %, as opposed to 89.1 % for MX patients.

Conclusion: After a five-year follow-up, no statistically significant difference was observed between the two groups of patients regarding the local-regional recurrence ($p = 0.967$) and overall survival rates ($p = 0.610$). Breast-conserving surgery is an oncologically safe surgical treatment for breast cancer.

Key words: Breast cancer; Mastectomy; Breast-conserving surgery; Breast centre; Radiation therapy.

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Introduction

The 20th century saw a gradual decrease in the number of radical mastectomy procedures as the treatment of choice for breast cancer. This decrease reflected in the trend that began with the Halsted radical mastectomy as the gold standard at the turn of 20th century, to mid-century modified radical mastectomy, to breast conserving surgery at the end of last millennium.

Breast conserving surgery was introduced in the 1970s, as recommended by the World Health Organisation (WHO). The first clinical trials (Milan I, NSABP B-06) ensued, which sought to compare the overall survival rates (OSR) of breast conserving surgery (BCS) and radical surgery (MX) patients. Breast conserving procedures, which conserved the breast tissue, included post-

operative radiation therapy (RT).^{1, 2} In the late 20th century, axillary lymphadenectomy also became less radical, following the introduction of sentinel lymph node biopsy in breast cancer patients.³ Today, the results of trials (AMAROS, Z0011) showed that axillary dissection can be safely omitted in case of metastatic sentinel lymph node followed by RT.^{4, 5}

The introduction of screening mammography has shown that diagnosing breast cancer at an early stage, thus also performing surgery early on, has an impact on the disease prognosis. Since screening mammography was introduced in the EU, the mortality rate in some member states has dropped by up to 30 %, a piece of data that also indicates the importance of timely breast cancer surgery.⁶ By contrast, when it comes to breast cancer that has already led to distant metastases, local surgical treatment produces little effect, as studies conducted thus far have not proven the benefits of surgical treatment for patients with metastatic cancer.⁷

Although BCS has been shown to be oncologically safe when compared to MX, there is an upward trend in the number of radical mastectomies in developed countries.^{8, 9} Several reasons are reinforcing the trend, among which one is certainly better-quality diagnostic radiology. It has been easier to detect multifocal tumours since the introduction of breast magnetic resonance imaging (MRI). Also, the introduction of BRCA1 and BRCA2 gene mutation tests has resulted in a growing number of radical surgical procedures, including prophylactic surgery, which mainly comes down to mastectomy, with or without breast reconstruction. With raised public awareness about breast cancer and constant fear of recurrence of the disease on the one hand and women being inadequately informed on the other, more women opt for MX rather than BCS.¹⁰

Following recommendations of the European Society of Breast Cancer Specialists (EUSOMA) and other professional organisations, as well as resolutions adopted by the European Parliament to establish units and centres to focus exclusively on breast pathology, the University Clinical Centre of the Republic of Srpska (UCC RS) established a Breast Centre.¹¹ Prior to the establishment of the UCC RS Breast Centre in 2009, more precisely, between 2004 and 2008, a mere 3.4 %, or 14 out of 410 breast cancer patients treated at the UCC RS underwent BCS. In the first five years after the

establishment of the Breast Centre, the number of patients who underwent BCS rose to about 40 % and in 2013 it surpassed the number of mastectomised women. Also, during that period, a conserving surgery in the axilla was introduced using the sentinel lymph node biopsy procedure.¹²

The aim of this study was to confirm the oncological safety of BCS in comparison with MX, as performed at the UCC RS, irrespective of the molecular subtype of breast cancer.

Methods

The trial was retrospective study on patients who underwent surgery between March 2009 and December 2013 and conducted at the UCC RS (Banja Luka, Bosnia and Herzegovina) after it was approved by the UCC RS Ethical Committee as the authorising body. The patients were examined prior to the surgery and their cases presented to the Tumour Board. All surgeries were performed under general anaesthesia. According to the type of surgery, the patients were divided into two groups. The first group consisted of patients who had BCS and the second of patients who had MX (skin-sparing mastectomy, nipple-sparing mastectomy, simple mastectomy). BCS group was followed by RT no later than two months after surgery or adjuvant chemotherapy. The Nottingham score was used to determine histological grade of the tumour. The resection margins were examined under the microscope and those that showed 'no ink on tumour' were considered negative.

The study included the patients who met the following requirements: female patients, diagnosed with invasive breast cancer, stages I or II according to the AJCC (The American Joint Committee on Cancer, 8th ed) classification, free resection margin (R0), radiation therapy conducted following BCS and available medical reports on post-operative follow-up. The study did not include patients who had been administered neoadjuvant chemotherapy.

SPSS Statistics 24 software was used to interpret the obtained data statistically and to present the results in tabular form. The χ^2 -test was used with a significance level of $p = 0.05$. The survival proportion was estimated using the Kaplan-Meier

method and compared using the log-rank test. The rates of local-regional and distant recurrence were calculated for a five-year follow-up, from the time of the surgery to the disease recurrence. The disease-free survival rates (DFSR) were obtained for a five-year follow up, from the surgery to the moment of local and/or distant recurrence. The overall survival rates (OSR) were also calculated for a five-year follow-up, from the time of the surgery to the patient's death.

Results

The study included a total of 305 female patients with primary invasive breast cancer. The first

Table 1: Clinical and pathological characteristics of patients

| Characteristics | BCS n = 186 | MX n=119 | P value |
|--------------------------|--------------|-------------|-------------------|
| Age | | | |
| ≤ 50 | 21 (11.3 %) | 8 (6.7 %) | .362 [†] |
| 51 - 69 | 105 (56.4 %) | 74 (62.2 %) | |
| ≥ 70 | 60 (32.3 %) | 37 (31.1 %) | |
| pT stage | | | |
| T1a | 3 (1.6 %) | 0 (0 %) | .000 [†] |
| T1b | 27 (14.6 %) | 9 (7.6 %) | |
| T1c | 104 (55.9 %) | 51 (42.8 %) | |
| T2 | 52 (27.9 %) | 57 (47.9 %) | |
| T3 | 0 (0 %) | 2 (1.7 %) | |
| pN stage | | | |
| N0 | 141 (75.8 %) | 81 (68.1 %) | .139 [†] |
| N1 | 45 (24.2 %) | 38 (31.9 %) | |
| Stage (AJCC) | | | |
| I | 130 (69.9 %) | 53 (44.5 %) | .000 [†] |
| II | 56 (30.1 %) | 66 (55.5 %) | |
| Grade | | | |
| G1 | 27 (14.5 %) | 12 (10.1 %) | .515 [†] |
| G2 | 112 (60.2 %) | 74 (62.2 %) | |
| G3 | 47 (25.3 %) | 33 (27.7 %) | |
| ER/PR status | | | |
| Positive | 152 (81.7 %) | 97 (81.5 %) | .964 [†] |
| Negative | 34 (18.3 %) | 22 (18.5 %) | |
| HER2 status | | | |
| Positive | 29 (16.0 %) | 28 (23.5 %) | .083 [†] |
| Negative | 157 (84.4 %) | 91 (76.5 %) | |
| Histological type | | | |
| IDC NST | 139 (74.8 %) | 90 (75.6 %) | .323 [†] |
| ILC | 9 (4.8 %) | 10 (8.4 %) | |
| Other types | 38 (20.4 %) | 19 (15.9 %) | |

[†] χ^2 test; BCS: breast conserving surgery; MX: mastectomy; AJCC: The American Joint Committee on Cancer classification, 8th ed.; ER: oestrogen receptor; PR: progesterone receptor; IDC NST: invasive ductal carcinoma no special type; ILC: invasive lobular carcinoma

group (BCS) comprised 186 patients (61 %) and the MX group 119 patients (39 %). Most of the followed patients in both groups were between 50 and 69 years old, with only very few younger than 50 (BCS = 11.3 %; MX = 6.7 %). Most patients (72.1 %) who underwent BCS had a tumour of up to 2 cm, while for the MX group it was half the patients (50 %). No statistically significant difference was observed between the two groups regarding the lymph node status. Most patients (BCS = 75.8 %; MX = 68.1 %) had no metastases in axillary lymph nodes. Also, according to the histological grade of the tumour, there was no significant difference between the groups, with most patients (60 %) belonging to histologic grade 2. Hormone oestrogen and progesterone receptor positivity (ER/PR) was near equal for both groups (BCS = 74.8 %; MX = 75.6 %). Expression of the HER2 (human epidermal growth factor receptor) oncogene was greater in the MX group (23.5 %), as opposed to the BCS group (16 %) (Table 1).

Table 2: Analysis of LRR, DM, DFSR and OSR according to operative techniques

| | BCS n = 186 | MX n=119 | P value |
|------|--------------|--------------|-------------------|
| LRR | 8 (4.3 %) | 5 (4.2 %) | .967 [†] |
| DM | 16 (8.6 %) | 20 (16.8 %) | .030 [†] |
| DFSR | 165 (88.7 %) | 97 (81.5 %) | .078 [†] |
| OSR | 169 (90.9 %) | 106 (89.1 %) | .610 [†] |

[†] χ^2 test; LRR: loco-regional recurrence; DM: distant metastases; DFSR: disease-free survival rate; OSR: overall survival rate; BCS: breast conserving surgery; MX: mastectomy

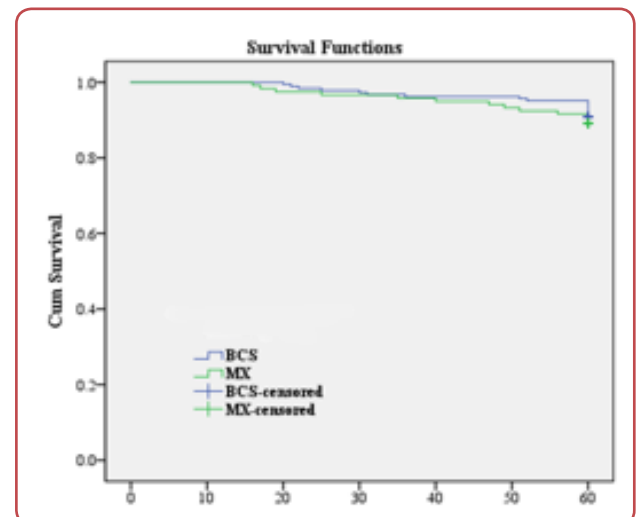


Figure 1: Overall survival proportion by operative techniques (months)

BCS: breast conserving surgery; MX: mastectomy

After a five-year follow-up, local-regional recurrence (LRR) was confirmed in 4.3 % patients who had undergone BCS and in 4.2 % patients who had MX. Over a five-year follow-

up, 17 (9.1 %) patients from the BCS group died, compared to 13 (10.9 %) patients in the MX group (Table 2). Using the Kaplan-Meier method, no statistically difference (Log Rank test = 0.307; $p = 0.580$) was obtained in the survival proportion between the BCS and MX groups.

Discussion

The results of first clinical trials in the last decades of 20th century indicated that even after a twenty-year follow-up, there were no significant differences between the OSR of patients who underwent BCS followed by RT over those who had MX. The Milan I trial showed that OSR was 75.7 % in MX patients relative to 73.9 % in patients with BCS.^{1, 2} Also, a study by the National Cancer Institute (NCI USA) that followed up patients for ten years returned no significant statistical results regarding OSR following BCS (77 %) and MX (75 %).¹³ In a 22-year follow-up study, Ariagade and colleagues found the OSR was significantly higher among BCS patients (60.3 % vs 49.5 %).¹⁴ The results of long-term (10-20 years) randomised studies that found no significant statistical difference in OSR between BCS and MX groups are consistent with the findings of this study, confirming no significant difference in survival between BCS and MX patients. After a ten-year follow-up, the Gustave Roussy Oncology Institute (France) published data that claims an 80 % survival rate following MX and 79 % survival rate following BCS.¹⁴ An 18-year follow-up study by the NCI claimed a 54 % OSR following conserving surgery and a 58 % OSR following radical surgery.¹⁵

The study found the rate of distant metastases significantly higher among the MX group (16.8 %), as opposed to patients who underwent BCS (8.6 %), a finding consistent with the fact the MX patients had tumours that were biologically more aggressive. Studies in which patients were followed during long-term intervals (20 years) returned a similar rate of distant metastases in the two groups.^{1, 2, 14, 16} Limitation of this study was a relatively short-term follow-up study (5 years), compared to those previously cited, which followed patients for much longer.

In the Milan I trial after a twenty-year of follow-up the rate of LRR in BCS patients was 8.8 % and 2.2 % in MX group.² In NSABP B-06 trial after ten-

year follow up in patients with BCS rate of LRR was 6.5 %.¹⁷ Plichta and colleagues in study with younger breast cancer patients found the LRR was higher among MX group (8.7 % vs 4 %).¹⁸ The results of two large European randomised trials showed similar rates of LRR between BCS and MX groups (10 % vs 9 %).¹⁹ When it comes to the rate of LRR of the disease, the study presented herein did not find a significant difference between the compared groups, ie between BCS and MX. The results show the same incidence of LRR of the disease after a five-year follow-up between BCS and MX groups.

The resection margin status appears to be a factor with a significant impact on the local recurrence rate. Today, the margin status after resection is considered negative when ink applied to the specimen reveals no cancerous cells touching its edge ('no ink on tumour').²⁰ A meta-analysis of studies aimed at assessing the influence of the resection margin width, namely, of 1, 2 and 5 mm, on the local recurrence rate did not find a significant difference between the different widths considered. The 'no ink on tumour' standard has also helped reduce the number of re-excisions done for the purpose of extending the surgical safety margin.¹⁷

The results of new trials suggest that post-operative RT in BCS reduces not only the risk of local and regional recurrences but also reduces the risk of breast cancer death.²¹ The results of a meta-analysis by EBCTCG (Early breast cancer trialists' collaborative group), which included 17 randomised trials, showed that adjuvant RT administered after BCS significantly reduced the potential of breast cancer cells to local recurrence and distant metastases.²² The study of Danish breast cancer cooperative group (DBCG) on a large population-based material suggest that patients with BCS have a better survival than patients who had mastectomy.²³ Also, Swedish national trial with six-year follow-up concluded that BCS followed by RT yielded better survival than MX patients irrespective of RT.²⁴

Conclusion

The results of the study confirmed the oncological safety of BCS in relation to MX in terms of LRR rates. Also, the results showed that MX group had a significantly higher rate

($p = 0.030$) of distant metastases in comparison with the BCS group. No statistically significant difference was found between the observed groups in terms of the LRR rate, DFSR and OSR ($p > 0.05$).

With adequate preoperative radiological diagnostics, histopathology reports, disease staging and an educated team of physicians, BCS followed by RT is an oncologically safe procedure. It is equally important for the patient to participate actively in her treatment in accordance with clearly presented information and data, which allow adequate decision-making.

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None.

Conflict of interest

None.

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