

Breast conserving surgery in multicentric breast cancer, preliminary data of our experience

S. Zervoudis^{1,2,3,4*}, G. Iatrakis^{1*}, P. Mares⁴, L. Boileau⁴, I. Grammatikakis⁵, N. Evangelinakis⁵, J.P. Daures⁴, I. Leteuff⁴, A. Avgoulea², T. Stefanos³, I. Navrozoglou³

¹TEI Technological University of Athens, Athens; ²Rea and Leto Hospital, Athens

³University of Ioannina, Department Obstetrics & Gynaecology, Ioannina

⁴University of Montpellier-Nimes, Department of Obstetrics & Gynecology & Biostatistics, Montpellier-Nimes (France)

⁵University of Athens, Attikon Hospital, 3rd Department of Obstetrics & Gynaecology, Athens (Greece)

Summary

Introduction: It is widely supported that multicentric disease of the breast (MCDB) is a contraindication of breast conservative surgery (BCS). **Materials and Methods:** This is a multicentric study (two breast cancer units from Greece, one from France) involving patients with at least two primary tumors in separate quadrants of the breast and no diffuse suspicious microcalcifications on mammography. Sixty-one patients were included in the study, but 49 were followed up to the end. Patients were randomly assigned in total mastectomy (TM) and BCS groups. End point of the study was disease-free survival rates three and five years after initial operation. **Results:** Three years after BCS, local recurrence (LR) was observed in two patients (7%) and one after five years (total recurrence rate:11%). A TM was performed in these patients, and in two there was no LR or distant metastasis (DM) five years after. The third patient was disease free two-years later. Three years after TM, eight patients (36.4%) had DM and 14 (63.6%) did not ($p = 0.004$). Five years after TM, eight patients (36.4%) had DM and 14 patients (63.6%) did not ($p = 0.03$). **Conclusion:** The results showed that conservative surgery was an alternative surgical option in multicentric breast cancer with good results regarding disease-free survival and recurrence.

Key words: Multicentric breast cancer; Conserving surgery; Total mastectomy.

Introduction

Multicentric disease of the breast (MCDB) is characterized by two or more primary tumors in separate quadrants of the breast. It was suggested that this kind of cancer is a contraindication of breast conservative surgery (BCS) [1]. However, there are no convincing data comparing BCS (wide excision of primary tumors) to total mastectomy (TM) in relation to survival. Furthermore, most existing research is retrospective [2, 3] or related to local disease control [3]. On the other hand, a possible impact on survival was shown in patients with ductal carcinoma in situ (DCIS) and multicentric (and contralateral) invasive tumors identified with preoperative magnetic resonance imaging (MRI) [4].

The purposes of the present study were: 1) to list patients characteristics with MCDB and 2) to prospectively compare the outcome of patients who underwent BCS with those who underwent TM in relation to disease-free survival (distant metastasis and local/regional recurrence).

Materials and Methods

This was a multicentric study involving patients from three breast cancer units (two from Greece and one from France). Patients included in the study had the following characteristics: 1) (at

least) two primary tumors in separate quadrants of the breast. These patients, classically, could be considered “ideal” candidates for TM; 2) there were no diffuse suspicious microcalcifications on their mammography.

Clinical information regarding age, tumor location, operation type, tumor size, lymph node involvement, stage, histologic grade, histopathology, necrosis, hormone receptor status, HER2/neu status, and disease-free survival were obtained from patient charts. Taking into account that tumor size and axillary lymph node involvement (Stage), hormone receptor status, and histologic grade have all been reported as important prognostic factors in breast cancer, these data were further analyzed. In total, 49 cases included in the study divided in two groups. In the first group (TM group), 22 cases (aged 23 to 83 years, mean = 57.5) were treated with TM and in the second one (BCS group), 27 cases (aged 29 to 75 years, mean = 58.1) were treated with BCS. Most patients were randomly divided in the above groups. However, three patients of the TM group ultimately refused TM and they were included in the BCS group. In the latter group, the following techniques were used, mainly depended on the size and the location of the tumors: 1) For seven patients, the round block (RB) technique (donut technique) was performed (Figure 1). This technique, originally described by Benelli in 1990 [5], allows a larger surgical field, securing a negative surgical margin of at least one cm around the lumps, and giving a good cosmetic result [6]; 2) for 20 cases, lumpectomy-tumorectomy (T), quadrantectomy (Q) (Figure 2), zonectomy (Z), and periareolar lumpectomy (periareolar tumorectomy [PT]) (Figure 3), were performed in nine, eight, two and one patients, respectively. In the present series, other oncoplastic techniques (vertical or lateral segmentectomy and batwing mastopexy) were not performed for the above cases. The procedures were explained to the patients who gave informed consent. Patients in the above groups had a histologically proven breast carcinoma and were staged both with the diameter of the

* These authors equally contributed to the study.



Figure 1. — Round block (RB) technique (donut technique) was performed, allowing a larger surgical field, securing a negative surgical margin of at least one cm around the lumps, and giving a good cosmetic result.



Figure 2. — Quadrantectomy was performed in eight cases.



Figure 3. — Periareolar lumpectomy (periareolar tumorectomy [PT]) was performed in one case.

largest tumor (LT) and the sum of the diameter of all tumors (ST). In this way, a patient with apparent earlier-stage with LT method, could be upstaged with ST method. However, in multiple foci of microinvasion (extension of cancer cells beyond the basement membrane within \leq one mm in greatest dimension), the size of only the largest focus was used. Dimpling of the skin, nipple retraction, or any similar skin changes were not recorded in data analysis because they do not change staging. None of the present patients had received multiple core biopsies, because the original tumor size should be reconstructed based on a combination of imaging and histologic findings. None of the present patients belonged to TX or NX classification, as these patients could not have a stage assigned to their disease, making them ineligible for inclusion in the study. In eight of the Q-T-Z-PT patients (BCS group), largest tumor was \geq two cm (2.1 - five cm) and resection of the tumors was achieved with a negative surgical margin both in frozen section and final pathology report. On the contrary, a patient of TM group, with a large tumor (five cm), had positive surgical margins in the final pathology report. Nevertheless, a positive surgical margin was discovered in two cases of small tumors

(< 2 cm and < 1 cm) in the final pathology report of the RB-Q-T-PT-Z patients.

The purpose of the present study was to compare free survival rates between TM and BCS patients three and five years after the initial operation. Initially, 61 patients were included in the study, but, in the final results, 12 patients were excluded because their surveillance period was less than three years and/or due to incomplete information. Data of some of the above patients will be included in a further study after the completion of at least three years after the initial operation. A negative clinical history and negative examination were used to designate a case as M0 (no metastasis). Chi-square analysis was applied in group comparisons (Mac Chi Square software). In cases of invalid results, due to cells with expected values less than 5, a Fisher-exact-test was used to measure the association between two variables in 2 x 2 contingency tables. In 2 x 3 contingency tables, the Freeman-Halton extension of Fisher's exact test was applied. In the above tests, p values were 2-sided and p values \leq 0.05 were considered significant. A further study is planned with more patients and further analysis of the data (using Kaplan-Meier curves and log-rank test).

Table 1. — Patients of both groups (total mastectomy [TM] and breast conservative surgery [BCS]) distributed according to positive (+) and negative (-) estrogen receptors (ER)/progesterone receptors (PR), HER2+/HER2-, grade (G) and histologic type (ductal carcinoma [DC], lobular carcinoma [LC] or other).

Group	Receptors				HER2/neu		Grade			Histology			
	ER+ PR+	ER-PR-	ER+ PR-	ER-PR+	HER2+	HER2-	G1	G2	G3	DC	LC	DC/LC	Other
TM	13	6	2	1	4	18	5	9	8	15	4	1	2
BCS	24	3	0	0	4	23	13	10	4	25	2	0	0
<i>p</i>	0.02				1.00		0.11			0.13			

Table 2. — Patients of both groups (total mastectomy [TM] and breast conservative surgery [BCS]) distributed according to Stage (I to IIIA) taking into account greatest diameter of tumor.

Group	Stage			
	I	IIA	IIB	IIIA
TM	9	5	5	3
BCS	14	5	5	3

Table 3. — Patients of both groups (total mastectomy [TM] and breast conservative surgery [BCS]) distributed according to Stage (I to IIIA) taking into account sum of tumors' diameter.

Group	Stage			
	I	IIA	IIB	IIIA
TM	3	9	5	5
BCS	10	8	5	4

Although better cosmetic results was the main reason that the present patients selected BCS, it must be emphasized that this factor was not examined after the operations and it was not included in the study (Figure 1).

Results

Most tumor characteristics were roughly similar between TM and BCS groups. However, percentages of positive (+) and negative (-) estrogen receptors (ER) and progesterone receptors (PR) differed in tumors of TM and BCS patients. In particular, in TM group, 13 (59%) patients were both ER+ and PR+, 6 (27%) patients were both ER- and PR-, two (9%) patients were ER+ and PR- and one (4,5%) patient was ER- and PR+. In BCS group, 24 (89%) patients were both ER+ and PR+ and three (11%) patients were both ER- and PR- ($p = 0.02$). Even so, in both groups, most patients had ER+ and/or PR+ (16 patients [73%] of the TM group and 24 [89%] of the BCS group) (Table 1) ($p = 0.3$). Rates of HER2+ were similar between groups with four patients in each group (18% and 15% for TM and BCS respectively) ($p = 1$). However, in BCS group, three HER2+ patients had both ER+ and PR+ and one HER2+ patient had ER- and PR-. In TM group, HER2+ patients had ER and PR in different combinations. Rates of grade 1, 2, and 3 tumors were similar in TM and BCS patients ($p = 0.11$) although a greater percentage of BCS patients had grade 1 tumors (five patients [23%] of the TM group and 13 patients [48%] of the BCS group). Interestingly, in TM group, grade 1 and/or grade 2 tumors had both ER+/PR+ in greater percentage (11 of 14 [79%]) compared with grade 3 tumors (three of eight [56%]), although this difference was not significant ($p = 0.08$). In TM group, 15 patients had ductal carcinoma, four patients had lobular carcinoma, and three patients had other histologic types or a histologic combi-

nation. In BCS group, 25 patients had ductal carcinoma and two patients had lobular carcinoma (Table 1).

Staging of both groups is shown in Tables 2 and 3.

As expected, taking into account sum of tumors' diameter upstaged some patients (six in TM group and four in BCS group). Different staging (Table 3 instead of Table 2) altered distribution of TM patients in Stages I and IIA ($p < 0.05$). Distribution of TM patients in Stages IIB and IIIA remained actually unchanged. In BCS patients, different staging did not alter significantly distribution of patients within stages.

Three years after BCS, local recurrence was observed in two patients (7%). Five years after BCS, local recurrence was observed in one more patient (total percentage of recurrences was 11%). A successful TM was performed in all three patients as second surgery procedure. In the first two patients, five years after TM, there was no new local/regional recurrence (LR) or distant metastasis (DM). Similarly, in the third patient, two years after TM, there was no new LR or DM. Therefore, none of the present patients had LR or DM, after TM as a second surgery procedure, in the follow-up period.

Three years after BCS, 26 (96.3%) patients had no distant metastasis (DM) and there was a DM in one (3.7%) patient. Interestingly, three years after TM, 14 (63.6%) patients had no DM and eight (36.4%) patients had DM ($p = 0.004$). "As expected", the greatest percentage (six out of eight patients in staging of Table 1 and seven out of eight patients in staging of Table 2) had Stage $\geq 2A$. Two of the previous eight patients, after two more years of observation, had no DM after appropriate treatment. Five years after BCS, 25 (92.6%) patients had no DM and there were two (7.4%) patients with DM. One of these patients had Stage I and one had Stage 2B in the initial staging of both

Tables 1 and 2. “On the contrary”, five years after TM, 14 (63.6%) patients had no DM and eight (36.4%) patients had DM ($p = 0.03$). Again, “as expected”, the greatest percentage: six out of eight patients (75%) in staging of Table 1 and seven out of eight (87.5%) patients in staging of Table 2) had Stage $\geq 2A$. DM comparisons between groups reached significance, however, small numbers could influence related results.

Discussion

Multicentric breast tumor (BT) could be defined as BT presenting as a separate focus outside the index quadrant and multifocal BT as BT present in two or more foci separated by five mm in the same breast quadrant [7]. However, they are different definitions of multicentric/multifocal (M/M) tumors in several studies. Taking into account that there is no distinct border between the quadrants of the breasts and evaluating the actual borders radiologically between the tumor foci is difficult, other authors considered M/M as one entity and defined M/M tumors as more than one tumor foci in the same breast histopathologically [8].

The reported incidence (RI) of multicentricity of breast cancer may depend on the extension of the pathological review and therefore varies in different references. As an example the RI for DCIS varies widely from 18% to 60%, raising questions about the importance of multicentricity. However, DCIS multicentricity is more likely to be around 30% to 40% [7]. Furthermore, pathological examination may incorrectly interpret contiguous intraductal spread as multicentricity. Similarly, >95% of local recurrences after treatment of DCIS occur in the same quadrant as the index lesion. This finding could be interpreted as residual untreated disease rather than multicentricity [7].

Surgical management options for breast cancer include mastectomy or BCS (surgical removal of the tumor, with negative surgical margins, followed by moderate-dose radiation therapy to eradicate any residual disease) [9]. Although it was suggested that the latter approach is not suitable for MCDB, more than ten years ago, the first suggestions appeared for BCS in MCDB [10]. To analyze the present data, patients staged initially with the diameter of the largest tumor. However, it could be suggested that taking the combined diameters of the multicentric tumors, and not just the diameter of the largest tumor, may give a clearer indication of the actual breast cancer stage, an approach that could alter the final decision related to the planned procedure. The mode by which the diameter of the tumor is measured may be extremely important because it was shown that tumor size (before any tissue is removed for special studies, such as for hormone receptors or HER2/neu status) is an important prognostic factor for multicentric and multifocal breast cancer. Recently, it was found that the diameter of the largest deposit provides a better fit in a multivariate model for overall survival than aggregate diame-

ter (and aggregate volume) [11]. Therefore, it is suggested that tumor size in multicentric and multifocal breast cancer should (continue to) be measured using the diameter of the largest deposit [11]. Furthermore, some physicians could be hesitant to assign a classification of M0, feeling that there is always a remote possibility that occult metastatic disease may exist. However, the present authors used a negative clinical history and a negative examination to designate a case as M0 according to related staging guidelines [12]. The present data dispute that MCDB is not suitable for BCS. On the contrary, it seems that conservative surgery, at least, does not adversely influence disease-free survival (DFS). In case that the present data will be confirmed in further studies, it could be hypothesized that BCS actually improves DFS. Operation method could be added to well known factors predicting DFS as the positivity of the ER and PR, histologic grade, the presence of necrosis, pT stage, pN stage, and the presence of inflammatory breast cancer [8]. On the contrary, the presence of adjuvant chemotherapy and radiotherapy and chemotherapy type such as taxanes or anthracycline-based regimens were not related with DFS in multicentric tumors [8].

In accordance with the present findings, in the aforementioned retrospective trials [2,3], it was suggested that in selected patients with MCDB, wide conservative surgery is a safe therapy [2] that is not associated with poor local disease control and can be considered whenever acceptable cosmetic results can be achieved [3]. The “wide” negative surgical margins of tumor resections must be emphasized in BCS procedures. These findings should not be confused with the fact that multicentric (and multifocal) disease of the breast imparts an unfavorable prognosis on the disease-free survival of breast cancer patients in comparison to unifocal tumors and the presence of multicentric (and multifocal) tumors is associated with advanced pT and pN stages (pathologic classification [8]).

Conclusion

The present study showed that conservative surgery is an alternative surgical option in multicentric surgery with good results regarding the “disease-free survival” and the percentage of “recurrence”. Moreover the oncoplastic techniques performed give very good cosmetic results with high rate of satisfaction in women who avoid the damaging mastectomy. Further studies with more cases should confirm the present experience.

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Address reprint requests to:
 S. ZERVOUDIS, M.D., PhD
 REA Hospital, Department of Mastology,
 Syggrou Avenue 383, Athens 17564 (Greece)
 e-mail: szervoud@otenet.gr