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A retrospective study on multifocal and multicentric vs. unifocal breast cancer. Preliminary results

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Abstract

Multifocal (MF) and multicentric (MC) breast cancers have been comprehensively studied, but they still remain a controversial subject for many senologists in regards to the best treatment options. Conservatory approach is reserved preponderantly to unifocal localization of the invasive breast carcinoma while in MF and MC the radically techniques are still the main option. The real impact of MC and MF breast cancers on survival is still unknown, but it is presumed to be worse. MF and MC breast cancers are currently over treated by radical mastectomy (RM). The AMAROS trial and also the Z0011 trial recently demonstrated that less surgery does not necessarily mean less local control or worse survival outcomes. About 450 women that underwent surgery for breast cancers stages I-III were included in this monocentric retrospective study; clinical and pathological data were obtained from the database of the Institute of Oncology "Prof. Dr. Alexandru Trestioreanu" Bucharest. Our primary objective was to see if there is any difference in disease free survival in early breast cancer patients primary treated by conservative surgery according to unifocal (UF) vs. MF vs. MC feature of the invasive component. Our secondary objectives were to identify if there is any correlation between the conservative or radical type of surgery and other clinical and histologcal characterstics; if there is any differences in survival between UF vs. MF vs. MC breast carcinoma. Median follow-up was of 51 months. MC and MF cancers were present in 38 patients (8.4%) and 13 (2.9%) respectively and most of them were treated with mastectomy (6 MF and 19 MC) rather than with breast conservative surgery (BCS). In the entire data analyzed there was no statistical difference between event free survival (EFS) in the subgroup that underwent BCS vs. radical surgery (RS): 21 events (16.4%) vs. 53 events (16.61%) (p=0.957), median EFS 99.79 mo 95% CI [92.67-106.91] mo vs. 98.19 95% CI [92.81-103.56] mo (p=0.773). We found a significant correlation between recurrence and a family history of cancer (p=0.035), the tumor/node/metastasis (p<0.001), type of surgery (p= 0.035). Relapse rate wasn't significantly different whatever the type of surgery done. Median EFS wasn't different between patients that underwent BCS and those that underwent RS. BCS is a reasonable option in selected UF/MC/MF cancers, particularly in younger women with small breast tumors.
Keywords: *breast conserving surgery, multicentric/multifocal breast cancer, survival, unifocal, relapse, recurrence*

Introduction

The simultaneous presence of multiple breast cancer lesions, is a well-known issue of the last several years, and until the publication of some randomized trials which targeted the association between quadrantectomy and radiotherapy, it was disincentive to treat breast cancer with non-mutilating techniques[1-2].

The presence of more than one distinct tumor in different quadrants of the breast, is referred to as multicentric (MC) breast cancer, and multifocal (MF) breast cancer is defined also by the presence of more than one lesion, but in the same quadrant[3].

The incidence of MF/MC breast cancer is still unclear, mostly due to the misdiagnosing preoperatively by mammography and ultrasound or post-operatively at pathological examination. In studies made on the mastectomy specimens the incidence has been reported of 40-70% of cases[4-5].

As a result of the high incidence of breast carcinomas, different strategies for diagnosis and prevention for women with a high risk for breast cancer have been developed, such as surveillance, chemoprevention therapy (i.e. tamoxifen), bilateral oophorectomy and/or subcutaneous bilateral prophylactic mastectomy[6].

The increased preoperative use of magnetic resonance imaging, also increased the detection of additional breast lesions. With this preoperative imaging method, finding multiple tumors in the same breast, the rates of mastectomy have also suffered an ascending trend. Based on old, retrospective which suggested a high rate of local relapse in women with MC breast cancer, undergoing breast conserving surgery (BCS), many surgeons still preffer masstectomy in this cases[7].

Receptors for estrogen and progesterone should be measured in primary breast tumors and also in metastatic disease, in order to determine if the patient should or shouldn't receive hormonal therapy[8].

Recent retrospective studies, like the one made by Gentilini et al.[8], reported small local recurrence rates following BCS, in patients with MF/MC breast cancer. The rates of local recurrence were comparable with the ones observed in patients with unifocal (UF) breast

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cancer, thus making the authors to conclude that BCS is a reasonable surgical option for women diagnosed with multicentricity of the breast.

MC and MF breast carcinomas have a higher involvement of the lymph nodes, compared to the UF breast cancer, and current data suggests that these types of breast cancers have worse overall outcomes than UF breast cancer. The outcome in breast cancer is dependent on several factors, such as hormone receptor expression and the size of the tumor.

In this retrospective cohort study, we aim to investigate the impact of MC/MF breast cancer, defined according to the tumor/node/metastasis (TNM) classification, on disease free survival, but we also aim to investigate the recurrence rates, correlation between MC/MF and other pathologic, immune histologic features, lymphatic and vascular invasion, and the impact on surgical approach according to MC vs MF vs. UF status in current practice in Romania.

Methods

In this retrospective monocentric cohort study, we analyzed 5125 patient files, from which 450 have met the inclusion criteria. All of the patients were addressed for surgery to Institute of Oncology „Prof. Dr. Alexandru Trestioreanu" Bucharest between January 2007 and January 2012.

Informed consent was obtained from all patients included in the study.

Inclusion criteria were: age greater than 18 years, primary treated by surgery, stages IA-IIIA, invasive histology, patients exposed to adjuvant chimiotherapy (CHT), radiotherapy (RT) and hormonal therapy (if applicable) and a minimum follow up of 36 months from the time of diagnosis. In the exclusion criteria table we included patients with metachrone homolateral breast cancer, patients with other localization synchrone cancer or bilateral breast cancer (Table 1).

We used the internationally recognized definition for MC and MF disease which labels MF breast cancer as lesions localized in the same quadrant, and MC as lesions that can be found in different quadrants. Patients that presented with both MC and MF breast cancer, were defined as being multicentric.

The collected data was analyzed with SPSS Statistics version 22.0. Statistical significance was defined as $p<0.05$ in two-sided test results. Comparison and correlation of categorical variables were made by X2 test. Hazard ratios and 95% confidence intervals (95% CI) were calculated and validated using the Cox proportional hazards model. Survival curve was made using the Kaplan Meier test and the long rank test was used to determine the differences in EFS between groups.

Results

The clinical cohort subsisted of 450 patients with histologically confirmed breast cancer.

In this cohort, 412 (91.6 %) patients had UF- BC [median age: 54 years (range 24-81)], 27 (6%) had MF- BC [median age: 57, 44 years (range 36-79)], and 11 (2.4%) had multicentric BC [median age: 56 years (range 35-72)]. 24-91)]. Of the patients in the UF group 12.9 % (53 patients) were premenopausal, and 63.1% (260 patients) were postmenopausal. In the MF group 14.8% (4 patients) were premenopausal and 62.9% (17 patients) were postmenopausal, and in the MC group 18.2% premenopausal and 54.5% postmenopausal. The rate of premenopausal women was not significantly (Pearson v2 $p>0.05$) higher in MC (18.2 %) and MF (14.8 %) than in UF (12.9 %) patients.

There was not found a statistical significant difference between the 3 groups (UF, MF, MC) regarding the tumor staging (Pearson v2 $p>0.05$). Most of the cases in the selected study group were stages T1/T2.

Regarding the lymph nodes with capsular rupture, the analyzed data showed a significantly (Pearson v2 $p<0.05$) difference between the three groups. In the UF group 279 patients (67.7%) had no capsular rupture and in 106 (25.7%) of them the rupture was present. MF 22 (81.5%) with and 2 (7, 4) the capsular rupture was present; in the MC subgroup, all the patients were free of lymph nodes with capsular rupture.

We couldn't find any difference in regards of the tumor grading, most of the patients for UF (55, 1%) and MC (72.7%) being G2, while for the MF (55.6%) the majority was G3.

In 421 patients were found records about adjuvant CHT (93.6%) of which 230 patients (51.1%) received anthracycline only containing regimen, 75 patients (16.7%) taxane-antracycline either sequential or concomitant and in 39 patients (8.7%) a regimen taxanes based was administrated. In 77 patients (17%) other

Table 1 Inclusion and exclusion criteria for the study

Inclusion Criteria	Exclusion Criteria
■ Age >18 years ■ Primary treated by surgery breast cancer stage IA-IIIA ■ Invasive histology ■ Exposed to adjuvant CHT, RT and HT (if applicable) ■ Minimum follow up of 36 months from the time of diagnosis	■ *In situ* carcinoma ■ Phyllodes tumor ■ Metachrone homolateral breast cancer ■ Bilateral cancer ■ Other localization synchrone cancer

Table 2 Basic characteristics of the study group

Variable/Population	Unifocal N=412(91, 6%)	Multifocal N=27(6%)	Multicentric N=11(2. 4%)	P
Age				
Median **Range**	54 24-81	57,44 36-79	56 35-72	0,350
Menopausal status				
Premenopausal **Perimenopausal** **Menopausal** **Unknown**	53 (12.9%) 97 (23.6%) **260 (63.1%)** 2 (0.4%)	4 (14.8%) 5 (18.5%) **17 (62.9%)** 1 (0.3%)	2 (18.2%) 3 (27.3%) **6 (54.5%)** 0 (0%)	0.945
Tumour grade				
G1 **G2** **G3**	30 (7.3%) **227 (55.1%)** 137 (33.25%)	2 (7.4%) 10 (37%) **15 (55.6%)**	1 (9.1%) **8 (72.7%)** 2 (18.2%)	0.167
Lymphnodes with capsular rupture				
No **Yes** **Unknown**	**279 (67.7%)** **106 (25.7%)** 27 (6.5%)	**22 (81.5%)** **2 (7.4%)** 3 (11.1%)	**11 (100%)** 0 (0%) 0 (0%)	**0.016**
Adjuvant CHT				
Antracycline only **Antracycline and Taxanes** **Taxanes only** **Other regimen** **Unknown**	**199 (48.3%)** 72 (17.5%) 38 (9.2%) 75 (18.2%) 28 (6.8%)	**22 (81.5%)** 3 (11.1%) 0 (0%) 1 (3.7%) 1 (3.7%)	9 (81.8%) 0 (0%) 1 (9.1%) 1 (9.1%) 0 (0%)	**0.017**
Radiotherapy				
Tumour's bed **Tumour's bed and lymphnode's areas** **Boost** **Unknown**	**139 (33.7%)** **136 (33%)** 22 (5.3%) 115 (30%)	**15 (55.5%)** **7 (25.9%)** 0 (0%) 5 (18.5%)	**7 (63.6%)** **4 (36.4%)** 0 (0%) 0 (0%)	0.093
Lymph vascular invasion				
No **Yes** **Unknown**	**367 (89.1%)** 24 (5.8%) 21 (5.1%)	**19 (70.4%)** 4 (14.8%) 4 (14.8%)	**10 (90.9%)** 0 (0%) 1 (0.1%)	0.075
PgR				
0% **1-10%** **>10%** **Unknown**	97 (23.5%) 50 (12.1%) **254 (61.7%)** 11 (2.7%)	8 (29.6%) 8 (29.6%) **10 (37.3%)** 1 (3.5%)	2 (18.2%) 2 (18.2%) **7 (63.6%)** 0 (0%)	0,056

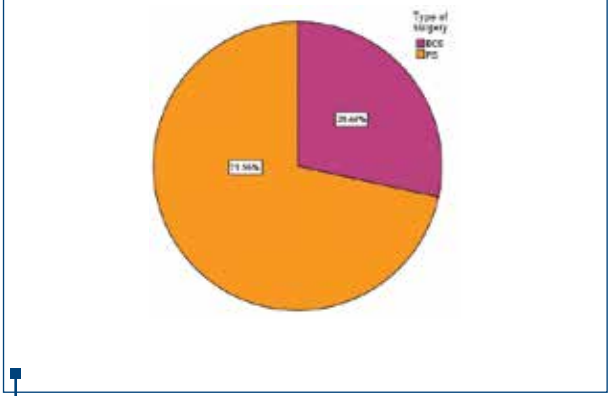

Figure 1. ***BCT and RS repartition in general breast cancer population***

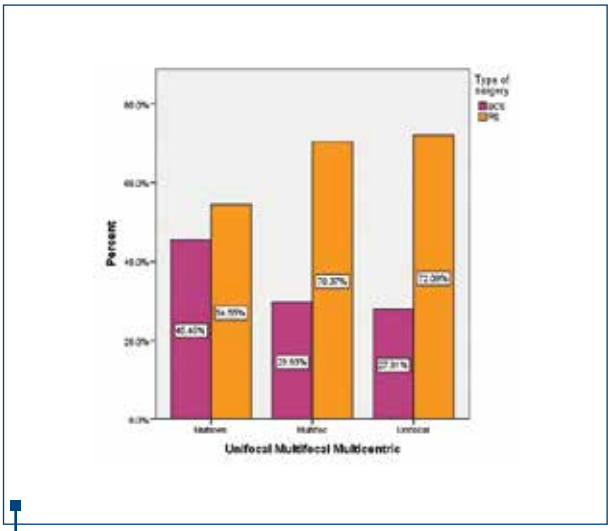

Figure 2. ***Conservative and radical surgery proportion inside UF, MF, MC subgroups***

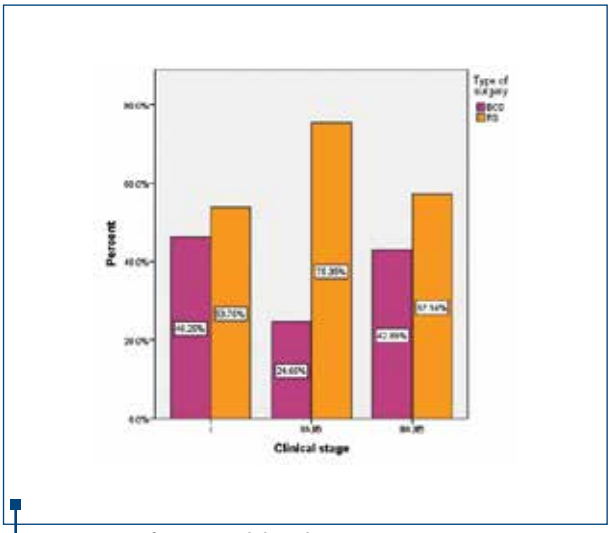

Figure 3. ***Type of surgery and clinical stages***

regimens such as CCyclophosphamide Methotrexate 5 Fluorouracil were prescribed.

In 73.4% cases (309 patients) were found registrations about postoperative irradiation in which, in 32.7% cases (147 patients) lymph nodes' area was included and in 4.9% (22 patients) supplementary tumors bed was provided.

As regarding UF/MF/MC status, were found marginally correlated with lymphovascular invasion (p=0.075) and progesterone receptor expression (p=0.56). The basic characteristics are shown in Table 2.

Surgical approach was found to be significantly correlated with pathologic tumor pT (p=0.04) and lymph node stage pN(0.023) and marginally with size of invasive component of the carcinoma (p=0.068) and capsular rupture (p=0.078).

We then analyzed the study cohort with regards of the type of surgery chosen; from the total of 450 patients (100%), 128 (28.4%) underwent breast conservative therapy (BCT) and 322 (71.6%) underwent radical surgery (RS) (Figures 1 and 2). There was no difference between the age of the patients (median age for BCT was 52 and for RS was 55, p >0.05).

Data showed a significant difference (Pearson v2 p <0.05) in respect to the body mass index (BMI) of the patients [BCT: 59 patients (46.1%) with a BMI ≤25 and 34 patients (26.6%) with a BMI 25-29; radical surgery 108 patients (33.6%) BMI ≤25 and 115 patients (35.7%) BMI 25-29]. Additionally, in the case of tumor staging, there were significantly (p<0.0001) more patients with stages IIA, IIB in the RS group (Figure 3).

The tumor's clinical size also played a significant role in the choice of treatment, with 207 (64.3%) patients from a total of 263 patients with tumors bigger than 2 cm, which underwent radical mastectomy (p <0.0001).

There was no difference (p=0.844) found between the two groups regarding the histological type, the vast majority (83.6%) of them being ductal invasive, from which 110 (85.9%) in the BCT group and 266 (82.6%) in the radical approach group. The basic characteristics are shown in Table 3.

As regarding recurrence, in BCS vs. RS in univariate analysis, it was found a significant correlation with Charlson index (p=0.012), family history of cancer (p=0.035), cTNM (p<0.0001), type of surgery (0.035), size of invasive component (0.021), tumor grade (p=0.002), pN (p=0.001), lymph nodes' capsular rupture (p=0.007), surgical specimen margins' infiltration (p =0.031), lymphovascular invasion (p=0.038), RT providing and marginally with *in situ* carcinoma identification (p=0.058). Proceeding to Cox regression it was found that only family history of cancer (HR =3.736, 95%CI [0.848-16.457], p=0.042) and margins infiltration (HR=1.657, 95% CI [0.756-3.632], p=0.027) were prognostic for EFS.

Median EFS wasn't different between patients that underwent BCS 94.54 mo, 95% CI [87.54-101.55] and those that underwent RS, 99.30 mo, 95% CI [94,36-104,24], log rank 0,004, HR=0.985 95 %CI [0.598-1.62], p=0.952 (Figure 4).

Table 3 The basic characteristics of the population

Variable/Population	Total N=450 (100%)	Breast conservative surgery N=128 (28.4%)	Radical surgery N=322 (71.6%)	P
Age				
Median **Range**	54.50 24-81	52 24-80	55 29-81	0.064
BMI				
≤25 **25-29** **≥30** **Unknown**	**167 (37.1%)** 149 (33.1%) 95 (21.1%) 39 (8.7%)	**59 (46.1%)** 34 (26.6%) 25 (19.5%) 10 (7.8%)	108 (33.6%) **115 (35.7%)** 70 (21.7%) 29 (9%)	0,041
cTNM				
I **IIA,IIB** **IIIA,IIIB** **Unknown**	80 (17.8%) **357 (79.3%)** 7 (1.6%) 6 (1.3%)	37 (28.9%) **88 (68.8%)** 3 (2.3%) 0 (0%)	43 (13.3%) **269 (83.5%)** 4 (1.2%) 6 (1.9%)	**<0.0001**
Tumour's clinical size				
<1cm **1cm-2cm** **>2cm** **Unknown**	2 (4%) 178 (39.6%) **263 (58.4%)** 7 (1.6%)	2 (1.6%) **70 (54.7%)** 56 (43.8%) 0 (0%)	0 (0%) 108 (33.5%) **207 (64.3%)** 7 (2.2%)	**<0,0001**
Histological type				
Ductal invasive **Lobular invasive** **Mixt (ductal and lobular)** **Other type**	**376 (83.6%)** 24 (5.3%) 39 (8.7%) 11 (2.4%)	**110 (85.9%)** 6 (4.7%) 9 (7%) 3 (2.3%)	**266 (82.6%)** 18 (5.6%) 30 (9.3%) 8 (2.5%)	0.844

Relapse rate wasn't significantly different whatever the type of surgery was: overall 16.7% (25 patients) with 17.2% (22 patients) in conservative group vs. 16.5% (53 patients) in radical group (p=0.852). In unicentric bearing patients, relapse rate was 16% (66 patients) vs. 18.5% (5 patients) in those with multifoci invasive carcinoma and 36.4% (4 patients) in MC appearance of the breast cancer (p=0.196).

Discussion

In this retrospective population based study, we found that EFS was comparable for the UF and MC/MF groups, regardless of the type of surgery (RS or conservative surgery).

The incidence was lower for MF and MC breast cancer, than the incidence in other studies[9-14]. This fact can be attributed to the fact that the data we studied was the one that was available in the patient's charts, with

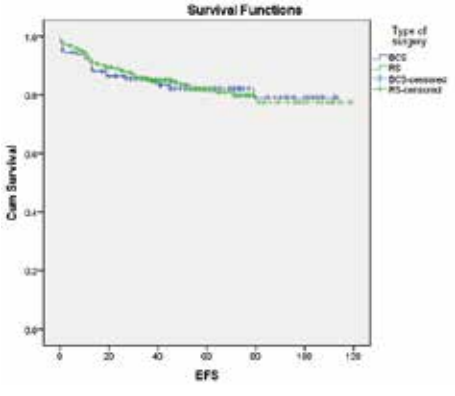

Figure 4. Cumulative survival according to type of breast cancer's surgery approach: conservative or radical

no specific pathology/radiology desire in focusing to diagnose MC or MF disease. We also presume that in the UF group, were also malignant foci that were not identified. The relapse rate was equal between the UF and the MF groups (16%, respectively 18.5%), while in the case of MC group the rate was higher (36.4%).

Of those patients treated with BCS, only 2.9% were MC/MF. Out of 450 patients included in the study, 322 had RS (71.6%) and only 128 (28.4%) BCS, and only 10% of them for multicentricity and multifocality. Therefore, it is either alone presence of MF or MC breast cancer that represents a strong factor in determining the type of local therapy or that it is highly linked to other factors which influence this decision[15].

Our study has several limitations. Although our data suggests that MC breast cancer is associated with a higher rate of node involvement that can suggest a more aggressive disease; and also that it is associated with a higher rate of relapse, our survival studies are on small periods on time, hence, this is limiting our ability to understand the long-term clinical implication of our finding.

Despite the limitations of a monocentric retrospective study, our experience can support the hypothesis that these types of breast cancer have a potentially more aggressive outcome.

Ultimately, this study did not yet managed to answer the question of surgical therapy, showing that there is an acute need of future studies, stratified on focality that will eventually help physicians making the correct decision when choosing the surgical treatment.

Conclusions

The subject of multicentricity and multifocality of breast cancer is still a highly debated one, worldwide and even more in our country. The lack of standardized guidelines for diagnosing and treating this disease, not only makes it hard for researchers to indentify the real incidence and overall outcomes, but also for surgeons when choosing the adequate treatment. ■

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