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ORIGINAL ARTICLE

Clinical characteristics and management of a Greek female patient cohort with breast conserving treatment

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Summary

Purpose: *The purpose of this retrospective single-center study was to examine histopathological characteristics and treatment options in a cohort of Greek female patients treated with breast conserving surgery (BCS) and to evaluate potential predictive factors of breast cancer (BC) local recurrence.*

Methods: *The clinic's medical records from 1995 up to the end of July 2016 were scanned in order to identify female patients treated with BCS. We recognized 1175 patients who underwent BCS, representing 35.8% of the entire sample (3281 patients).*

Results: *The mean age of the patients enrolled in this study was 54.7 years, with a median follow-up period of 58.5 months. Nine deaths (0.8%) were registered with 5-year overall survival (OS) rate being 100%. Regarding adjuvant therapies, radiotherapy (RT) was assigned to 94.4% of the patients, endocrine therapy to 86.0%, chemotherapy to 51.3%, while all therapies were given simultaneously to 38.3% of the sample patients. Herceptin was administered to 14.1% of the patients. Twenty-eight recurrences (2.4%) with 3 deaths (10.7%) were confirmed. Over all traditional parameters studied, only lymph node status appeared to be statistically correlated with local recurrence (p=0.005). T3 stage can be considered as a hint that this tumor size might be a risk factor of local recurrence. Age at diagnosis seems to be an independent factor of BC local recurrence.*

Conclusions: *A very low rate of local recurrence (2.4%) was validated which can be attributed to patients being appropriately selected for BCS, who were then enrolled in this study, and to the uniformity of the RT plan.*

Key words: *breast cancer, breast Conserving Therapy, local recurrence, quadrantectomy, risk factors*

Introduction

Traditionally, until the late 1970s the surgical treatment of BC was basically limited to mastectomy. Breast conserving treatment (BCT) consists of BCS and whole breast RT, aiming to achieve long-term local disease control with minimum local morbidity. Women referred to BC centers with screen-detected lesions are often patients with early-stage BC and therefore suitable candidates for BCT.

This fact can be attributed to a series of factors, such as early detection of abnormal mammographic findings, higher level of knowledge among women concerning issues related to BC awareness [1] and the evolution of modern surgical approaches (oncoplastic surgery) . For the majority, BCT is responsible for an acceptable cosmetic result [2] associated with lower levels of psychological morbidity, notably less anxiety and depression cases and

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improved body image, sexuality and self-esteem, compared to mastectomy [3,4]. Two systematic reviews performed many years ago showed equivalence in terms of disease outcome between BCT and mastectomy [5,6].

Methods

The current study was performed in a single centre, is of retrospective nature and evaluates a Greek female population. Our breast clinic in Athens acts as a referral clinic, thus admitting patients from all over Greece. All patients of this referral breast clinic who underwent BCT beginning from the opening of the breast clinic in May 1995 up to the end of July 2016 were included in this study, so as to allow for a minimum follow up period of one year, i.e. until the end of July 2017. Patients who were lost to follow up were excluded from the analysis (25 cases). The date of diagnosis in the sample ranged from July 1995 to July 2016. Women who died from causes other than BC and had at least one year of follow-up prior to that event were retained in the analysis. The study protocol was approved by the participating institutes' ethics committee.

The following data were analysed for each patient according to the clinic's records: age at diagnosis, menstruation status, tumor size, tumor grade, number of positive lymph nodes excised, surgery details, as well as ER, PR and C-erbB-2 status. The last three parameters were measured in a scale of 0 up to 3+, as frequently described in the literature [7] but their binary form (i.e. positive - negative expression) was also estimated and explored. Furthermore, the expressions of Ki-67 and p53 were also recorded, along with the presence of multifocality, microcalcifications and necrosis. Finally, information on the assigned treatment type (chemotherapy, RT, hormonal therapy with tamoxifen) was also assessed. Notable is the fact that no patients received immunotherapy. The main variable of interest was relapse (binary: 0= No, 1= Yes).

Statistics

Statistical analyses were performed using the R Statistical Software, version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/) and all figures were produced using the *ggplot2* package of R. The categorical parameters were summarized by their absolute (N) and relative (%) frequencies in the sample. All continuous parameters had skewed distributions (after the Shapiro-Wilk normality test results) and thus, were described by their median (MED), their interquartile range (IQR) and their minimum and maximum value, though the mean (M) has been selectively added when deemed necessary. Any missing values were explicitly mentioned for every parameter under investigation and were excluded from the calculation of the various summary statistics.

The differentiation of skewed quantitative parameters according to binary variables, such as dichotomous ER/PR expression (i.e. positive-negative), was tested using the Wilcoxon test. The x^2 test was used to check on the potential relation between qualitative parameters of interest, and when its assumptions were not met (i.e. all expected frequencies must be larger than 5) the Fisher's exact test was used instead. A significance level of 5% was used throughout the analyses, but results that were

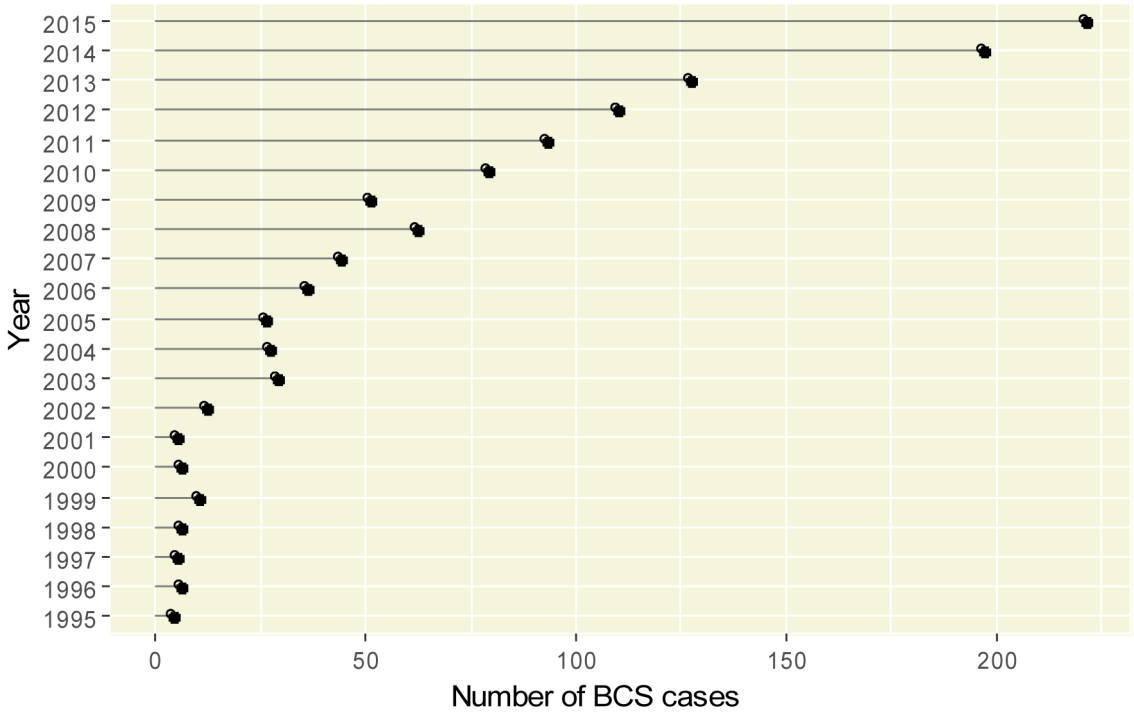

Figure 1. Absolute frequencies of the breast conserving surgery (BCS) cases per year for the current study (2016 is excluded from the chart as a non-completed year).

significant at the 10% significance level were also reported, as potentially deserving further investigation in future studies.

Results

According to the medical records of the specific referral breast clinic, 1175 out of 3281 (35.8%) BC patients underwent BCT in the time period under study. In particular, Figure 1 depicts how the number of BCT cases ranged per year starting from 1995 up to 2015; year 2016 was excluded from the graph as a non-complete year. Age at breast surgery ranged from 19 to 90 years with mean age equal to M= 54.7 years (SD= 12.7 years). Considering the menopausal status of the patients, 422 women (35.9%) were pre-menopausal, 58 women (4.9%) were peri-menopausal and 695 women (59.1%) were post-menopausal. The median follow-up period in the sample was MED=58.5 months (IQR=67.2 months, M=74.5 months). Nine deaths were recorded (0.8%), with 5-year OS being 100%.

The majority of women in the sample (593 women, 51.6%) had intermediate histological tumor grade (II), 399 women (34.7%) had high tumor grade (III) and only 157 women (13.7%) had low tumor grade (I); overall, there were 26 missing grade values. The diameter of the tumor ranged from 1mm up to 75mm with a somewhat right skewed sample distribution as expected, and 13 missing values; the median tumor size was MED=15.0mm (IQR=11.0mm). The TNM-staged tumor sizes appeared in the following frequencies: 860 T1 (73.2%), 297 T2 (25.3%), 9 T3 (8.0%) and 9 Tx (8.0%). The TNM recording also provided information about the lymph node stage in the sample patients: 780 N0 (66.4%), 301 N1 (25.6%), 48 N2 (4.1%), 19 N3 (1.6%) and 27 Nx (2.3%).

After analyzing the results of immunohistochemical tests conducted, it was found that the median value of Ki-67 was MED=15% (IQR=23%, max=90%) indicating considerable overexpression among the sample patients (22 missing values). The expression of p53 ranged from 0 to 100% with MED=10% (IQR=35%, M=23.5%, 186 missing values). Using a threshold of 10%, 821 patients (69.9%) had overexpression of Ki-67, whereas 530 patients (45.1%) had overexpression of p53.

Regarding estrogen and progesterone receptors, ER expression was positive in 955 patients (81.6%) with 5 missing values; in particular , 162 women (13.8%) had moderate ER expression (++) and 793 (67.8%) had high ER expression (+++), while the remaining 215 women (18.4%) had negative or weak ER expression (-/+). PR expression was positive in 738 women (63.1%), of which 454 (38.8%) had PR= +++ and 284 (24.3%) had PR= ++ (6 missing values). In combination, 721 women (61.4%) were both ER and PR positive. C-erbB-2 was positive in 370 patients (31.8%) and negative in the rest 795 patients (68.2%), after excluding 10 missing values. Overall, 109 patients (9.3%) were triple-negative (i.e. ER, PR, C-erbB-2 negative).

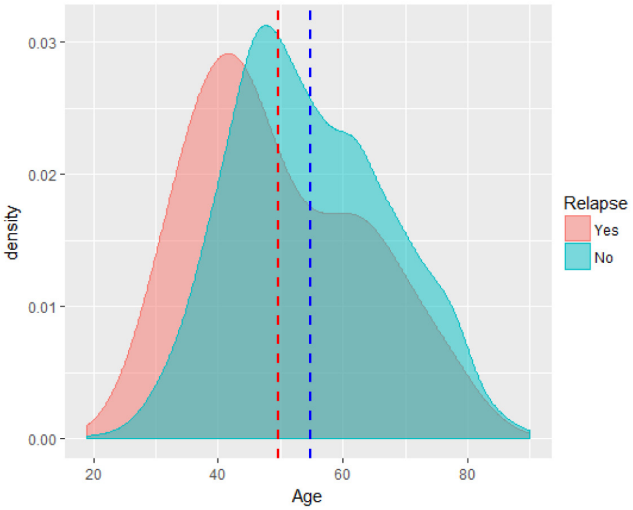

Figure 2. Density plot of age at diagnosis per relapse category (Yes/No), with a vertical dashed line for the sample mean age of each group.

Table 1. Quantitative characteristics of sample and association with relapse. Association is assessed via the Wilcoxon two-sided test

Parameter	*Non-relapsed cases (n= 1171;97.6%)*	*Relapsed cases (n= 28;2.4%)*	*p value*
	Median (IQR), range	*Median (IQR), range*	
Age (years)	54.0 (19.0), 19-90	44.5 (20.0), 31-76	0.027
Tumor size (mm)	15.0 (11.0), 1-75	17.0 (10.5), 5-72	0.86
Ki-67	15.0 (23.0), 0-90	12.5 (16.8), 0-70	0.23
p 53	10.0 (35.0), 0-100	5.0 (31.2), 0-95	0.74

Multifocality was identified in 68 women only (5.8%, 5 missing values), necrosis was found in 130 women (11.1%, 4 missing values), while in 96 women (8.2%, 3 missing values) microcalcifications were observed.

In terms of the various therapies assigned, RT was assigned to 1103 patients (94.4%), hormonal therapy was given to 1004 patients (86.0%), while chemotherapy was suggested to 599 patients (51.3%). It is notable that in the case of 450 women all three aforementioned therapies were assigned. Herceptin was only given to 165 patients (14.1%). Each of the four therapy-related variables had 7 missing values in the sample.

Association with relapse

Out of the 1175 women of the sample, only 28 recurrences (2.4%) were identified, out of which 3 deaths (10.7%). Table 1 depicts the variation and association of quantitative characteristics between relapse and non-relapse cases. Of these, only age was found to be associated with relapse (p=0.027); in particular, the relapsed cases had a median age that was 10 years lower than the non-relapsed cases with median age under relapse being 44.5 years vs. 54.0 years for non-relapses. The density plots of age and the respective means for the relapse and non-relapse groups are depicted in Figure 2. Tumor size, Ki-67 and p53 were not significantly associated with relapse, although the latter parameter had a lot of missing values in the subsample of relapses, so the power of the corresponding statistical test is deemed low.

Table 2 shows the difference of qualitative characteristics between relapsed and non-relapsed cases. Here, the histological tumor grade was not

Table 2. Qualitative characteristics of the sample patients and association with relapse

Parameter	*Non-relapsed cases (n= 1171;97.6%)*	*Relapsed cases (n= 28;2.4%)*	*p value*
	n (%)	*n (%)*	
Menopausal status†			0.94
Pre-menopausal	411 (35.8)	11 (39.3)	
Peri- menopausal	57 (5.0)	1 (3.6)	
Post-menopausal	679 (59.2)	16 (57.1)	
Grade†			0.89
I	154 (13.7)	3 (10.7)	
II	577 (51.5)	16 (57.1)	
III	390 (34.8)	9 (32.1)	
Tumor size stage (TNM)†			0.09
Tx	8 (0.7)	1 (3.6)	
T1	840 (73.2)	20 (71.4)	
T2	291 (25.4)	6 (21.4)	
T3	8 (0.7)	1 (3.6)	
Lymph node stage (TNM)†			0.005
Nx	23 (2.0)	4 (14.3)	
N0	763 (66.5)	17 (60.7)	
N1	297 (25.9)	4 (14.3)	
N2	46 (4.0)	2 (7.1)	
N3	18 (1.6)	1 (3.6)	
ER			0.50
Positive	934 (81.8)	21 (75.0)	
Negative	208 (18.2)	7 (25.0)	
PR			0.94
Positive	721 (63.2)	17 (60.7)	
Negative	420 (36.8)	11 (39.3)	
C-erbB-2			>0.99
Positive	361 (31.8)	9 (32.1)	
Negative	776 (68.2)	19 (67.9)	

†Fisher's exact test was performed instead of x^2 test

Table 3. Association between relapse and therapies assigned on first diagnosis (7 cases with missing values have been excluded; thus n=1168). To appropriately illustrate the clinical significance, percentages have been calculated per row, i.e. over the number of patients in each therapy group

Parameter	*Number of patients in each therapy group*	*Non-relapsed cases (n=1140;97.6%)*	*Relapsed cases (n=28;2.4%)*	*p value*
		n (%)	*n (%)*	
Radiotherapy†				0.016
Yes	1103	1080 (97.9)	23 (2.1)	
No	65	60 (92.3)	5 (7.7)	
Chemotherapy				0.96
Yes	599	584 (97.5)	15 (2.5)	
No	569	556 (97.7)	13 (2.3)	
Hormonetherapy†				0.27
Yes	1004	982 (97.8)	22 (2.2)	
No	164	158 (96.3)	6 (3.7)	
Herceptin†				0.78
Yes	165	162 (98.2)	3 (1.8)	
No	1003	978 (97.5)	25 (2.5)	

†Fisher's exact test was performed instead of x^2 test

significantly different according to relapse or not (p=0.89). Similarly, the menopausal status was not statistically associated with relapse (p=0.94). Tumor size (as stemming from TNM) was barely significantly differentiated between relapsed and non-relapsed cases, whereas lymph node status (also stemming from TNM) was clearly significantly differentiated between relapsed and non-relapsed cases. Specifically, T3 stage appeared in a higher percentage among the relapsed cases compared to the other T stages in the sample (p=0.09); the related percentage rose from 0.7% for the non-relapsed cases to 3.6% for the relapsed ones. The same held for N2 and N3 lymph node stages whose percentages almost doubled when passing from the non-relapsed to the relapsed cases (4.0 to 7.1% and 1.6 to 3.6%, p=0.005). No statistically significant association with relapse was revealed for multifocality, necrosis and microcalcifications (all p values>0.05, not included in Table 2).

If we focus only on the relapsed cases and look at their evolution over time, that is how they evolved between the first diagnosis and the relapse, there are some interesting things to note. The median time difference between the two diagnoses was 5.5 years (IQR=9.2, range= 0-24).

Only 9.5% of the women that experienced relapse went from grade III to grade II; another 9.5% moved from grade I to grade III, 14.3% went from grade II to grade III, while the majority of patients (66.7%) retained their previous grade level (either II or III).

The median difference between the tumor size at second and first diagnosis was -3mm (IQR=16, range=(-60)-57), indicating smaller tumors at the time of relapse. Considering the TNM-related tumor size stage, 50% of women with T1 tumors developed tumors of the same stage while 12.5% turned to T2 and 37.5% to Tx; 50% of the women with T2 tumors developed T1 tumors the second time while 16.7% had T3 and 33.3% had Tx tumors; two women with T3 and Tx tumors developed T1 tumors on relapse. Seven women of N0 lymph node stage at first diagnosis had a similar node stage on relapse, one woman developed N1 disease and 7 women N0 stage once more; one woman of N1 initial node stage went to N0, and two went to Nx stage tumors. The two women among the relapsed cases that initially had N2 stage tumors then developed Nx, and a woman of N3 stage then developed N0 stage tumor.

16.7% of the initially negative ER women turned to positive on relapse, whereas 7.1% went from initially positive to negative. The respective figures for PR were 11.1% and 18.2%. Regarding C-erbB-2, 27.3% of the initially negative women then appeared as PR positive and 57.1% of the initially positive women turned to C-erbB-2 negative status.

The values of Ki-67 and p-53 did not change much between the two diagnoses (median difference= 0 in both cases); specifically, the difference of Ki-67 between the two time points ranged from -55% up to 35% and for p53 this range extended from -20% up to 50%. No statistical significance

was found for any of the aforementioned variables comparing their values at first diagnosis vs. relapse, though this was expected due to the very small number of relapsed cases in the sample.

Treatment methods and relapse

The association of relapse with the various treatments assigned on first diagnosis was thoroughly investigated. The results are depicted in Table 3. What is interesting is the fact that there were only 2.1% relapsed cases out of the 1103 women assigned to RT at first diagnosis , whereas the respective relapse percentage for women not assigned to RT was 7.7% (p=0.016). The rest of the therapeutic methods assigned on first diagnosis did not present any statistically significant pattern in relation to relapse. The percentage of relapse in case of chemotherapy assignment (2.5%) was slightly higher but not significantly different than in the case of no such treatment (2.3%). Similarly, hormonal therapy had 2.2% relapsed cases in the sample compared to 3.7% of relapses in absence of such therapy. Herceptin treatment had a 1.8% relapse rate versus 2.5% among women that did not receive herceptin.

Isolating only the sample women that experienced relapse and investigating the treatments assigned on first diagnosis and on relapse, here are a few findings. Half the women that were not initially assigned to RT were then suggested to follow this treatment; also, 21.1% of the women that had RT after the first diagnosis were not assigned to this treatment on relapse. Moreover, 95% of the women that had endocrine treatment on first diagnosis were also advised to do the same on relapse and 66.7% of the women that did not initially receive this kind of treatment were later told to do so. Chemotherapy was not assigned for a second time in 15.4% of the women who had been assigned accordingly on first diagnosis, while 70% of the women that had not initially received it were then advised to follow this treatment. Finally, herceptin was given once more to 33% of women who received it on the first diagnosis, while it was given for the first time on relapse to 90% of the cases that had not received it initially. As before, the therapies assigned between the two time points (first diagnosis and relapse) did not differ significantly, though the respective statistical tests had limited power due to the small number of relapsed cases in the sample.

Other interesting correlations

We investigated the potential correlation between tumor size stage and Ki-67/p53 expressions. Significance occurred in both cases (x^2=56.7, p<0.001 for Ki-67; x^2=9.9, p=0.02 for p53). Notably, the median Ki-67 rose from 15 to 35% by a step of almost 5% for T1, T2, T3, Tx respectively (IQR ranged from 15 to 40%). Regarding the median p53, it dropped from 27.5% (in Tx) to 10% (in T1 and T2) to 2.5% (in T3) with IQR ranging from 15 to 51%.

Lymph node stage was also significantly associated with Ki-67 (x^2=22.3, p<0.001); the median Ki-67 in the sample rose from 23 to 25% when comparing N0 to N2/N3 and equaled to 27.5% under Nx. Lymph node stage was not associated with p53 (x^2=3.1, p=0.54), although the median p53 dropped from 10% in N0/N1/N2 to 5% in N3.

As expected, the differentiation of tumor size by tumor grade was highly significant (p<0.001) as of course was the respective tumor stage variable (p< 0.001); the sample median tumor size for grade I tumors was 10mm (IQR=7mm) as opposed to the sample median sizes for grade II and III tumors that were equal to 15mm (IQR=9mm) and 18mm (IQR=11mm), respectively.

There was also a clear association of the lymph node stage (stemming from TNM) with tumor grade (p<0.001). Specifically, the relative frequency of N0 in grade I cases was 82% vs. 66% in grade II cases and 61% in grade III, the relative frequency of N1 in grade I cases was 13% raising to 28% for grade II/III cases and the relative frequency of N2 started from 0% for low differentiated tumors up to 7% for highly differentiated grade tumors.

Tumor size stage was significantly associated with ER (p< 0.001), PR (p= 0.02) and C-erbB-2 (p=0.02). More specifically, T1 tumors rose from 60% in ER negative patients to 80% in ER positive patients, while T2 tumors dropped from 40 to 20%, respectively. Similarly, T1 tumors rose from 70% in PR negative patients to 80% in PR positive patients, whereas T2 tumors dropped from 30 to 20%, respectively. The picture got reversed regarding C-erbB-2, where T1 tumors fell from 80% in C-erbB-2 negative patients to 70% in C-erbB-2 positive patients, while T2 tumors increased from 20 to 30%, respectively. C-erbB-2 was also significantly associated with lymph node stage (p=0.007), with N0 stage cases decreasing from 70 to 60%. and N1 and N2 stage cases increasing by 10% from C-erbB-2 negative patients to C-erbB-2 positive patients.

Ki-67 was also highly associated with tumor grade (p<0.001), increasing from 5% under grade I to 10% under grade II and soaring up to 30% under grade III (respective IQR= 6%, 13% and 30%). On the other hand, a significant relation was revealed between tumor grade and the following parameters: ER (p<0.001), PR (p<0.001) and C-erbB-2 (p<0.001). Indicative is the fact that

the percentage of high grade tumors (i.e. grade III) in negative and positive ER cases was 80% and 20%, respectively. Similarly, the percentage of high grade tumors in negative and positive PR cases was 60% and 20%, respectively. On the contrary, the percentage of grade III tumors increased from 30% to 50% in negative and positive C-erbB-2 cases respectively.

Discussion

Long-term follow-up data from several randomized clinical studies have demonstrated that BCT in appropriately selected patients with early BC is an oncologically safe procedure with survival and local/systemic recurrence rates similar to those verified from patients treated with mastectomy [8-10]. Nowadays, BCS is performed more frequently due to the implementation of wide population-based mammographic screening programs, the development of modern RT techniques, and the introduction of new therapeutic adjuvant agents. Studies evaluating predictive factors of BC local recurrence are of paramount importance as they permit the assessment of the progression of disease after primary conservative treatment.

The rate of local recurrence in the present study was 2.4%, while the 5- and 10-year OS rates were 100% and 95.6%, respectively. RT played an important role in the crucial issue of local disease control. Several studies have outlined the benefit of RT demonstrating about 70% decrease of the local recurrence rate (6 to 45% without RT) [11]. On the same issue, we revealed that the local recurrence rate in the group not receiving RT was almost 4-fold higher (7.7 vs 2.1% relapsed cases) than that observed in the RT group. It is notable that all 9 deaths reported in this study occurred after 60 months of follow-up. The OS rates were quite high compared to what reported by other authors [11]. However, it should be highlighted that this is reasonable given the considerably low recurrence rate observed. The generalization of this finding is probably limited or should at least be confirmed by other studies in the future.

The effect of young age has been well proven in most studies on prognostic factors [12-14]. The mean age of patients at the time of diagnosis and at the time of relapse differed by 10 years, suggesting that age could be a potential predictive factor of local recurrence. Previous clinical data suggest that increased expression of HER-2 increases cellular resistance to radiation and thus increases recurrence rate after BCS [15]. In a case–control study, Hafty and his colleagues showed that in the group with recurrence compared with the control group increased HER-2 expression was a predictive factor of breast cancer recurrence [16,17]. Since trastuzumab was not available to all HER-2 positive patients, due to the lack of this agent before 2004, in this study it was not possible to establish any relationship between c-erbB-2 expression and local recurrence.

Triple negative phenotype was described as an independent prognostic factor for OS and local recurrence in several studies [18-20]. In their retrospective study, Chen et al. demonstrated that BCS followed by systemic treatment was not a risk factor for tumor relapse in TN patients and should not influence the choice of surgical modality in favor of mastectomy based on histology only [21]. Likewise, in our study, where triple negative tumors were more frequent (25%) in the relapsed group than in the non-relapsed group (9.8%), it was not possible to determine any correlation between this particular molecular subtype and the risk of local recurrence.

Regarding the margins of resection, controversies arise from the lack of consensus on the safely removed breast tissue volume and end up to the definition of what can be called “clear margins”. Margins microscopically characterized as disease-free are the least prerequisite following breast conserving interventions for treating malignancy. Further enhancement to the support of this increasingly accepted surgical practice emerged upon the announcement of a 33-studies’ meta-analysis conclusions. According to its results, positive margins were responsible for ipsilateral breast tumor recurrence at an odds ratio of 2.44, whereas close margins had an odds ratio of 1.74, and, in any case, both showed statistical significance when comparison to negative margins took place [20]. When looking at different threshold for negative margins, 1 mm was as good as wider margins. The data on ink on surgical limits were insufficient and there were minimal data on this margin included in a meta-analysis [22]. For this reason, the most commonly used negative margin is that of 1 mm and, therefore, this is what is considered as clear margin cut-off in our institute.

A notable finding concerns tumor size which is barely significantly differentiated between relapsed and non-relapsed cases, with T3 stage appearing 5-fold more frequently in the former group of patients compared to the latter. This might be considered as a hint that tumor size may be a risk factor of local recurrence, but further investigation is required by future studies.

Even more importantly, lymph node status is significantly different between relapsed and non-relapsed cases; N2 and N3 lymph nodes ap-

proximately doubled when passing from the non-relapsed to the relapsed cases, suggesting a strong association with local recurrence which is statistically verified.

Regarding the rest of the variables investigated in the current study, such as p53, Ki67, multifocality, necrosis etc, it was not possible to establish any potential association with local recurrence.

Conclusions and Limitations

In our patient group, the rate of local recurrence and/or distant metastasis was 2.4% (28 out of 1175 cases). This rate is low compared to other published figures when lumpectomy is followed by RT. Factors contributing to this result may be: (i) RT played a major role in controlling local recurrence of BC treated with minimal surgery procedures; (ii) a uniform plan for RT was carried out by a single radiation oncologist and was applied to 94% of the sample patients; (iii) most of our patients were node-negative with stage I, II BC; and (iv) surgical margins were clear in almost all of the cases. Among all the traditional predictive factors, age at diagnosis and lymph node status seem to be considerably associated with a higher risk of local recurrence in patients treated with BCS according to international guidelines, while there is also a hint regarding the impact of tumor size on local recurrence that should be further investigated.

A limitation of the current study is its retrospective nature; however, we have tried to minimize this constraint by including data from only a single referral center. Additionally, some variables had many missing values and therefore were not adequately investigated.

Conflict of interests

The authors declare no conflict of interests.

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