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Loco-Regional Recurrence after Conservative Breast Surgery Followed by Radiotherapy versus Mastectomy Alone for T1-2 and N0-1 under the Umbrella of Modern Adjuvant Chemotherapy

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Abstract

Background: Breast cancer is one of the most commonly observed malignancies in women worldwide. The aim of this retrospective study is to identify and assess the risk factors that might predict loco-regional recurrence after breast conservative surgery (BCS) and modified radical mastectomy (MRM) after the introduction of modern adjuvant chemotherapy.

Results: In this study 191 (65.2%) patients underwent MRM and 102 (34.8%) underwent BCS. Except for age and pathological T stage, the distribution of the other clinico-pathological parameters between the two procedures has not significant differences. Tumor size has a local recurrence risk by 4 folds after BCS in T2 stage compared to T1 stage (P=0.02). Lympho-vascular invasion (LVI) shows increase of risk of recurrence to 1.4 after MRM (P-0.02). It shows dramatic increase after BCS to 41 folds (P=0.000). The risk of local recurrence is equal to two folds for positive LVI after BCS compared with MRM (P=0.005). DCIS has increased local recurrence risk by 12 folds after BCS (P=0.001) which has been eliminated if MRM was performed.

In bivariate analysis, negative DCIS has tendency to reverse the risk of local recurrence. After MRM, the risk of local recurrence in ER negative cases and PR negative cases is increased by about 4 folds and 2.7 folds respectively (p=0.005, 0.042 respectively).

Conclusion: For BCS; T stage, Lympho-vascular invasion and DCIS are risk factors for LRR. For MRM; LVI, positive ER and PR are risk factors for LRR. Radiotherapy may have a role in decreasing the recurrence rate after BCS and may be recommended after MRM for T1-2, N0-1 stages.

Keywords: Breast cancer; Breast Conservative Therapy; Early Breast Cancer; Breast Cancer Local Recurrence

Introduction

Breast cancer is one of the most commonly observed malignancies in women worldwide.

In two prospective randomized trials with long-term follow-up for early-stage breast cancer, breast-conserving surgery followed by radiotherapy (BCS+RT) and modified radical mastectomy alone (MRM) produced similar survival rates [1,2]. With accumulating evidences from prospective clinical studies on breast-conserving therapy, the consensus among experts is that there are no significant differences in the local recurrence and mortality rates between conserving therapy and radical mastectomy in breast cancer patients. As BCS+RT offers a better appearance, more functionality, and more psychological benefits than radical mastectomy as well as fewer complications and shorter hospitalization duration than other therapies, there is a progressive shift from total mastectomy (TM) to BCS+RT for treating early-stage breast cancer [3-7]. However, a considerable proportion of patients with early-stage breast cancer still undergo mastectomy because of multifocal or multi-centric tumors, diffusely scattered micro-calcifications, and persistent positive margin after repeated attempts at BCS, or patient preference. Young age, hormonal status, DCIS and lympho-vascular invasion (LVI) has been established as risk factors of local recurrence after mastectomy.

Some authors believe that advances in systemic regimens over the last decades have substantially reduced the risk of local recurrence in early-stage breast cancer and limited the role of adjuvant local treatment however; this is a point of debate [9-11].

The aim of this retrospective study is to identify and assess the risk factors that might predict loco-regional recurrence after BCS followed by radiotherapy in comparison to MRM after the introduction of modern adjuvant chemotherapy.

Patients and Methods

This is a retrospective study that included 325 patients who had undergone modified radical mastectomy followed by adjuvant chemotherapy and/or hormonal therapy or breast conserving surgery followed by adjuvant chemotherapy and/ or hormonal therapy with whole breast irradiation at South Egypt Cancer Institute, Assiut University, Egypt in the period from June 2010 to December 2015. All cases were primary diagnosed as early breast cancer (T1, T2 and N0, N1) with no metastasis. In this study, demographic data and data about the primary tumor site, size, stage and histopathology as well as associated comorbidity and operative, postoperative data were recorded. All patients have bilateral sono-mammography and if not conclusive MRI may be considered, pelvi-abdominal ultrasonography, chest x-ray and if suspicious CT chest could be considered. Bone scan was done if alkaline phosphatase was raised or in symptomatizing patients. Patients with positive surgical margins, prior cancer, and those with synchronous bilateral breast cancer were excluded from the study. The study was approved by the local Institutional Review Board Committee and conducted in accordance with the Declaration of Helsinki. For patients underwent breast-conserving surgery a wide local excision of the primary tumor with level I and II axillary lymph nodes dissection have been done. The tumor was widely excised with at least a 2 cm free margin. Axillary dissection was performed through the same incision in the outer tumors and through a separate incision in the inner tumors. For patients underwent modified radical mastectomy, level I and II axillary dissection was performed. At histopathology examination, positive surgical margin was defined as identification of cancer cells within 5 mm of the resected margin; negative surgical margin was defined as absence of cancer cells within 5mm of the resected margin. All patients received adjuvant chemotherapy. Endocrine therapy was given for at least two years. All patients who underwent breast-conserving surgery received whole breast irradiation. Adjuvant chemotherapy was started within 3–6 weeks after surgery. For patients with lower-risk disease chemotherapy regimen was six cycles of anthracycline-based chemotherapy (FEC). FEC (5- fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2) every 3 weeks for total of 6 cycles. For patients with higher-risk disease, three cycles of FEC (5- fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 every 3 weeks) were given followed by docetaxel 100 mg/m^2 every 3 weeks for three cycles. Only patients with HER2-positive breast cancer offered adjuvant trastuzumab. Endocrine therapy was offered according to the hormonal receptor status (HR) for Estrogen and Progesterone receptors (ER and PR) and menopausal status of patients; where Tamoxifen was used in premenopausal women and Aromatase Inhibitors (AIs) were used in postmenopausal women for five years in patients with HR +ve disease. In each group patients' characteristics including those suspected to be correlated to local recurrence were analyzed including age, tumor size (T), lymph node status (N) hormone status and histo-pathological characteristics. The disease was staged according to the 2010 TNM Staging for Breast Cancer (AJCC) system [12]. At follow up, patients were monitored every month for the first 6 to 12 months after treatment, in 2- or 3-month intervals for the next 2 years and at least 6-month intervals thereafter. Follow-up time was counted fromthe date of diagnosis to the date of the first event, or to the last known confirmed date of breast cancer disease- free status. Totally, 27 (9%) patients were lost to follow up. Biopsy was performed to confirm all loco-regional recurrences histologically.

The chi-square test or the Fisher's exact test was used to compare patient characteristics between the treatment groups. Loco-regional recurrence (LRR) was defined as the first tumor recurrence at tumor bed for BCS or in the field of mastectomy or chest wall, axillary lymph node, and/or Supra-clavicular lymph node area. Associations with local recurrence after BCS or MRM were evaluated using univariate analysis of risk factors for LRR followed by multivariable Cox proportional hazards regression model and summarized with hazard ratios 95 % confidence intervals (CIs). P value ≤0.05 was considered statistically significant.

Results

In this study, 325 patients with early breast cancer have been evaluated retrospectively from June 2010 till the end of 2015 to detect the risk factors of local recurrence. Only 293 patients could have enough data to be included in the study.

In this study 191 (65.2%) patients have undergone MRM, and 102 (34.8%) patients have undergone BCS. Except for age and pathological T stage, the other clinico-pathological parameters distribution between the two procedures has not significant differences (Table 1). The age distribution between the two procedures was significant (p=0.000) which is attributed to larger number of patients with BCS compared to smaller ones with MRM were present in the age category less than 40 years. Most patients with pathological T1 stage (61%) have done BCS while most patients with pathologic T2 stage (79%) have performed MRM (P=0.000).

In this study, we analyzed the risk factors of local recurrence according to operative type.

Table 2 and Table 3 show risk factors estimation for local recurrence after BCS and MRM. Young age (<40 years) at diagnosis was associated with 30% increase in ipsi-lateral breast tumor recurrence (IBTR) after BCS and 65% increase after MRM however these increases did not reach significant differences.

We also compared local recurrence according to tumor size which shows significant increase in local recurrence by 4 folds after BCS in T2 stage compared to T1 stage (P=0.02). This increase in the risk of local recurrence was not found after MRM. No significant difference has been found in this study when local recurrence after MRM has been compared to that after BCS according to T stage.

Variable		MRM=191	BCS=102	Total=293	P-value
Age	<40y	21	26	47	0.000
	>40y	170	76	246	
T stage	T1	44 (40%)	65 (60%)	109	0.000
	T2	147 (80%)	37 (20%)	184	
N stage	N0	80	48	128	0.391
	N1	111	54	165	
LVI	+ve	42	18	60	0.485
	-ve	149	84	233	
DCIS	+ve	33	24	57	0.226
	-ve	158	78	236	
ER	+ve	116	54	170	0.188
	-ve	75	48	123	
PR	+ve	109	53	162	0.402
	-ve	82	49	131	
L.R	+ve	22	11	33	0.900
	-ve	169	91	260	

Table 1: Clinico-pathological data of the whole patients

Variable		Recurrent	Non-recurrent	R.R	CI	P-value
Age	<40	4	17	1.6	0.429_4.124	0.396
	>40	18	152			
T stage	T1	6	38	1.3	0.429_2.977	0.644
	T2	16	131			
N stage	N0	8	72	1.6	0.356_2.077	0.445
	N1	14	97			
LVI	+ve	6	36	1.4	1.527_3.145	0.0231
	-ve	16	133			
DCIS	+ve	5	28	1.5	0.500_3.290	0.291
	-ve	17	141			
ER	+ve	7	109	4	0.211_1.321	0.005
	-ve	15	60			
PR	+ve	8	101	2.6	0.279_1.675	0.042
	-ve	14	68			

Table 2: Univariate analysis of risk factors of Local Recurrence (MRM group)

Variable		Recurrent	Non-recurrent	R.R	CI	P-value
Age	<40	3	23	1.15	0.335_4.246	0.684**
	>40	8	68			
T stage	T1	4	61	3	0.108_1.421	0.018*
	T2	7	30			
N stage	N0	5	43	1.1	0.329_3.431	0.863**
	N1	6	48			
LVI	+ve	9	9	41	6.165_334.95	0.000*
	-ve	2	82			
DCIS	+ve	8	16	12	1.565_43.380	0.0001*
	-ve	3	75			
ER	+ve	5	49	1.1	0.221_2.435	0.400*
	-ve	6	42			
PR	+ve	6	47	1.1	0.299_3.117	0.917*
	-ve	5	44			

Table 3: Univariate analysis of risk factors of local recurrence in BCS

We did not observe any statistically significant difference between patients with N0 and N1 nodes after BCS or MRM.

While lympho-vascular invasion (LVI) shows increase of relative risk (RR) of recurrence to 1.4 after MRM, it shows dramatic increase after BCS to 41 folds (P=0.02, 000 respectively).

The presence of DCIS has been found to increase local recurrence risk by 12 folds after BCS (P=0.001) however this risk has been eliminated if MRM was performed.

In bivariate analysis, negative LVI reverses the relative risk of local recurrence and negative DCIS has tendency to reverse this relative risk of local recurrence. Positive LVI has a significantly raised RR to 2 fold (Table 4).

Variable		MRM	BCS	R.R	CI	P value
Age	<40	3/21	3/26	0.81	0.183_3.528	0.702**
	>40	16/158	7/73	0.95	0.421_2.270	0.899**
T stage	T1	5/44	3/65	0.4	0.128_1.995	0.148**
	T2	14/147	7/37	1.98	0.581_3.034	0.114**
sN stage	N0	7/80	5/48	1.19	0.139_1.227	0.713**
	N1	12/111	5/54	0.86	0.324_2.327	0.641**
LVI	+ve	8/42	7/18	2	0.712_3.947	0.005*
	-ve	11/149	3/84	0.48	0.016_0.943	0.018*
DCIS	+ve	5/33	8/24	2.2	0.552_3.903	0.112**
	-ve	14/158	2/78	0.3	0.091_1.668	0.061**
ER	+ve	6/116	4/54	1.400	0.364_4.170	0.598**
	-ve	13/75	6/48	0.72	0.347_2.060	0.412**
PR	+ve	7/109	5/53	1.5	0.252_7.308	0.523**
	-ve	12/82	5/49	0.69	0.310_2.182	0.421**

Table 4: Bivariate analysis of risk factors of local recurrence between MRM and BCS

In this study we could not detect any risk of local recurrence after BCS for ER negative and PR negative cases, however in case of MRM, the risk of local recurrence in ER negative cases and PR negative cases is increased by about 4 folds and 2.7 folds respectively (p=0.005, 0.042 respectively) (Table 2 and 3).

Discussion

The present study is concerned with analyzing the risk factors associated with loco-regional recurrence (LRR) after BCS in comparison to standard mastectomy because significant local recurrence after BCS if present will eliminate the rational of breast conservation [13,14].

In this study we analyzed 293 cases of female breast cancer to detect the risk factors of loco-regional recurrence, of which 191 (65.2%) patients have undergone MRM, and 102 (34.8%) patients have undergone BCS. The age distribution between the two procedure was significant (p=0.000) which is attributed to larger number of patients with MRM compared to smaller ones with BCS at age category older than 40 years. Also, the pathological T stage distribution (T1, T2) between the two surgical procedure was significantly different (p=0.000). Except for age and T stage, suspected risk factors of local recurrence in MRM and BCS are equally distributed in each operative type.

This study revealed that the presence of ductal carcinoma in situ (DCIS) and lympho-vascular invasion (LVI) are associated with an increased risk of LRR after BCS. ER and PR negative cases are associated with increased risk of LRR after mastectomy but not after BCS. The presence of positive DCIS in the BCS group increases the risk of LRR by about twelve folds compared with negative DCIS cases (R.R=12.88 , p=0.0001). However, in case of MRM, there is no significant difference in risk of local recurrence between positive and negative DCIS. Negative DCIS has tendency to reverse the relative risk of local recurrence between MRM and BCS. DCIS is an established risk factor for LR after breast conservative therapy (BCT) [15-17]. This can be explained by the fact that DCIS develop through the ducts in the breast but not invade the underlying tissue. This results in a non- palpable tumor difficult to be removed with cancer-free margins [15-18]. The presence of DCIS is an important prognostic factor for patients treated with breast-conserving surgery; however this may be not true for patients treated with mastectomy [19].

In this study the presence of lympho-vascular invasion at the group of BCS is associated with increased risk of local recurrence to 41 fold (P=0.000). In bivariate analysis, negative LVI significantly reverses the relative risk (RR) of local recurrence between MRM and BCS while positive LVI has a significantly raised RR to 2 fold (Table 4).

In the analysis of the EORTC 10801 and the DBCG 82 TM trials, they found that lympho-vascular invasion results in a higher risk of LRR after BCT [20]. Contrary to this, positive LVI compared with negative LVI shows increase of RR of recurrence to only1.6 after MRM. In the study of mastectomies for T1-2 tumors O'Rourke et al found a 36% risk of chest wall recurrence with lympho-vascular invasion in comparison to a 19% risk for patients without lympho-vascular invasion. This difference maintained its significance on multivariate analysis, as did tumor grade and lymph node status [21].

Our results show that, the risk of local recurrence after BCS and MRM in patients under the age of 40 years is insignificantly

increased by about 30% and 45% respectively compared to those above 40 years. This finding may be due partly to the association of young age with other factors predictive of local recurrence including an extensive intra-ductal component and close or positive resection margins [22]. Using multivariate analysis to estimate other known prognostic factors have shown that age may be not an independent predictor of loco-regional recurrence [23,24]. In our results, although patients with T2 who underwent BCS has 4 times chance of LRR in comparison with T1 (P=0,018), no significant difference in LRR between BCS and MRM was detected according to T stage. Other studies show no significant difference between T1 and T2 in local recurrence risk either after BCS or MRM [25,26].

This study shows that there is no increase in the risk of loco-regional recurrence from N0 to N1 after MRM or BCS. Many other studies show similar results [27-29]. Other studies show controversy regarding the risk of chest wall recurrence in the subgroup of patients with 1 to 3 positive nodes (N1), with three randomized trials from the Danish Breast Cancer Cooperative Group (DBCG) and the British Columbia Cancer Agency recently reporting rates of 30% or more [30,31]. This rate is significantly higher than the ≤ 15% risk predicted from historical mastectomy series for patients with 1 to 3 positive nodes [29]. The low number of axillary nodes in the dissection specimens in these trials may explain the high risk of loco-regional recurrence. When BCS is compared with MRM for N0 and N1 in this study, there is no increased risk of loco-regional recurrence.

While ER and PR status have no impact on LR in BCS group, LR risk increase by about 4 and 2,7 folds in ER and PR negative cases respectively in comparison to ER and PR positive cases in the MRM group (P=0.005, 0.04 respectively). Other studies have similar results [24,32-34]. The relative local failure in ER and PR negative cases in the MRM group may be explained by the lack of adjuvant radiotherapy in this group [35-37].

Conclusion

Identification of the risk factors for loco-regional recurrence may have impact on the decision for the treatment of breast cancer. For BCS; T stage, Lympho-vascular invasion and DCIS are risk factors for LRR. For MRM; LVI, -ve ER and PR are risk factors for LRR. Radiotherapy may have a role in decreasing the development of recurrence after BCS in particular for cases with ER and PR positive status and may be recommended after MRM for T1-2, N0-1 stages.

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