Prognostic Factors of Treatment Failure for Early Breast Cancer after Breast Conserving Surgery

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Abbreviations:

ALND - Axillary Lymph Node
Dissection ;
BCS - Breast Conserving Surgery;
DCIS - Ductal Carcinoma In Situ;
EBC - Early Breast Cancer;
EIC - Extensive Intraductal Component;
IBTR - Ipsilateral Breast Tumor
Recurrence;
LDFS - Local Disease Free Survival;
OAS - Overall Survival;
RT - radiotherapy;
SPSS - Statistical Package for Social
Science;

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Rezumat

Factorii prognostici de eșec ai tratamentului pentru cancerul de sân incipient după operația de conservare a sânelor

Introducere: Cancerul de sân este cel mai frecvent tip de cancer la femeile din țările occidentale dezvoltate și devine și mai semnificativ în multe țări în curs de dezvoltare. Chirurgia de conservare a sânelor a devenit standardul de aur pentru pacienții cu cancer de sân (stadiul I, II) cu cancer de sân timpuriu, cu o selecție adecvată a pacienților. Factori de risc importanți pentru eșecul tratamentului, includ starea marginilor de rezecție, vârsta, multicentricitatea tumorii și utilizarea radioterapiei și a terapiei hormonale adjuvante.

Scopul: Stabilirea variabilelor de prognostic pentru recidiva tumorilor mamare ipsilaterale în cancer de sân incipient după chirurgia conservatoare de sân și rata de supraviețuire.

Materiale și metodă: Am analizat 100 de paciente cu cancer de sân incipient care au suferit chirurgie de conservare a sânelor. Datele au fost analizate pentru eșecul tratamentului; analiza a fost efectuată prin test Chi-pătrat (χ^2), regresie multivariată Cox și Kaplan Maier pentru analiza supraviețuirii.

Rezultate: 100 de pacienți au suferit chirurgie de conservare a sânelor pentru cancer de sân incipient. Au fost 75% dintre pacienții cu vârsta peste 40 de ani. Tumorile T2 au fost observate la 87% dintre pacienți și la 53% dintre pacienți au fost implicați noduli. Modelul de recurență a fost de 14%; Pe analiza multivariată, gradul și marja tumorilor au fost corelate cu supraviețuirea locală fără boală. Supraviețuirea fără boală locală la 3 ani și supraviețuirea globală a fost de 86% și, respectiv, 97%.

Concluzie: Chirurgia conservatoare a sânilor este o chirurgie acceptată pentru cancerul de sân timpuriu, cu un rezultat bun. Gradul și marja tumorilor au fost corelate cu supraviețuirea locală fără boală.

Cuvinte cheie: cancer de sân în stadiu incipient, chirurgie conservatoare a sânilor, recidivă a tumorii mamare ipsilaterale

Abstract

Introduction: Breast cancer is the most common cancer in women in developed Western countries and is becoming even more significant in many developing countries. Breast conserving surgery (BCS) has become the gold standard for patients with early breast cancer (EBC) (Stage I, II) with an appropriate patient selection. Important risk factors for treatment failure, include margin status, age, tumour multicentricity and use of radiotherapy and adjuvant hormone therapy. **Aim:** To establish the prognostic variables for ipsilateral breast tumour recurrence (IBTR) in EBC after BCS and the survival rate.

Materials and Methods: We analyzed 100 patients with EBC who underwent BCS. Data were analyzed for treatment failure, an analysis was performed by Chi-square (χ^2) test, Cox multivariate regression and Kaplan Maier for survival analysis.

Results: 100 female patients underwent BCS for EBC. There were 75% of patients above 40 years old. T2 tumours were observed in 87% of patients and 53% patients had nodal involvement. There was a pattern of recurrence of 14%; Using the multivariate analysis tumour grade and margin were correlated to local disease free survival. The 3 years local disease free survival and overall survival was of 86 % and 97% respectively.

Conclusion: Breast conservative surgery is a highly accepted surgery for early breast cancer with good result. Tumour grade and margin were correlated to local disease free survival.

Key words: early breast cancer, breast conserving surgery, ipsilateral breast tumour recurrence

Introduction

Breast cancer is the most common cancer in women in developed Western countries and is becoming even more significant in many developing countries (1).

The results after breast conservative surgery and postoperative radiotherapy were very similar to those after mastectomy, breast conserving therapy becomes the treatment of choice for early breast cancer and no significant difference in long term survival has been observed (2).

Although breast conserving surgery has become the gold standard for patients with early breast cancer, mastectomy remains an option and it is necessary for at least 20% of the women with multicentric tumours, widespread

ductal carcinoma in situ (DCIS), and large or recurrent tumours (3).

Appropriate patient selection is critical to the success of the BCS and it is an attempt to balance an acceptable low rate of local recurrence in the breast with good cosmetic outcome (4).

A complete history and physical examination bilateral mammography and ultrasound for breast and axilla tissue biopsy and patient desire, all play roles in patients selection and determine which surgery is best for each individual patient

Generally, recurrence is defined as the appearance of any new breast tumour, invasive or in situ, in the ipsilateral residual breast, in the overlying skin or in the ipsilateral axilla (5).

Risk factors for patients treated with

conservative therapy, including high histologic grade, extensive intraductal component (EIC), tumour necrosis, oestrogen receptor negativity, anatomic tumour size, age younger than 40 years, and vascular invasion. Beyond established risk factors, genetic testing allows the identification of high-risk patients (BRCA mutation carriers) who may benefit from bilateral mastectomy rather than BCS. Human genetic variation and DNA methylation may be relevant for local failures assessment (6).

Material and Methods

Out of 112 female patients diagnosed with early breast cancer who were admitted to Al-Amal Oncology Center, Taiz, Yemen, between June 2014 and May 2017, 100 patients were eligible for inclusion, 12 patients were excluded based on the presence of synchrotrous/metachronous contralateral breast carcinoma and on the presence of multicentric and multifocal breast cancer. The median follow up period was of 22 months.

In our research, the assessment was based on the clinical examination, bilateral mammography and ultrasound for breast and axilla (with BIRAD category), tissue biopsy and metastatic work up to exclude metastasis.

Patients underwent BCS which was defined as the surgical removal of the tumour with staging axillary lymph node dissection and postoperative radiation therapy. The standard dose of radiotherapy (RT) given was of 5000 cGy administrated to the whole breast over a five week period divided into 25 daily sessions of radiotherapy, the standard boost of radiation was a further 1000 cGy given over 5 days.

Axillary Lymph Node Dissection

Underwent for level I and level II. Level III was taken only if it was involved intraoperative.

No = No regional lymph node metastasis is histologically present.

N1 = Metastases in 1 to 3 axillary lymph nodes.

N2 = Metastases in four to nine axillary lymph nodes.

In our study a safety margin more than or equal to 1 cm called negative margin, positive margin is defined by the presence of tumour cells immediately at the resection edge (at an inked margin) and the close margin defined as cancer cells in-between the negative and the positive margin (not involving the resection edge and less than 1 cm).

The local recurrence is defined by tumour recurrence in the ipsilateral breast. The regional recurrence happens when there is a nodal recurrence in the ipsilateral axillary or in the internal mammary lymph nodes. Local regional recurrence means the tumour recurrence in both the ipsilateral breast and lymph nodes.

Local disease free survival (LDFS) is defined from the time of surgery to the date of local recurrence/last follow up.

Overall survival (OAS) is defined from the time of surgery to the date of the last follow up/death of the patients.

The statistical analysis was performed using SPSS (statistical package for social science), version 22. The P value was significant at 0.05. The comparison between the study groups was performed using Chi-square (χ^2) test. Cox multi-variate regression was used to determine the preferential effect of important variables on LDFS and Kaplan Maier for survival analysis.

Result

The mean age at the time of diagnosis was 49 years (range, 26 - 75 years).

A total of 100 patients underwent BCS. Eighty seven patients (87%) had T2 tumour, fifty three patients (53%) had nodal involvement (N1-N2), seventy six patients (76%) had well (G1) and moderate (G2) tumour grade, thirty three (33%) patients had hormone receptors negative breast cancer, ninety (90%) patients had negative margins as according to (Table 1).

A pattern of treatment failure of female patients with EBC who underwent BCS showed that the incidence of IBTR was of 14% (Fig. 1).

A total of 14 patients had a recurrence, 12

Table 1. Clinicopathological characteristics of the primary tumour and lymph nodes in female patients with early breast cancer who underwent breast conserving surgery

	Number N = 100	Percent %
Age		
≤ 40	25	25%
> 40	75	75%
Family history		
Positive	19	19%
Negative	69	69%
Unknown	12	12%
Tumour size		
T1	13	13%
T2	87	87%
Lymph node groups		
N0	47	47%
N1	22	22%
N2	31	31%
Histology		
Infiltrating ductal	72	72%
Infiltrating lobular	19	19%
Others	9	9%
Grade		
Well = G1	11	11%
Mod = G2	65	65%
Poor = G3	24	24%
Safety Margin Statues		
Positive	4	4%
Negative	90	90%
Close	6	6%
EIC		
Present	13	13%
Not present	87	87%
LVI		
Positive	16	16%
Negative	84	84%
ER and PR status		
Positive	67	67%
Negative	33	33%
Adjuvant systemic treatment to radiotherapy		
Chemotherapy	28	28%
Hormonal	5	5%
Chemotherapy + hormonal	59	59%
None	8	8%

ER: oestrogen receptors PR progesterone receptors

LVI: Lymphatic vascular invasion; EIC: Extensive intraductal component.

patients (85.7%) had local recurrence, 1 patients had regional recurrence (7.1%), 1 patients with locoregional recurrence (7.1%) (Table 2).

The incidence of IBTR is of 57.1% (8 patients) in six months and less, 7.1% (1 patient) had a recurrence in the first year and 35.7% (5 patients) in the second year (Fig. 2).

Figure 1. A pattern of treatment failure (recurrence)**Table 2.** A pattern of observed recurrence in patients undergoing BCS and RT

	Number (N = 14)	Percentage %
IBTR		
• Local recurrence	12	85.7%
• Regional recurrence	1	7.1%
• Locoregional recurrence	1	7.1%
Site of recurrence		
• At the operative bed or within 3 cm from the incision	13	92.9%
• Others	1	7.1%
IBTR ipsilateral tumour recurrence		

The Pearson's chi-square test for independence between the IBTR and different categorical variables showed that, EIC, hormone receptors

Figure 2. Time period to recurrence of 14 female patients with EBC (early breast cancer) who underwent BCS (breast conserving surgery)

Table 3. Comparisons of categorical variables among groups were evaluated using Chi-square test for categorical variables

Chi-Square Tests		df	P value
Progression	Age	1	0.318
	Tumor size	1	0.312
	lymph node	2	0.000
	Histological type	2	0.353
	Grade	2	0.001
	LVI	1	0.009
	Margin	2	0.000
	EIC	1	0.003
	Hormones receptors	1	0.003
	Adjuvant therapy	1	0.001

df: Degree of freedom; LVI: Lymphatic vascular invasion; EIC: Extensiveintraductal component

status, histological grade, margins status, lymph node, LVI and adjuvant therapy were significantly associated with IBTR with P value (0.003 - 0.003 - 0.001 - 0.000 - 0.000- 0.009-0.001 respectively) and there's no significant for IBTR and age, tumour size, histological type with P value (.318 - 0.312- 0.353 respectively) (*Table 3*).

On multivariate analysis only tumour grade and margin were correlated to LDFS (*Table 4*).

The three year local disease free survival is of 86% (*Fig. 3*) and the three year overall survival is of 97% (*Fig. 4*).

Figure 3. The Kaplan Meier curve for local disease free survival in breast cancer cases**Table 4.** Factors influencing local disease free survival Results of Multivariate on Cox proportional hazards model analysis

	p value	HR	95.0% CI for HR	
			Lower	Upper
Age	0.137	0.195	0.023	1.681
Family history	0.130	0.100	0.005	1.969
Tumour Size	0.935	0.913	0.102	8.199
Lymph Node	0.237	16.645	0.157	1,767.10
Histological Type	0.855	0.716	0.020	25.637
Grade	0.009	138.38	3.439	5,567.72
LVI	0.537	2.514	0.135	46.825
Margin	0.004	492.544	7.530	32,216.48
EIC	0.046	40.893	1.073	1,558.05
Hormone receptors	0.901	0.000	0.000	4.16E+98
Adjuvant therapy	0.948	0.000	0.000	5.17E+101

HR: hazard ratio; CI: confidence interval; LVI: lymphatic vascular invasion; EIC: extensiveintraductal component.

Figure 4. The Kaplan Meier curve for overall survival rate in breast cancer cases

Discussion

The risk of local recurrence in the breast after breast conserving surgery is between 1% and 2% per year and it is relatively constant over time, with an overall ten year risk of 10-20%. However, the reported incidences do vary considerably between series, due to differences in patient's selection, the extent of surgery and usage of postoperative adjuvant radiotherapy and systemic treatment. Although the risk of local recurrence after mastectomy has generally been considered to be much lower than after breast conserving surgery, most of the randomized comparative studies have not demonstrated any significant difference in this respect (7,8). According to our study, approximately 14% of women had IBTR after breast conserving surgery with a peak incidence of 57.1% in six months, 7.1% had a recurrence in one year and 35.7% in the second year. NSABP B 06 trial reported nearly 5% rate of locoregional recurrence in patients undergoing breast conservative surgery at 5 years (9). The EORTC trial demonstrated 11.8% rate of locoregional recurrence at 5 years (10).

Although mammography is a dominant screening tool, the importance of Clinical breast examination should not be over looked. A significant number of cancers would have

been missed if clinical breast examination (CBE) had not been performed. In contrast with cancers detected by mammography alone, those detected by clinical breast examination had more aggressive features. Clinical breast examination (CBE) is a low-cost assessment that could improve the detection of breast cancer and could prompt breast ultrasonography in the case of a negative mammogram (11).

Local recurrence of a tumour after breast conserving therapy often occurs as a single nodule with or without axillary node recurrence. The usual sites of local recurrence are in the same quadrant as the primary tumour (48%), in another quadrant (41%), or both (11%) (12). In our study 92.9% had recurrence at the same operative bed or within 3 cm from the incision.

Tumour size wasn't correlated to any of the outcome results in this study, but in several studies clinical size of tumour more than 2 cm (T2) was associated with higher risk of IBTR (13).

In our study positive margins correlate with IBTR and local disease free survival on multivariate analysis. In 30 of 43 studies reviewed by Singletary, the local recurrence rate was increased in the cases that had persistent positive margin compared with negative margins. This effect appeared to be independent of the size of the margin (14). Authors found the 10-year local recurrence free survival rate for young women (≤ 40 years) with positive margins to be significantly lower compared with negative margins (34.6% vs. 84.4%, respectively; $p = 0.008$). The effect of positive margin status for invasive cancer is not only limited to local control, but also to distant metastasis and survival (15).

On ivariable analysis, the patients with close or positive margins, in combination with age < 45 years, Grade III, LVI, and ≥ 4 positive nodes, have a 5-year local recurrence (LR) $> 10\%$ despite whole breast plus boost radiotherapy. So these patients should be considered for more re-resection surgery (16).

In the present study the axillary lymph node- correlates to IBTR. Despite a strong

association between axillary lymph node status and survival associated with local recurrence in breast conserving therapy, while present, is not as strong or as consistent, it may be due to the almost universal use of radiotherapy and adjuvant therapy in node positive patients (17).

Sentinel lymph node biopsy is a minimally invasive procedure which is an alternative to axillary lymph node dissection (ALND) in staging the axilla in patients with early invasive breast cancers and clinically negative node. It has the potential to improve the accuracy of axillary staging while reducing the number of unnecessary axillary dissection and decreasing morbidity. The safety of the sentinel lymph node biopsy was underscored by the NSABP B-32 trial which showed that overall survival (OS), disease free survival (DFS) and regional control (RC) were statistically equal between the sentinel lymph node and standard axillary node dissection when the node was negative (18).

Tumour grade and lymphovascular invasion were correlated to IBTR in this study. Voogd et al, stated that vascular invasion and to a lesser extent high histological grade, appeared to cause an increased risk of local recurrence irrespective of the primary treatment (19). Some series have also found an increased risk of breast recurrence in patients with high histological grade tumours compared with low grade tumours (20). In this study tumour grade also correlates with local disease free survival on multivariate analysis.

Breast cancer patients with estrogen receptor positive and/or progesterone receptor negative have lower risks of mortality, improved outcomes and associated with a longer survival time after their diagnosis (21).

The 3 years local disease free survival and overall survival were of 86 % and 97% respectively, comparable to the result from another study with 10 years local disease free survival and overall survival of 88% and 70% respectively (22).

Conclusion

- Breast conservative surgery is a highly

Figure 5. The result of breast conservative surgery

accepted surgery for early breast cancer with good result.

- Lymph node, hormone receptors, lymphovascular invasion and the adjuvant therapy are correlated to IBTR.
- Tumour grade and safety margin are

correlated to IBTR and local disease free survival on multivariate analysis.

- The 3 years local disease free survival and overall survival was of 86 % and 97% respectively.

Conflict of Interests

The authors declare no conflict of interests.

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