

THE EFFECT OF AGE AND SAFETY MARGIN ON LOCAL RECURRENCE AND SURVIVAL AFTER BREAST CONSERVATIVE SURGERY FOR EARLY BREAST CANCER

Aldaqaf Mohammad¹

¹ Faculty of Medicine and Health Science „Taiz University“, Taiz, Yemen

ABSTRACT

Introduction. Breast cancer is the most common cancer among women. Though there is an annual increase in its incidence, the mortality remained relatively stable, probably reflecting the combined benefits of early detection and better treatment. During the 1980s, large randomized clinical trials had shown that breast conservative therapy became the treatment of choice for early breast cancer. Several risk factors for local recurrence after breast conservative surgery have been recognized: margin status, young age and other.

The objective of the study was to assess the effect of age and safety margin on local recurrence and survival after breast conservative surgery for early breast cancer.

Material and method. The study included 200 female patients admitted to the Al Amal Oncology Center, Yemen, with the diagnosis of early breast carcinoma (stage I, II), between January 2012 and December 2016, and treated with breast conservative surgery.

Results. The result of our study showed that 53 (26.5%) of female patients were ≤ 40 year-old, while 147 (73.5%) were > 40 year-old. 14 patients (7%) had recurrent ipsilateral breast tumor in this study. Regarding safety margin (SM), 190 patients had negative margin, 4 patients close margin and 6 patients were with positive margin. The five year overall survival rate in

RÉSUMÉ

L'effet de l'âge et la marge de sécurité sur la récurrence locale et la survie après la chirurgie conservatrice du sein pour le cancer précoce du sein

Introduction. Le cancer du sein est le cancer le plus fréquent chez les femmes. Bien qu'il y ait une augmentation annuelle de son incidence, la mortalité demeure relativement stable, probablement en raison des avantages combinés d'un dépistage précoce et d'un meilleur traitement. Au cours des années 1980, de grands essais cliniques randomisés ont montré que la thérapie de conservation du sein devient le traitement de choix pour le cancer du sein précoce. Plusieurs facteurs de risque de récurrence locale après la chirurgie conservatrice du sein ont été reconnus. Le statut de la marge, le jeune âge et d'autres ont été identifiés comme facteurs de risque importants pour la récurrence locale.

L'objectif de l'étude était d'évaluer l'effet de l'âge et de la marge de sécurité sur la récurrence locale et la survie après la chirurgie conservatrice du sein pour le cancer précoce du sein.

Matériel et méthode. L'étude a inclus 200 patientes admises au Centre d'Oncologie Al Amal, Yemen avec le diagnostic de cancer du sein précoce (stade I, II), de

patients \leq 40 year-old was 80.4%, while in patients $>$ 40 year-old was 87.1%. The five year overall survival rate in patients with (+)ve SM was 53.3%, 75% in those with close margin and 86.5% in those with (-)ve margin, which was significantly higher than (+) ve or close SM ($p = 0.001$).

Conclusion. In this study, we found that age and safety margin were independent risk factors for local recurrence and survival.

Key words: breast cancer, conservative surgery, recurrence.

Abbreviations: BCS: Breast conservative surgery, AJCC: American Joint Committee on Cancer, DFS: disease free survival, OS: overall survival, NHG: Nottingham Histologic Grade, SM: safety margin, SE: Standard Error.

INTRODUCTION

Breast cancer is the most common cancer among women. Though there is an annual increase in its incidence, the breast cancer mortality remained relatively stable, probably reflecting the combined benefits of early detection and better treatment. In Yemen, breast cancer is the most common cancer among women, representing 18.9% of total cancer cases¹.

During the 1980s, large randomized clinical trials had shown that the prognosis after breast conservative surgery (BCS) and postoperative radiotherapy was very similar to that after mastectomy, so the breast conservative therapy became the treatment of choice for early breast cancer.

Breast conservative therapy was defined as the surgical removal of the malignant tumor with a negative resection margin and postoperative radiation to the whole breast using a standard radiation protocol.

Unfortunately, there is no consistent definition for local recurrence used in the literature, making the comparison of studies somewhat challenging. According to literature, local recurrence is defined as the appearance of any new breast tumor, invasive

Janvier 2012 à Décembre 2016 et traités par la chirurgie conservatrice du sein.

Résultats. Le résultat de notre étude montre que 53 (26,5%) des femmes étaient âgées de moins de quarante ans et 147 (73,5%) étaient au-dessus. 14 patientes (7%) présentaient une tumeur du sein ipsilatérale récurrente dans cette étude. En ce qui concerne l'état de la marge de sécurité 190 patients avaient marge négative, 4 patients marginaux fermés et 6 patients étaient avec marge positive. Le taux de survie globale à cinq ans chez les patients \leq 40 est de 80,4%, alors qu'il est de 87,1% chez ceux $>$ 40 et le taux de survie globale à cinq ans chez les patients ayant un SM + 53 est de 53,3%, 75% chez ceux avec une marge proche et de 86,5 % chez ceux dont la marge (-) ve était significativement plus élevée que (+) ve ou SM proche, $p = 0,001$

Conclusion. Dans cette étude, nous avons trouvé que l'âge et la marge de sécurité étaient des facteurs de risque indépendants pour la récurrence locale et la survie.

Mots clés: cancer du sein, chirurgie conservatrice, récurrence.

Abbréviations: BCS: Chirurgie conservatrice du sein, AJCC: Comité mixte américain sur le cancer, DFR: Taux de survie sans maladie, OS: survie globale, NHG: degré histologique de Nottingham, SM: marge de sécurité, SE: Erreur standard.

or in situ, in the ipsilateral residual breast, in the overlying skin or in the ipsilateral axilla.

In recent studies, axillary recurrence is frequently recorded separately, and the term local recurrence is restricted to recurrence in the breast and in the overlying skin².

The risk of local recurrence in the breast after breast-conservative surgery is between 1% and 2% per year and is relatively constant over time, with an overall ten-year risk of 10-20%².

A new useful clinical definition of ipsilateral breast recurrence has appeared: the true recurrence was considered if it was located within 3 cm of the primary tumor bed and had a histological subtype consistent with the primary tumor².

Several risk factors for local recurrence have been recognized. Margin status, young age, an incompletely excised extensive intraductal component and inadequate radiotherapy dose (boost) have been identified as important risk factors for local recurrence³.

Almost all studies reported that young age, especially age $<$ 50 years, is a major independent risk factor for local recurrence after BCS⁴.

The margin is characterized as the closest microscopic distance between the inked lumpectomy tissue

edge and any cancerous tissue (invasive or ductal carcinoma in situ). Obtaining a negative lumpectomy margin is considered a basic prerequisite for standard-of-care BCS. Numerous studies have correlated lumpectomy margin status with risk of local recurrence⁵.

THE OBJECTIVE OF THE STUDY was to assess the effect of age and safety margin on local recurrence and survival after breast conservative surgery for early breast cancer.

MATERIAL AND METHODS

Our study included 200 female patients admitted to the Al Amal Oncology Center, Yemen, with the diagnosis of early breast carcinoma (stage I, II), between January 2012 and December 2016, and treated by breast conservative surgery.

Patients who met all study inclusion criteria and none of the exclusion criteria were included in this study.

Exclusion criteria from the study were: patients with locally advanced breast carcinomas, patients with metastatic carcinomas, patients with synchronous/metachronous contra-lateral breast carcinoma, patients who didn't receive adjuvant treatment and patients who dropped out their follow-up at the hospital clinic after finishing the treatment.

Diagnosis of early breast carcinoma was based on: clinical examination, mammography/ultrasound and tissue biopsy.

Statistical analysis was performed using SPSS (statistical package for social science), the P value was always 2 tailed and significant at 0.05 level.

Survival end points were calculated as follows:

- Disease free survival: to the date of local recurrence.
- Overall survival: to the date of either death or lost follow-up.

RESULTS

From the 200 female patients of the study group, 53 (26.5%) of female patients were ≤ 40 year-old, while 147 (73.5%) were > 40 year-old.

Table 1. Comparison of disease-free survival (DFS) rates in breast cancer cases according to age.

	≤ 40 years		>40 years		P value
	Estimate %	SE	Estimate %	SE	
First year	98.8	1.9	97.8	1.3	0.70
Second year	91.8	4.0	90.7	2.6	
Third year	86.5	5.2	86.2	3.1	
Fourth year	86.5	5.2	82.1	3.8	
Fifth year	81.1	7.2	78.6	4.4	

Table 3. Comparison of overall survival (OS) in breast cancer cases according to age.

	> 40 years		≤ 40 years		P value
	Estimate %	SE	Estimate %	SE	
First year	99.2	0.7	0.7	2.1	0.494
Second year	98.5	1.1	1.1	2.1	
Third year	96.7	1.7	1.7	4.2	
Fourth year	94.4	2.3	2.3	4.2	
Fifth year	87.1	4.1	4.1	8.9	

Table 2. Comparison of DFS rates in breast cancer cases according to SM.

	+ ve		close		-ve		P value
	Estimate %	SE	Estimate %	SE	Estimate %	SE	
First year	80	17.9	100	-	98.3	1	0.15
Second year	53.3	24.8	75	21.7	92.3	2.1	
Third year	53.3	24.8	75	21.7	87.5	2.7	
Fourth year	53.3	24.8	75	21.7	84.2	3.2	
Fifth year	53.3	24.8	75	21.7	84.2	3.2	

Table 4. Comparison of OS in breast cancer cases according to SM.

	(+ ve)		close		(-) ve		P value
	Estimate %	SE	Estimate %	SE	Estimate %	SE	
First year	100	-	75	21.7	99.4	0.5	0.001
Second year	80	17.9	75	21.7	99.4	0.6	
Third year	53.3	24.8	75	21.7	97.2	1.4	
Fourth year	53.3	24.8	75	21.7	96.4	1.8	
Fifth year	53.3	24.8	75	21.7	86.5	3.9	

Regarding safety margin status, 190 patients (95%) had negative margin, 4 patients (2%) close margin and 6 patients (3%) had positive margin.

14 patients (7%) had recurrent ipsilateral breast tumor in this study.

According to table 1, the five years disease-free survival rate in patients \leq 40 years-old was 81.1%, while in those $>$ 40 years-old was 78.6%. According to table 2, the five year disease-free survival rate in patients with (+)ve SM was 53.3%, 75% in those with close margin and 84.2% in those with (-)ve margin.

According to table 3, the five year overall survival rate in patients \leq 40 years-old is 80.4%, while in those $>$ 40 years-old was 87.1%. According to table 4, the five year overall survival rate in patients with (+)ve SM is 53.3%, 75% in those with close margin and 86.5% in those with (-)ve margin, significantly higher than (+)ve or close SM ($p = 0.001$).

DISCUSSION

The local recurrence is not only a source of psychological distress, but it is also associated with decreased survival. Therefore, finding ways to minimize local recurrence of cancer in the breast is very important. This can be realized in several ways: improving the treatment techniques in order to decrease the incidence of local breast recurrence, improving the selection of patients who are candidate for BCS.

In trials and studies of breast conservative treatment for early breast cancer, the extent of breast surgery ranges from lumpectomy, with a minimal surgical margin, to quadrantectomy. The wider the excision, the lower the risk of local recurrence⁶.

In the Milan II trial, the breast recurrence rate for patients with positive margins was 12% for those undergoing quadrantectomy, as compared with 17% for those in whom the primary surgical procedure was lumpectomy⁷.

There are difficulties in distinguishing "true" local recurrence from "new primary tumor", although some investigators have tried to do this by comparing location, histological type, Nottingham Histologic Grade (NHG) and DNA flow cytometry between primary tumors and local recurrences. It is likely that genetic markers will aid in distinguishing true recurrence from new primary tumors in the future⁸.

The majority of local recurrences occurs in the area of the previous excision and about 90% of the recurrences are invasive⁹.

Age is one of the most well-established risk factors for local recurrence after breast-conservative surgery. The risk seems to be a continuous function of the age, decreasing by 3% per year of increasing age. The lack of a consistent definition of young age has

contributed to the difference in the level of the risk associated variable¹⁰.

The definition of "young" age varies from 32 to 50 years-old, with the vast majority of authors using age 35 or 40 years-old as the cut-off. Elkhuzen et al found a four-fold risk for women under 45 year-old compared to women over 65 years¹¹. Younger patients are known to have a higher prevalence of high NHG, hormone receptor negativity and vascular invasion¹¹. This can partially explain the higher risk of local recurrence. Younger age has also been shown to be an independent predictor of breast cancer specific survival and distant disease-free survival after breast conservative surgery¹¹.

Several investigators have reported a significantly increased rate of local recurrence in patients with positive surgical margins compared to those with negative margins¹². While it is generally accepted that a positive margin is defined by the presence of tumor cells immediately at the resection edge, the negative and close margins have been defined as the absence of cancer cells immediately at the resection edge or within a distance of 1 to 5 mm¹³.

Apart from the differences between definitions, there are also institutional differences in the methods and the extent of margin evaluation, making it difficult to compare the magnitude of the increased risk associated with margin involvement¹⁴.

CONCLUSIONS

- Local recurrence is a significant risk factor for decrease survival.
- None of the prognostic factors studies regarding their effect on local recurrence was significant, probably due to relatively small sample size.
- In our study, safety margin status was not correlated with any of the outcomes.
- In our study, age was not correlated with any of the outcomes.

REFERENCES

1. Shoma A M, Mohammed M H, Nouman. Body image disturbance and surgical decision making in Egyptian post menopausal breast cancer patients. *World Journal of Surgical Oncology*. 2009; 7:66.
2. Abd-Alla HM, Lotayef MM, Abou Bakr A, Moneer MM. Ipsilateral in-breast tumor relapse after breast conservation therapy: true recurrence versus new primary tumor. *Journal Egypt Nail Cancer Inst*. 2006;1 8(3): 183-90.
3. Nuyten DS, Kreike B, Hart AA. Predicting a local recurrence after breast-conserving therapy by gene expression Profiling. *Breast Cancer Research* 2006; 8:R62.
4. Kreike B, Halfwerk H, Kristel P. Gene expression profiles of primary breast carcinomas from patients at high risk for

- local recurrence after breast-conserving therapy. *Clinical Cancer Research*. 2006; 12: 5705.
5. Newman LA and Kuerer H. Advances in breast conservation therapy. *Journal of Clinical Oncology*. 2005 ; 23(8): 1685-1697.
 6. Veronesi U. Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomized trials on 1,973 patients. *European Journal of Cancer*.1995; 31 A (10):1574-9.
 7. Freedman G, Fowble B, Hanlon A. Patients with early stage invasive cancer with close or positive margins treated with conservative surgery and radiation have an increased risk of breast recurrence that is delayed by adjuvant systemic therapy. *International journal Radiation Oncology Biology Physics*.1999; 44:1005-1015.
 8. Haffty BG. Local recurrence versus new primary: clinical analysis of 82 breast relapses and potential applications for genetic fingerprinting. *International journal Radiation Oncology Biology Physics*.1993; 27(3):575-83.
 9. Voogd AC. Local recurrence after breast conservation therapy for early stage breast carcinoma: detection, treatment, and outcome in 266 patients. Dutch Study Group on Local Recurrence after Breast Conservation (BORST). *Cancer*. 1999; 85(2):437-46.
 10. Voogd AC. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. *Journal of Clinical Oncology*. 2001; 19(6):1688-97.
 11. Enkhuizen PH. Local recurrence after breast-conserving therapy for invasive breast cancer: high incidence in young patients and association with poor survival. *International Journal Radiation Oncology Biology Physics*. 1998; 40(4):859-67.
 12. Park CC. Outcome at 8 years after breast-conserving surgery and radiation therapy for invasive breast cancer: influence of margin status and systemic therapy on local recurrence. *Journal of Clinical Oncology*. 2000;18(8):1668-75.
 13. Freedman G. Patients with early stage invasive cancer with close or positive margins treated with conservative surgery and radiation have an increased risk of breast recurrence that is delayed by adjuvant systemic therapy. *International journal Radiation Oncology Biology Physics*. 1999; 44(5):1005-15.
 14. Pittinger TP. Importance of margin status in outcome of breast-conserving surgery for carcinoma. *Surgery*. 1994; 116(4):605-8; discussion 608-9.