

SPECIAL ISSUES IN BREAST CANCER
**OUTCOME AND PROGNOSTIC FACTORS
IN THE CONSERVATIVE TREATMENT OF BREAST CANCER**

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Nasr E, Nasr D, Azoury F, Fares G. Outcome and prognostic factors in the conservative treatment of breast cancer. *J Med Liban* 2009 ; 57 (2) : 130-134.

ABSTRACT • BACKGROUND: The aim of this retrospective study is to evaluate the results and identify prognostic factors in early breast cancer.

MATERIALS AND METHODS: One hundred breast cancers, 79 stage I and 21 stage II, had a conservative treatment between September 1993 and February 1996. Median age was 57 years; median tumor size 15 mm. Pathology was infiltrating ductal carcinoma in 88%.

All patients underwent a conservative surgery followed by external radiotherapy. Twenty-eight patients received adjuvant chemotherapy and 64 patients received hormonal therapy. The median follow-up was 100 months.

RESULTS : The 10 years overall survival rate was 85% and the metastasis free survival rate was 88.5%. The 10 years local control rate was 85.7%. Women less than 45 years old had a worse prognosis.

CONCLUSION: These high rates of survival and local control confirm that breast conservation therapy yields favorable results, and that age is a major risk factor in women with early breast cancer.

INTRODUCTION

With the implementation of early screening more women are diagnosed with early stage breast cancer; the curative therapy remains however an important challenge.

For years, radical mastectomy was the only treatment option for breast cancer. The concept of conservative treatment was initially developed in Europe during the years 1960-1970. It consisted of breast conserving surgery followed by radiation. The principle goals being the equivalence in terms of survival compared with mastectomy, a good local control and esthetic outcome. Conservative treatment has been established for early stages breast cancer. In fact, six randomized controlled trials comparing mastectomy to conservative manage-

ment reported identical outcomes in terms of survival [1-6]. Knowing that overall survival of the patients is quite identical in these trials, local control is far better with the addition of radiotherapy to breast conserving surgery. Overall survival with conservative treatment varies between 70 and 80% and local recurrence between 4 and 18%. Local recurrence after mastectomy varies between 2 and 9% [1-6].

On the individual setting, local recurrence compromises the possibility of breast conservation and is responsible of the systemic dissemination and ultimately to the decrease of the overall survival.

Analysis of clinical and pathological prognostic factors predict local control and select patients that are candidates for a conservative treatment with a good cosmetic outcome in the majority of patients with stage I and II breast cancer [7-9].

We present in this retrospective study the outcome of conservative treatment in 100 patients treated for early breast cancer. All patients were treated with breast conserving surgery followed by radiotherapy. The primary goals of the study were outcome and the impact of the different prognostic factors in this population.

MATERIAL AND METHODS

Between September 1993 and February 1996, 100 patients diagnosed with early stage breast cancer were treated with a breast conserving approach (Table I).

Median age was 57 years (26-79). Stage distribution (according to TNM staging classification) was: 84 T1, 16 T2, 92 N0 and 8 N1. The tumor size was small: a median of 15 mm (5-45 mm). Pathologic tumors were distributed as follows : 88 infiltrating ductal carcinomas, 5 lobular carcinomas, 3 medullary carcinomas and 4 mucinous carcinomas. SBR histological grade was available for 65 patients and was distributed as follows: grade I for 22 patients, grade II for 28 and grade III for 15. Hormonal receptor status was: ER positive in 69 cases and PR positive in 57. Her2neu status was not studied. Surgical margins were positive in 8 cases; and metastatic axillary nodes in 13 patients.

All patients had a conservative treatment consisting of surgery followed by radiotherapy with or without chemotherapy.

Radiotherapy was delivered to the whole breast at a dose of 50 Gy using two tangential fields with 6 MV photons with a linear accelerator. Fractionation was done according to a classical schema, with five fractions of 2 Gy per week, for a total of 25 sessions in 5 weeks (Table II).

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TABLE I
PATIENTS AND TUMOR CHARACTERISTICS

CHARACTERISTICS	PATIENTS
Age at diagnosis	
≤ 45 years	23
> 45	77
Stage	
T1	84
T2	16
Nodal status	
N0	92
N1	8
Tumor size	15 mm (5-45)
Histology	
Infiltrating ductal carcinoma	88
Infiltrating lobular carcinoma	5
Infiltrating medullary carcinoma	3
Infiltrating mucinous carcinoma	4
Histological grade	
SBR I	22
SBR II	28
SBR III	15
Not evaluated	35
Other characteristics	
Estrogen receptors positive	69
Progesterone receptors positive	57
Cerb-B2	Not analyzed
Positive margins	8

Only 25 patients had an additional boost to the initial tumor bed with a dose varying between 10 and 24 Gy. This boost consisted of an interstitial brachytherapy in 6 patients and external radiation in 19 patients. Eight patients had the boost delivered with 6 MV photons and electrons for 11 patients. Eleven patients had an irradiation to the ipsilateral supraclavicular region and no patient was irradiated to the internal mammary region.

Twenty-eight patients received adjuvant chemotherapy.

TABLE III
COMPARISON OF RESULTS ACCORDING TO AGE

Overall survival	
> 45 years	92.6%
≤ 45 years	67.4% (<i>p</i> = 0.001)
Local recurrence free survival	
> 45 years	90.2%
≤ 45 years	67.1% (<i>p</i> = 0.001)
Metastasis free survival	
> 45 years	92.8%
≤ 45 years	72.6% (<i>p</i> = 0.001)

TABLE II
TREATMENT CHARACTERISTICS

TREATMENT	N
Conservative surgery	100
Radiotherapy to the breast	100
Boost	25
Brachytherapy	6
External radiation with photons	8
External radiation with electrons	11
Supra-clavicular radiation	11
Irradiation to internal mammary nodes	0
Chemotherapy	
CMF	20
FEC	8
Hormonal therapy (Tamoxifen)	64

Twenty of those received a CMF regimen and 8 with a FEC regimen. The criteria for administering chemotherapy were young age and/or positive nodes. Chemotherapy was delivered after surgery in 12 patients, after radiotherapy in 10 and concurrently in 6 patients.

64% of the patients received adjuvant hormonal therapy with tamoxifen.

STATISTICAL METHODS

Overall survival, local control and distant metastasis rates were calculated from the time of treatment using the Kaplan-Meier method. Log rank tests were used for unifactorial comparisons with a degree of signification of 0.05 (*p* < 0.05). Median follow-up was 100 months.

RESULTS

At 10 years, overall survival (OS) was 85% and metastases free survival was 88.5%. Ten patients had a metastasis in one or more sites: liver (4 patients), nodes (4), bone (3), lungs (2) and bone marrow (2).

Twelve patients died of an unknown cause. The youngest patient (29 years old) died of bone and hepatic metastases 9 months after the end of the radiotherapy.

Local control at 10 years was 85.7%. We observed 11 local recurrences after breast conserving treatment, two of those were intraductal carcinomas.

PROGNOSTIC FACTORS

Unifactorial analysis was conducted studying: age, tumor size, nodal status and margins. Of all factors, only young age reached significant status in predicting outcome. For patient younger than 45 years, OS was 67.4%. Metastasis free survival 72.6% and local control was 67.1% compared with 92.6%, 92.8% and 90.2% respectively (*p* = 0.001) for patients older than 45 years (Table III) (Figures 1, 2, 3).

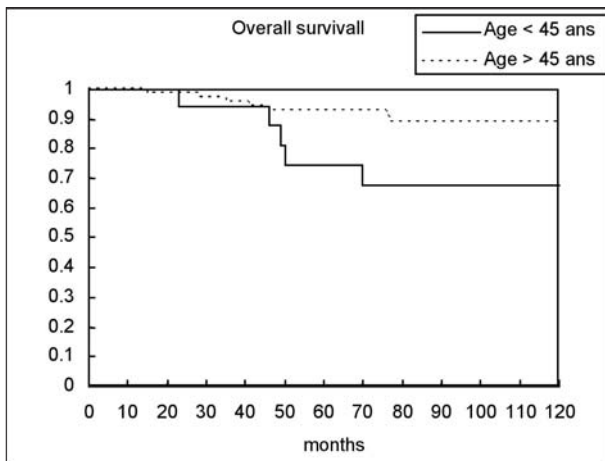


FIGURE 1. Survival according to age.

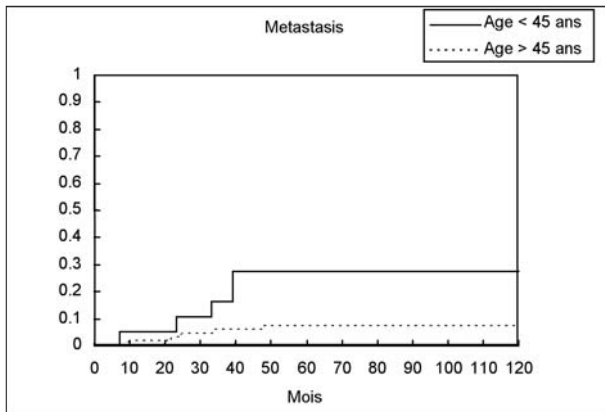


FIGURE 2. Metastasis according to age.

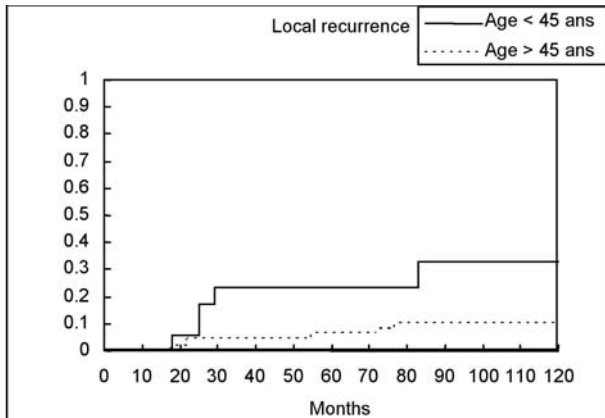


FIGURE 3. Local recurrence according to age.

DISCUSSION

In this study we present the characteristics and results of breast conserving treatment in stage I and II breast cancer. The analysis of the results of the current study show in fact identical results when compared to the current data available in the medical literature, in terms of survival, metastasis free survival and local control depending of the prognostic factors.

Many studies comparing radical mastectomy to more conserving approaches in early stage breast cancer [3-6] showed identical overall survival rates and local control [10-11]. In our study, overall survival as well as metastasis free survival compare favorably with other series in the medical literature [3-6].

After conservative treatment local relapse varies between 4 and 20% [12-14] depending on patient's age, tumor size, margin status, the presence of vascular invasion and the presence of an extensive intraductal component. Local relapse after conservative treatment has major psychological and prognostic effects. In fact, an evolutive relapse is often perceived by the patient as a failure of the curative intent of the breast conservation. On the other hand many authors consider the relapse, even if it is local, a more pronounced risk factor to systemic dissemination of the disease and by that bias a cause of significant reduction of the survival chances of the patients [15-17]. Regarding this issue, Cowden et al. [18-19] observed a shorter median time to metastasis and a higher risk of distant metastasis after the occurrence of a local relapse. Likewise, Engel et al. [20] reported a distant relapse rate three times higher in the group of patients experiencing a local relapse. Vicini et al. [21] showed a higher mortality and metastasis rate in breast cancer patients treated with conservative approaches when local relapse occurs. On the other hand, Fisher showed in a study [3] that a reduction of local recurrences has a positive effect on survival and leads to a 4% gain in overall survival. Fourquet et al. [22] showed in their series of 56 local relapses, a lower survival rate when the relapse occurs within the first three years of the conserving treatment.

For other authors, local relapse has little or no effect on overall survival. In their series of 215 patients diagnosed with early stage breast cancer and treated with a conservative approach, Horigushi et al. [23] found a relapse rate of 6.6% and no negative effect on survival. McBain et al. [24] showed in their series of 161 patients suffering from local relapse, identical 5 years overall survival to the group who didn't experience a local relapse.

In our study we haven't found a direct relation between local relapse and the apparition of distant metastases or a detrimental effect on survival. In fact, only three of the eleven patients who showed a local relapse presented later on a distant metastasis.

Among the risk factors of local recurrence after conservative treatment, tumor size remains an object of controversy.

Classically a conservative treatment was offered to patients with tumors of less than 3 cm diameter. Tumor size is considered by many to be directly linked to local relapse. In many studies a palpable tumor is considered a negative prognostic factor [25-26]. In fact, in the EORTC 22881 trial, the presence of a palpable tumor and/or a tumor of more than 2 cm was significantly associated with a higher risk of local relapse.

Knowing that median size on pathology in our study was 1.5 cm, with extremes of 0.5 and 4.5 cm, we haven't

found any significant influence of size on the prognosis of the patients.

For many authors, young age is an independent prognostic factor predicting higher relapse rate. In the study of Fourquet et al. [22], relapse rate in women younger than 35 years was 29% at 10 years whereas for women > 55 years it was only 3% at 10 years. Fowble et al. [27] reported in a series of 980 patients a relapse rate of 24% for patients < 35 years and 14% for patients > 35 years.

Jobsen et al. [28] showed that positive margins for women younger than 40 years had higher relapse rates (36.9%) compared to older women (2.2%).

In their series of 2410 patients treated with a conservative approach, Arriagada et al. [29] found, after a follow-up of 10 to 15 years, that only young age at diagnosis predicted a higher risk of death.

The EORTC 22881 trial [26] also states clearly the importance of young age (< 40 years) as significant prognostic factor related to the occurrence of local relapse. This study brought important evidence to the clinical benefit of a boost on the tumor bed especially in the younger patients. In fact, for patients younger than 40 years, local relapse is lowered from 19.5% to 10.2% ($p = 0.002$) after the addition of a local boost. This risk is lowered from 10 to 6% in patients between 41 and 50 years; with longer follow-up the utility of the boost reached statistical significance in all age groups.

CONCLUSION

The current study shows identical results with the data present in the medical literature, with excellent survival rates and long term local control after conservative treatment. The adjuvant radiotherapy is well tolerated and provides a good esthetic outcome. Young age at diagnosis (< 45 years) has a negative impact on survival and is directly linked to local and distant relapse.

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