Trakia Journal of Sciences, No 4, pp 71-76, 2015

Available online at:
http://www.uni-sz.bg
ISSN 1313-7050 (print) doi:10.15547/tjs.2015.04.012
ISSN 1313-3551 (online)

Original Contribution

METASTASES OF PATIENTS WITH EARLY STAGES OF BREAST CANCER

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ABSTRACT
Breast cancer is the leading cause of death in women with malignancies. Three thousand-one hundred and forty-five new cases are registered in Bulgaria in 2000 and 1300 of the patients died. We investigated the reasons for relapse in 64 patients with breast cancer who had undergone surgical treatment in the Department of Surgery of the University Hospital, Stara Zagora. All the patients underwent adjuvant chemo-radio and hormonal therapy. The in variant and the multivariant analyses concluded that the causes of relapse are nodal stage (p=0.054) and initial tumor size(p=0.030). Other factors like age and the kind of adjuvant treatment had no statistical significant relation to early relapse.

Key worlds: breast neoplasms/pathology dlsease free survival ;recurrence

INTRODUCTION

In the patients with small primary cancer of breast, the standard therapeutically approach is breast conserving operation. [1- 4]

After resection of the tumor to sufficient distance in the surrounding healthy tissue and histologically negative edge with accompanied lymph dissection postoperative radiation treatment is applied. This depends on the status of the axillary's lymph nodes in the.

Postoperative radiation therapy is preserved for the patients with mastectomy, whose risk factors and the probability for reoccurrence are considerable. The size of primary tumor, the incomplete resection and one or some positive for metastasis axillary's lymph nodes come in consideration. [5-7] The present research has a task to notify results of patients treated with postoperative radiation therapy after mastectomy or organ-conserving operation as a part of their primary treatment.

Patients and methods:

In the current study there were enrolled 63 patients with breast cancer operated in the Department of Surgery, University Hospital, Trakia University, Stara Zagora during the period of 2000 to 2003. The breast-sparing operation was consisted in quadrantectomy in 16 patients. No of the patients underwent tumorectomy. Modified radical mastectomy was performed in the rest 47 patients and no microscopic incomplete resection was found again. All of the patients underwent lymphadenectomy. On the average 12 lymph nodes were removed. About 10 lymph nodes were removed from 82.5% of the patients. The clinical data of the patients are given in **Table 1.**

All of the patients received postoperative radiation therapy in the Department of X-Ray and Radiology in Radiological Department of Oncology Hospital in Staza Zagora, Republic of Bulgaria. The patients were follow-up to the 1st of December, 2005. Metastases were found in 17 patients during the follow-up period. Four had loco-regional disease and in 13 cases metastases was mixed. Average age of the researched population was 59 years (median 57, 45-84). Sixteen patients received the postoperative radiation therapy after breast-sparing operation and 44 - after mastectomy.

Postoperative radiation therapy of the breast was conducted in all of the patients with breast-sparing operation. After mastectomy it was conducted in high risk patients. This was determined from pT phase > 3cm, involvement

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of pectoral fascia or two or more lymph nodes. Irradiation was conducted with tangential fields using Co^{60}. The patients received individual planned procedures on the basis of conventional computer tomography. A dose of 50Gy was applied. Isodose of 5x2Gy per week was prescribed in 90%. According to ACRU equivalent dose was approximately 52,5Gy. Irradiation to upper axillary's lymph nodes and to supraclavicular region was conducted when 2 or more metastasis in axillary's lymph nodes were present. Irradiation of parasternal lymph nodes was performed in the presence of engaged axillary's lymph nodes. The dose is 50Gy again, applied as 90% isodose.

Table 1. *Patients and characteristics of a tumor according to the type of operation:*

Characteristics	Organ-conserving operation (n = 16)	Modified radical mastectomy(n = 47)
T staging		
T1	11	22
T2	5	20
T3	0	5
N staging		
N0	12	18
N1	4	25
N2	0	4
G stage grouping (IUAC TNM) staging system),		
GI	7	9
GII	9	31
GIII	0	7
Age		
45-49	4	7
≥ 50	12	40
ER/PR status		
positive	10	28
negative	1	5

Fifty four patients received adjuvant chemotherapy (86%), the most used regimen was FEC 29/54 (53.7%) and CMF were applied the rest of 25 patients (46.3%). The application of hormonal therapy was documented in 55 of the patients (87%). Chemotherapy and hormonal therapy were applied according to the status of the patient and the gynecological politics.

The period between the surgical treatment and appearance of recurrence was considered as disease-free survival (DFS)

The results were analyzed with the StatView™ package for Windows, v 4.53 (Abacus Concepts Inc., Berkeley, California, USA). The descriptive statistical tests, including the median, mean and standard deviation were calculated according to the standard methods. Contingency tables were studied by χ^2-test and Fisher's exact test. Cumulative survival curves were drawn by the Kaplan-Meier method and the difference between the curves analyzed by the Mantel-Cox (Log-rank) test. The Cox proportional hazard model was used in the multivariate analysis, performed with factors, which were significant in the univariate analysis. Factors with $p<0.05$ were considered statistically significant for survival.

RESULTS

Region of local collapse

Loco-regional recurrence was seen in 4 patients. Two of these recurrences were on thoracic wall, one in axillary's lymph nodes and one was mixed. In one of the diagnosed patients with recurrence system failure was present. One patient with breast-sparing operation and radiation therapy had local recurrence in the breast. In her case at the 2nd stage after three courses of chemotherapy mastectomy was performed. The proportions in local control 3 years after radical operation for invasive tumors were 13 and 4 after breast-sparing operation. The rate of recurrence did not depend on the application of hormonal therapy, ($p=0.095$, Fisher's exact test), administering of chemotherapy ($p>0.999$, Fisher's exact test), or type of chemotherapy ($p=0.236$, χ^2 test).

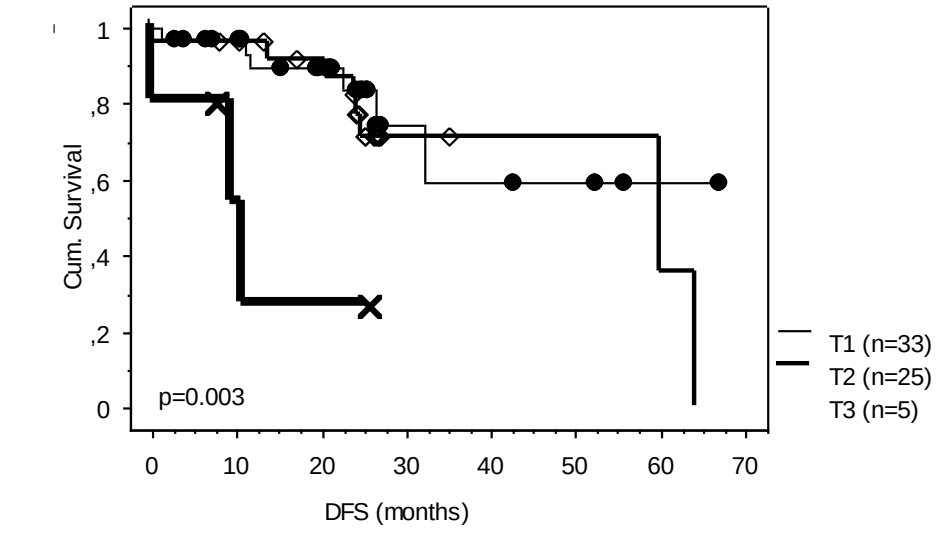
Factors affecting the disease free survival

Several clinical and tumor characteristics were studied for elucidation of their possible effect on the disease free survival (DFS) of the patients with breast cancer treated with adjuvant radiotherapy These factors were the T and N staging, estrogen receptor/progesterone receptor status (ER/PR status) patient age, type of surgical procedure, use of hormonal therapy, use of chemotherapy, and type of chemotherapy. In univariate analysis only two of the factors appeared to be significantly associated with the disease free survival **(Table 2)**: T and N staging. The Kaplan-Mayer survival curves were drawn and showed that patients with T1 and T2 tumors have significantly longer DFS compared to the patients with T3 tumors (p=0.003, Log-rank test) **(Figure 1A)**. Analogously, those women without regional lymph metastases at the time of the operation developed recurrence significantly later (median of 64 mo) than that with metastases in regional lymph nodes (median of 33 mo, p=0.013, Log-rank test) **(Figure 1B).** When the Kaplan-Mayer survival curves were drawn according to the G stage grouping (the International Union Against Cancer Tumor-Node-Metastasis staging system), it has appeared that no of the patients in G1 stage developed recurrence during the follow-up period, whereas the median DFS for patients in G2 stage was 60 mo, and in G3 stage only 26 mo **(Figure 1C)**.

Table 2. *Uni- and multivariate analyses for DFS of patients with breast cancer treated with adjuvant radiotherapy.*

Variables	*Univariate analysis*			*Multivariate analysis*		
	p-value	HR ($e^{\square}$)	95% CI	p-value	HR	95% CI
T staging	**0,014**			0.093		
T1	**0.005**	0.123	0.029 – 0.937	**0.030**	0.194	0.044 – 0.852
T2	**0.013**	0.168	0.042 – 0.684	0.085	0.282	0.067 – 0.173
T3*		1			1	
N staging	**0.023**			0.054		
N0		0.229	0.065 – 0.815		0.274	0.074 – 1.021
N1+N2*		1			1	
Age	0.181					
45-49 yrs		0.248	0.033 – 1.910			
≥ 50 yrs*		1				
Chemotherapy	0.806					
no		1.208	0.269 – 5.432			
yes*		1				
Type of chemotherapy	0.507					
CMF		0.694	0.236 – 2.040			
FEC*		1				
Type of operation	0.932					
MM		0.951	0.303 – 2.988			
QM*		1				
ER/PR status	0.932					
negative		1.004	0.282 – 3.575			
positive*		1				
Hormonal therapy	0.189					
no		NE				
yes*						
*- referent category; NE – can not be estimated						

When the variables significant in univariate analysis (T and N staging) were entered in the multivariate Cox proportional hazard model, both of the co-variables lost their significance **(Table 2).** It turned out that only the T3 tumor invasion stage was a significant unfavorable factor for the DFS compared to the T1 stage **(Table 2).**



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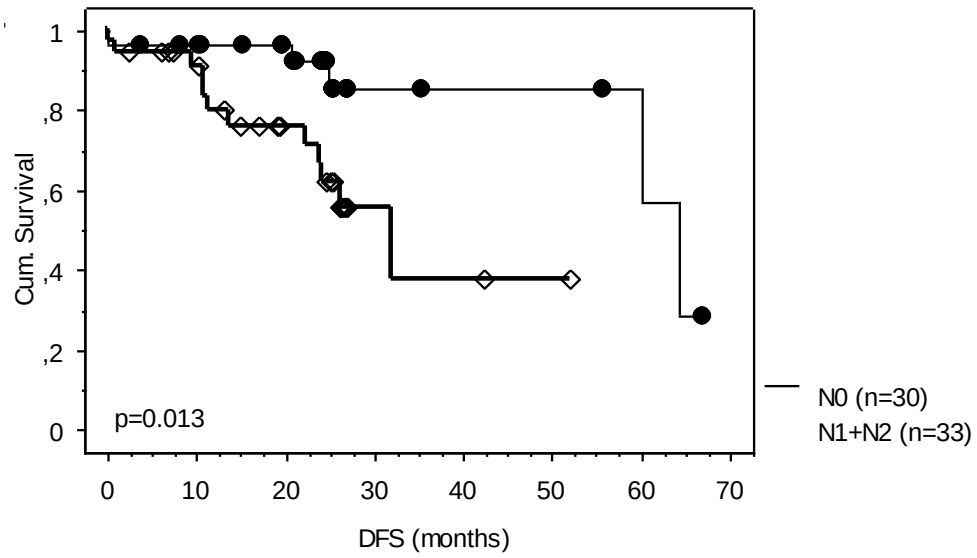

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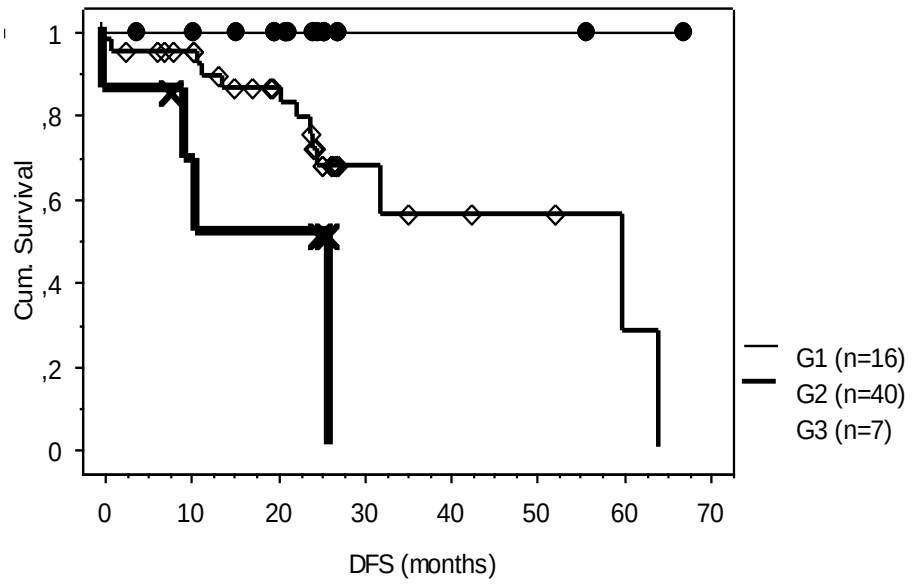

C

Figure 1. Kaplan-Mayer survival curves for DFS of patients with breast cancer treated with adjuvant radiotherapy according to the T staging (**A**), N staging (**B**) and G stage grouping (IUAC TNM staging system) (**C**).

DISCUSSION

A number of randomized researches show that the local control is increased through postoperative irradiation in high risk patients after mastectomy. This was confirmed by conducted studies of groups from Stockholm and Oslo, which demonstrated a better local control with irradiation of thoracic wall and of the ipsilateral lymph nodes in high risk patients after mastectomy.[8]

There are proofs that after radical operation the survival can be increased with postoperative radiation therapy.[9, 10]

The studies determined that survival after mastectomy improves with irradiation of thoracic wall and ipsilateral lymph nodes. Necessity of postoperative radiation therapy after mastectomy in high risk patients was confirmed. According to our own experience a better local control was achieved with the addition of postoperative radiation therapy. Only seventeen recurring cases were found in this group of patients in spite of their risky profile.

In patients with breast-sparring operation the local control increases with the application of postoperative irradiation.[4]

At first the research regarding this matter did not show any considerable improvement in the survival.[4, 11]

A previous randomized analysis showed considerable improvement in life expectancy in patients who received radiotherapy after breast-sparing operation compared to these without such therapy.[12]

In our group of patients postoperative radiation therapy was applied to all with breast-sparing operation. According to a number of authors bad results in breast-sparing operations lie upon the unachieved complete resection and incompletely reduced tumors.[13]

According to Fowble (1998) the rate of local failure varies from 4% to 31 % as it is higher in the invasive tumor components and in ductal carcinoma *in situ*.[14]

In our research 4 patients with breast-sparing operation developed local recurrence. One of them had mixed recurrence in uncertain positive resection edge. From the 16 patients with breast-sparing operation, who had a localized tumor in one quadrant. No additional irradiation was applied at the tumor spot.

There are number of studies regarding this matter proving the advantages of boosted versus non-boosted irradiation. Most often these are additional 10 Gy in the tumor spot plus 50Gy at the whole breast.[7]

On the other hand the factors affecting the cosmetic results as a consequence of boosted irradiation must not be forgotten. The cosmetic changes in the patients are worse with boosted irradiation. However the surgical factors can help for the improvement of the cosmetic results. [2]

Large number of studies have shown that the most important prognostic factors for disease-free survival of patients with breast cancer are the nodal status, size of the tumor, hormonal status. This was confirmed by our results on the studied group.[11]

CONCLUSION

Good results are achieved in local control in our analysis of the patients with radical operation. They support the method of postoperative radiotherapy for the high risk patients. Our results for the patients with breast-sparing operation, together with the results of randomized researches have lead to the consideration about the need of re-excision in the patient with positive resection edges. One the other hand it is important to revise the needs and accompanied advantages of the boosted dose in the patient with low grading and age above 65 years.

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