

TREATMENT FOR MALE BREAST CANCER – 30-YEAR EXPERIENCE AT THE UNIVERSITY HOSPITAL FOR TUMORS IN ZAGREB, CROATIA

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Summary

The study includes records of male patients treated for breast cancer at the Department of Surgery, University Hospital for Tumors, Zagreb, Croatia between 1969 and 1999. In that period, 71 male patients were treated for primary carcinoma of the breast; one of them had cancer in both breasts. The follow-up included the interval between disease onset and diagnosis, age, stage, localization, histologic finding, hormone receptors, metastases and treatment options. The mean age at cancer onset was 62 years, or about 11 years later than in female patients. Age, axillary lymph node status, tumor grade and tumor size were shown to be significant prognostic factors. Primary treatment choice depended upon clinical status of the tumor, age and patient's general condition. The statistical significance was shown between a stage estimated at presentation and stage according to TNM classification ($\chi^2 = 43.99$; d.f. = 6; $p < 0.01$), survival duration by TNM ($\chi^2 = 45.27$; d.f. = 15; $p = 0.00007$), and between treatment type and duration of survival ($\chi^2 = 45.26$; d.f. = 30; $p = 0.04$). The correlation between the patient's age and duration of survival, anamnesis and survival, and hormone receptors and survival was not statistically significant.

KEY WORDS: *breast cancer, male, treatment*

LIJEČENJE RAKA DOJKE U MUŠKARACA – 30 GODINA ISKUSTVA U KLINICI ZA TUMORE U ZAGREBU

Sažetak

Analizirani su podatci muškaraca liječenih od karcinoma dojke na Kirurškom odjelu Klinike za tumore u Zagrebu u razdoblju 1969-1999. Tijekom navedenog razdoblja liječen je 71 muškarac s primarnim karcinomom dojke. Jedan od njih imao je karcinom obje dojke. Praćeno je vrijeme od pojave bolesti do dijagnoze, dob, stadij, lokalizacija, histološki nalaz, hormonski receptori, metastaze i liječenje. Srednja dob pojave karcinoma bila je 62 godine, što je za oko 11 godina kasnije nego u žena. Pokazalo se da su dob, status aksilarnih limfnih čvorova, gradus i veličina tumora važni prognostički čimbenici. Izbor primarnog liječenja ovisi o kliničkom statusu tumora, dobi i o općem stanju bolesnika. Statistička značajnost nađena je između procijenjenog stadija prigodom dolaska i stadija prema TNM klasifikaciji ($\chi^2 = 43,99$; d.f. = 6; $p < 0,01$), u duljini preživljenja s obzirom na TNM ($\chi^2 = 45,27$; d.f. = 15; $p = 0,00007$), te vrste liječenja i duljine preživljenja ($\chi^2 = 45,26$; d.f. = 30; $p = 0,04$). Povezanost dobi bolesnika i duljine preživljenja, anamneze i preživljenja, te hormonskih receptora i preživljenja nije bila statistički znakovita.

KLJUČNE RIJEČI: *karcinom dojke, muškarci, liječenje*

INTRODUCTION

Male breast cancer is uncommon, representing approximately 1% of all cancers. In the Republic of Croatia, breast cancer accounts for 0.3%

of all cancers in men. The ratio of male to female is 1: 65. The incidence rate of male breast cancer in Croatia, standardized to the world population, was 0.6/100.000 and 0.8/100.000 for the periods 1978 -1982 and 1983-1987, respectively. Accord-

ing to these records, Croatia ranks in the middle in relation to other countries of the world (1).

PATIENTS AND METHODS

Patients were followed up according to the duration of anamnesis. In 22.5 % and 29.6% of the cases, anamnesis was shorter than 3 and longer than 12 months, respectively (Table 1). The shortest anamnesis lasted 1 month, and the longest 26 months. In our patients, the average duration of anamnesis was 9 months (\bar{x} = 9.10 months, s = 6.11 months; median = 8 months; mod = 5 months).

Table 1.
DURATION OF ANAMNESIS AT PRESENTATION

ANAMNESIS (months)	NUMBER	%
< 3	16	22.5
3-6	14	19.7
6-12	20	28.2
> 12	21	29.6
Total	71	100.0

The age structure of our patients is shown in Table 2: 16.9% of patients were age 49, but the disease was most frequent in men aged of 60-69 years (32.4%). The youngest patient was 45, and the oldest 82 years of age. The mean age of our patients was 60 years approximately. (\bar{x} = 58.90 years, s = 15.71 years; median = 62 years; mod = 66 years). (Table 2.)

Table 2.
AGE STRUCTURE AT PRESENTATION

AGE (yrs)	NUMBER	%
< 49	12	16.9
50-59	21	29.6
60-69	23	32.4
≥ 70	15	21.1
Total	71	100.0

Two of the patients reported their male relatives as having some breast diseases, and 3 reported breast cancer in their female relatives. Twelve patients reported as having some other parallel disease, too. The patients were divided in 3 groups, depending on the tumor size, or the

presence of local or distant metastases at the time of diagnosis (the so-called stage of the disease at presentation showed in Table 3).

Table 3.
STAGE OF THE DISEASE AT PRESENTATION

STAGE	NUMBER	%
1	24	33.8
2	35	49.3
3	12	16.9
Total	71	100.0

1 - tumor size up to 5 cm; 2 - tumor of any size with the presence of regional metastases; 3 - tumor of any size with the presence of distant metastases.

Localization and spread of the disease were evaluated at physical examination, and on rtg slides and laboratory tests (Table 4). The majority of our male patients, similar to female patients, had a relatively higher frequency of the disease in the left breast (66.2%), compared to the right (32.4%). One of the patients developed bilateral breast cancer, which with the frequency rate of bilateral carcinoma in men being 1.4%, is considered a very rare occurrence.

Table 4.
TUMOR LOCALIZATION AT PRESENTATION

BREAST	NUMBER	%
left	47	66.2
right	23	32.4
both	1	1.4
Total	71	100.0

Treatment strategies were individually tailored. Only one patient, for his poor general condition and pulmonary metastases, could not undergo surgery and the diagnosis was made by fine needle aspiration cytology. The applied treatment modalities are shown in Table 5. The majority of the patients underwent modified radical mastectomy and postoperative radiation treatment. Both simple mastectomy and modified radical mastectomy, as a single treatment, were performed in cases where surgery played a palliative role aimed at obtaining a pathohistologic diagnosis and improving the quality of life. Radical mastectomy was applied in patients who, due to tumor fixation to the pectoral musculature, should undergo resection of breast muscles.

Table 5.

TREATMENT MODALITIES APPLIED

TREATMENT MODALITY	NUMBER	%
MRM+RT	47	66.2
MRM	6	8.5
MS	7	9.9
RM+RT	7	9.9
MRM+H	1	1.4
Unoperated	1	1.4
CT+H+RM+RT	2	2.8
Total	71	100.0

MRM – modified radical mastectomy, RT - radiotherapy, MS – simple mastectomy, RM – radical mastectomy, H - , CT - .

The most frequent was the occurrence of invasive ductal carcinoma (49), followed by medullary (11), carcinoma *in situ* (2) and finally, sarcoma (1) (Table 6).

Table 6.

TUMOR HISTOLOGIC FINDING

HISTOLOGY	NUMBER	%
Ca. ductale invasivum	49	69.0
Ca. papillare	6	8.5
Ca. medulare	11	15.5
Sarcoma	1	1.4
Ca. in situ	2	2.8
Undefined	2	2.8
Total	71	100.0

In the University Hospital for Tumors in Zagreb, hormonal receptor levels have been evaluated since 1980, so the level was measured in 43 patients alone (Table 7.).

Table 7.

HORMONAL RECEPTORS

HORMONAL RECEPTORS	NUMBER	%
negative	16	22.5
positive	27	38.0
indefinite	28	39.4
Total	71	100.0

As positive hormonal receptor values were considered ≥ 5 fmol/mg protein and ≥ 10 fmol/mg protein for estrogen and progesterone receptors, respectively.

The lungs are the most frequent localization of metastases (Table 8).

Table 8.

DISTANT METASTASES

METASTASES	NUMBER	%
lungs	16	22.5
bones	2	2.8
liver	3	4.2
lungs+bones	1	1.4
lungs+liver	1	1.4
lungs+bones+liver	1	1.4
none	47	66.2
Total	71	100.0

The patients were followed up at regular control examinations. For patients who for any reason were lost to follow-up, the data about the development of the disease were taken from the National Cancer Registry. In addition, the inspection of medical documentation from other hospitals in which the patients were possibly treated or died in, showed the survival time or remission. Part of the records were collected by heteroanamnesis. The obtained records were analyzed using univariant and bivariant statistical methods. Data analysis was performed using the SAS statistical package.

RESULTS

Comparison of the evaluated clinical stage of the disease at presentation with pathohistologically confirmed TNM stage showed the frequent occurrence of errors, so the clinical evaluation proved correct in 11 patients (45.8%). These patients were evaluated as having stage I, which also complies with stage I according to the TNM classification. Stage II (TNM) was confirmed in 25% of the patients, and no less than 29.2% of patients clinically grouped as stage I were at stage III according to the TNM classification. Of 35 patients with clinical stage II, one (2.9%) had TNM stage I, 9 patients (25.7%) had TNM stage II, 20 patients (54.1%) had TNM stage III, and 5 patients (14.3%) had TNM stage IV of the disease. Of twelve patients clinically grouped into stage III, 33.3% were actually with TNM stage III, while 66.7% of them were TNM stage IV. Table 9 shows a contingency table of both stage frequencies at presentation and according to the TNM classification. The difference between the stage evaluated at presentation and

the stage according to TNM classification is statistically significant as confirmed by χ^2 -testom. ($\chi^2 = 43.99$; d.f. =6 ; $p < 0.01$). The data show a relative unreliability of the clinical impression at stage evaluation, also reported by some other authors (2-8).

In our patients, the average duration of survival was about 60 months ($\bar{x} = 61.10$ months, mean = 30.04 months; median = 63 months; mod = 36 months). The shortest survival duration was 3 months, and the longest 150 months. The relationship between patient's age and survival duration is shown in Table 10. The largest share of long survival (5 > years) was reported in the second age group (patients under 49 years of age), where of overall 12 patients, 9 or 75% survived for 5 or more years. The smallest share of long survival was reported in the fourth age group (patients over 70 years of age), where of 15 patients, 4 or 26.7 % survived for 5 or more years.

The correlation between patient's age and survival duration was not statistically significant ($\chi^2=20.25$; d.f.=15; $p=0.16$).

Table 11 shows the relationship between anamnesis and survival duration.

The group of 16 patients in whom the treatment delay was less than 3 months, 10 patients survived for more than 5 years (62.5 %). In the group with anamnesis duration of 3-6 months, 9 of 14 patients (71.4 %) survived for 5 or more years. Eleven of 20 patients (55%) in the group with anamnesis duration of 6-12 months survived for 5 or more years, while in the group with anamnesis longer than 12 months, the five-year-survival was reported in only 5 of 21 patients (23.8 %). There is no statistically significant correlation between the two variables ($\chi^2 = 11.95$; d.f. = 15 ; $p = 0.68$).

The correlation between the localization of the disease and survival duration is not statisti-

Table 9.

COMPARISON OF STAGE AT PRESENTATION AND STAGE BY TNM CLASSIFICATION

Stage at presentation		TNM CLASSIFICATION				Total
		I	II	III	IV	
	1.	11	6	7	0	24
	2.	1	9	20	5	35
	3.	0	0	4	8	12
Total		12	15	31	13	71

Table 10.

RELATIONSHIP BETWEEN PATIENT'S AGE AND SURVIVAL DURATION

Age at presentation (yrs)		SURVIVAL DURATION (yrs)					Total	
		<1g.	1-2	2-3	3-4	4-5		>5
	≤49	0	0	0	2	1	9	12
	50-59	2	0	3	1	1	14	21
	60-69	2	2	2	2	6	9	23
	≥70	2	1	4	3	1	4	15
Total		6	3	9	8	9	36	71

Table 11.

RELATIONSHIP BETWEEN DURATION OF ANAMNESIS AND SURVIVAL

Duration of anamnesis (months)		SURVIVAL DURATION (yrs)					Total	
		<1	1-2	2-3	3-4	4-5		>5
	<3	1	0	2	1	2	10	16
	3-6	1	0	1	1	1	10	14
	6-12	1	1	2	2	3	11	20
	>12	3	2	4	4	3	5	21
Total		6	3	9	8	9	36	71

cally significant. Of 47 patients with tumor in the left breast, 25 survived longer than 5 years (53.2%), while of 23 patients with right breast cancer, 10 survived longer than 5 years (43.5%). The patient with bilateral breast carcinoma survived for 11 years. He died at the age of 80 for rupture of esophagus varicosity.

The relationship between the stage of the disease according to the TNM classification and survival duration is shown in Table 12.

In all 12 patients with stage I, the reported survival duration was longer than 5 years. Of 15 stage II patients, 13 survived longer than 5 years (86.7%), while in stage III patients, five-year-survival was reported in only 32.3% (10 of 31 patients), or in 7.7% of stage IV patients (1 of 13 patients). The reported differences in survival duration with regard to the TNM stage of the disease are statistically significant ($\chi^2 = 45.27$; d.f. = 15; p = 0.00007).

The relationship between hormonal receptor levels and five-year-survival is shown Table 13.

As anticipated, the five-year-survival accounted for 68.8% of patients with positive hormonal receptors (11 of 16 patients) compared to 38% (11 of 27 patients) of those with negative hormonal receptors.

In 28 patients, hormonal receptor values were not measured. The differences in survival duration according to reported hormonal receptors are not statistically significant ($\chi^2 = 16.25$; d.f. = 10; p = 0.09).

Table 14 shows the relationship between the type of treatment and survival duration. As mentioned earlier, the majority of patients (47) were surgically treated with MRM. All of the patients received postoperative radiation treatment with the usual dose of 45 Gy. The five-year-survival was reported in 61.7% of the patients. The type of treatment depended on patient's general condition, clinical picture and stage of the disease. It can be observed that in the group of 7 patients who received almost all types of treatment, five-year-survival was not reported. The correlation between the type of treatment and survival duration was statistically confirmed ($\chi^2 = 45.26$; d.f. = 30; p = 0.04).

The comparison of the applied treatment modality and development of distant metastases did not confirm a statistically significant correlation ($\chi^2 = 26.68$; d.f. = 36; p = 0.87). In addition, no statistically significant correlation was confirmed between the applied treatment and regional metastases occurrence ($\chi^2 = 14.98$; d.f. = 12; p = 0.24).

Table 12.

RELATIONSHIP BETWEEN STAGE OF THE DISEASE BY TNM CLASSIFICATION AND SURVIVAL DURATION

		SURVIVAL DURATION (yrs)						Total
		<1	1-2	2-3	3-4	4-5	>5	
TNM classification	I	0	0	0	0	0	12	12
	II	0	0	0	1	1	13	15
	III	3	1	5	4	8	10	31
	IV	3	2	4	3	0	1	13
Total		6	3	9	8	9	36	71

Table 13.

RELATIONSHIP BETWEEN HORMONAL RECEPTOR LEVELS AND 5-YEAR SURVIVAL

		Survival duration (yrs)						Total
		<1	1-2	2-3	3-4	4-5	>5	
Hormonal receptors	neg.	1	0	2	1	1	11	16
	pos.	1	3	2	3	7	11	27
	indef.	4	0	5	4	1	14	28
Total		6	3	9	8	9	36	71

DISCUSSION

Male breast cancer is a rare occurrence. As it is almost impossible to carry out a randomized prospective study, evaluate prognostic factors and the most convenient treatment modality, the majority of studies on male breast cancer, as well as our study, rely on retrospective data collected in one or more centers over several years (9-12). This is the reason why a useful conclusion on possible benefits of some treatment modalities cannot be reached, but the incidence, survival and other potentially important clinical case characteristics can be described.

In our series of overall 71 men with breast cancer, we attempted to evaluate basic characteristics of the disease and treatment results. Compared with the incidence rate of male breast carcinoma in three Scandinavian centers between 1943 and 1982, Ewertz et al. found a small incidence rate increase of 15 a year in the Danish Cancer Registry (13). This incidence trend of male breast carcinoma is in contrast with a 30-percent incidence rate increase reported for female breast cancer in the US in the last 30 years (14). The incidence rate difference between males and females shows a possible effect of various ethiological factors in two genders (15). Many authors agree that men develop breast carcinoma in later age than women (16,18, 15, 19, 20). The mean age in our series was 62 years, or for about 11 years later than women. Haagensen reports the mean age of patients of 60-65 years, symptom duration of 18 months, and 66% operable patients in the group (21, 22). Some authors report the same survival duration in both male and female breast carcinoma (23, 24, 10, 16, 25).

Five-year survival of 40% in our series almost complies with the Cricholow's report (35 %). The low survival rate he ascribes partly to a later age and delayed diagnosis in men with breast carcinoma (23). In the report of his 56 patients treated from 1959-1968, Slack ascribes the poorer prognosis in male breast cancer to a larger number of stage II and III patients. He reports that men and women have a similar prognosis, if the same stage of the disease is taken into consideration (26). Langlands et al. in their report on 88 patients, find more than 60% of the patients having stage III of the disease. As the most important prognostic factor they point out the presence or absence of metastases in axillary lymph nodes, with only 10% of axillary positive patients with a 10-year survival. (4). In the Crichlow's study, only 4 % of patients with positive lymph nodes survived 10 years. The survival rate in both female and male stage III patients is almost equally low. The central localization of male breast cancer is also considered as on of the reasons for poorer prognosis (23).

Handley shows that female patients with central lesions have poorer prognosis, probably due to a high frequency of metastases along the internal mammarian artery. This may partly explain the poorer prognosis in men in whom breast carcinoma almost always lies centrally (27). The published studies (14, 28, 2, 29, 11, 27, 28) mainly include age, axillary lymph node status and tumor size as potentially significant prognostic factors. The histological grade of malignancy also has a prognostic significance, but in relation to its strong correlation with axillary lymph node status and tumor size, the significance of its effect vanishes in a multivariate anal-

Table 14.

RELATIONSHIP BETWEEN APPLIED TREATMENT MODALITY AND SURVIVAL DURATION

		Survival duration (yrs)						Total
		<1	1-2	2-3	3-4	4-5	>5	
Treatment method	MRM+RT	3	1	6	5	3	29	47
	MRM	1	0	2	1	1	1	6
	MS	0	1	1	1	1	3	7
	RM+RT	0	1	0	0	3	3	7
	MRM+H	1	0	0	0	0	0	1
	Unoperated	0	0	0	0	1	0	1
	CT+H+RM+RT	1	0	0	1	0	0	2
Total		6	3	9	8	9	36	71

ysis (Huultborn) (29). Many studies (14, 28, 2, 27) report the age at the time of diagnosis as a prognostic factor for male breast carcinoma.

In their analysis of incidence rates reported in National Cancer Centers of Nordic countries, Adam et al. show that a mortality risk from male breast cancer increases more than 3 times in men over 80, compared with men under 40 years of age (30). Similar to the age at death from male breast cancer in the US and Japan (32), the logarithm of death rate increases lineary with the age logarithm. This complies with the results from our study in which the analysis of age and treatment modalities shows that older men have, by far, shorter survival time. At any rate, the literature results are vague and require future study, with effects on a worse survival prognosis in older men with breast carcinoma being of the main interest. About 35% of the patients in our study had regional spread, and 11% had distant metastases. Several studies show that the time interval to presentation of breast tumor patients is twice longer in men than in women, which also explains their higher stage of the disease at the time of diagnosis (16, 31, 3, 25). The combination of more advanced stage of the disease, delay in diagnosis and older age produces poorer prognostic factors, showing the necessity of education and earlier follow-up of suspicious lesions in male breast.

The significance of various treatment modalities to prognosis, and survival rate in particular, cannot be evaluated from available retrospective studies. Several such studies follow up the results of male breast cancer with regard to the initial surgical treatment. In his review of 301 patients followed up at Christy Hospital in Machester over 15 years, Ribeiro (18) reports no difference in local recurrence in men in whom radical mastectomy was performed, compared with those undergoing simple mastectomy and postoperative radiation (25). Similarly, in 166 patients from the Swedish Cancer Registry there was no difference in survival duration between men in whom radical mastectomy was performed and those who underwent either simple mastectomy or local excision (3). In 39 patients treated at the MD Anderson, Houston, Texas, with breast-conserving surgery, excision biopsy or simple mastectomy with local irradiation, lo-

cal recurrence was controlled better than with radical mastectomy. The recurrence rate was similar in both groups (32). In two other reviews including 50 patients each, no difference in survival duration between patients undergoing radical mastectomy and modified radical mastectomy was observed. These studies suggest that either modified radical mestectomy of radical mastectomy with radiation therapy can produce the same effect for men with the early stage of the disease (9, 33). In their series, Simon et al. (35) report simple mastectomy performed in 17%, modified radical mastectomy in 59%, and radical mastectomy in 15% of patients. Ribeiro (25) reports the same results in patients undergoing radical mastectomy, or simple mastectomy, in whom postoperative irradiation was performed, while Ouriel (25) and Hudson (12) describe the same results in patients undergoing radical, or modified radical mastectomy. Haagensen (27) shows better five-year-survival results in patients with modified radical mastectomy than in those who uderwent radical mastectomy and skin excision. Robinson (34) finds out that local excision or simple mastectomy with postoperative irradiation produce better results than radical mastectomy. Hultborn (29) reports 10-year-survival of 53% in a group treated with radical mastectomy, while in groups treated with modified radical mastectomy, simple mastectomy and local excision 10-year-survival accounted for 58%, 37% and 57%, respectively. The results of treatment methods applied to our patients are mainly descriptive, showing that the primary treatment choice depends upon clinical status of the tumor, then age and general condition of the patient. Radical mastectomy is associated with a lower rate of axillary recurrence, modified radical mastectomy with a somewhat higher rate, and simple mastectomy with the highest rate of axillary recurrence.

We are aware that, based on the presented and analyzed group of our patients, we cannot give any recommendations regarding treatment of male breast cancer. Considering the short distance between the tumor and male chest wall, as well as the fact that lymph is drained in the posterior portion of the big chest muscle, radical mastectomy appears to be the most logical choice. The conclusion is further corroborated by

the knowledge that axillary recurrence is not a frequent occurrence despite the frequent lymph node involvement. The majority of men in our study underwent one type of mastectomy procedure, being the most frequent modality of treatment in several other studies, too (14, 2,10). In our study, modified radical mastectomy was the most frequent procedure, and similar to other studies, the initial popularity of radical mastectomy faded in time. Primary treatment methods differ and are very often conditioned by age and tumor clinical status. No statistically significant correlation between the primary treatment modality and survival pattern. The surgical technique varies considerably, with the surgical procedure applied to the majority of patients being less extensive than recommended in Anglosaxon literature. Haagensen maintains that since male breast carcinoma is characteristic of wide skin involvement, skin graft for covering the defect is very important; if the surgeon performs a wide enough skin excision, the wound cannot be closed without graft (21). In our patients, skin grafting was not used.

CONCLUSIONS

Male breast carcinoma is a rare, but important occurrence. Diagnosis is relatively easy and usually made by biopsy. At the present time, delayed diagnosis is not as frequent as in the past.

The published literature, and our study as well, considers age, axillary lymph node status and tumor size as significant prognostic factors. The right treatment method for male breast cancer can include: surgical procedure, radiation therapy, hormone or cytostatic treatment, and a combination of these treatments. The significance of various treatment modalities to prognosis, and survival rate in particular, cannot be evaluated from published retrospective studies. The results of treatment modalities applied to our patients are mainly descriptive, showing that the primary treatment choice depends upon clinical status of the tumor, then age and general condition of the patient. The right treatment choice for male breast cancer should include mastectomy with axillary dissection and postoperative irradiation. The role of system chemotherapy still requires a full evaluation. Considering the high in-

cidence rate of estrogen-positive tumors in men, adjuvant hormonal therapy can produce better results compared to female patients. Antiestrogen administration, used to complement other treatment methods, plays a very important role.

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