

Scientific Article

Impact of Adjuvant Radiation Therapy in Patients With Male Breast Cancer: A Multicenter International Analysis



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Abstract

Purpose: Breast cancer in men accounts for approximately 1% of all breast cancers. Breast cancer trials have routinely excluded men. The aim of this analysis was to determine the effect of different treatment factors, in particular, postoperative radiation therapy (RT) on long-term outcomes.

Methods and Materials: Seventy-one patients with male breast cancer treated in 5 closely cooperating institutions between 2003 and 2019 were analyzed.

Results: Almost all patients (95%) underwent surgical resection. Forty-two patients (59%) received chemotherapy, and 59 (83%) received adjuvant hormonal therapy. Of the 71 patients, 52 (73%) were treated with RT. The rate of recurrence was 20% in the whole cohort, with a locoregional recurrence rate of 3%. In the entire group, the 5-year local control (LC) was 95%, whereas 5-year progression-free survival (PFS) and 5-year overall survival (OS) were 62% and 96%, respectively. There was a lower rate of relapses after adjuvant RT (19% vs 32%, $P = .05$) without in-field relapse after postoperative RT (0%) versus 10% in patients without RT ($P = .02$). In the

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multivariate analysis performed, hormonal therapy administration was found to have a possible significant effect on LC and PFS. Administration of adjuvant RT and stage affect PFS. In patients who received RT, there were no grade 3 or 4 acute toxicities.

Conclusions: Adjuvant RT is an effective and safe treatment for male breast cancer patients with no infield relapses and better PFS. Hormonal therapy administration was found to have a possible effect on LC and PFS.

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Introduction

Male breast cancer accounts for approximately 1% of all breast carcinomas. No randomized trials are investigating postoperative radiation therapy in male breast cancer owing to its rarity, and most clinical trials on breast cancer have routinely excluded men.¹ The most common clinical symptom in patients with breast cancer is the appearance of a painless retroareolar mass. Other symptoms include skin ulceration, nipple bleeding or retraction, and axillary adenopathy.² Mutations in the tumor-suppressor genes, especially in *BRCA2*, and a family history are the most established risk factors for breast cancer in men.³ The most common histology is invasive carcinoma, with a very high rate of estrogen-receptor (ER) positivity compared to women and only 9% are HER2 positive. Approximately 10% of cases present with ductal carcinoma in situ.¹ The management of male breast cancer may include surgery, chemotherapy, radiation, and hormonal therapy in analogy to the treatment guidelines for breast cancer in women.⁴⁻⁷

The goal of this retrospective study was to determine the effect of different treatment factors, in particular, postoperative RT, on long-term local control (LC), PFS, and overall survival (OS) of male patients with breast cancer.

Methods and Materials

We reviewed the medical records of 71 patients with male breast cancer treated in 5 closely cooperating institutions in Egypt and Germany between January 2003 and January 2019 (Table 1). All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Most of the patients had grade 2 lesions (N = 50, 70%). Disease stage was reclassified according to the Union for International Cancer Control staging system, eighth edition. There were 15 stage I (21%), 29 stage II (41%), 17 stage III (24%), and 5 stage IV (7%) patients. ER information was available in 49 patients and progesterone-receptor (PR) in 62 patients. The ER and PR status were positive in 95% and 90% of available cases, respectively. HER2/neu score was available in 20 patients

(28%). Fifteen patients had negative HER-2-breast cancer, and only 5 patients had positive HER-2-breast cancer.

Sixty-seven patients (95%) were operated on (mastectomy N = 64 and lumpectomy N = 3), and only 4 patients did not undergo operation (5%). Forty-two patients (59%) received chemotherapy, and 59 patients (83%) received hormonal therapy after surgery. Most of the patients (85%) with advanced-stage disease received chemotherapy compared with 46% of patients with early-stage ($P = .006$). The most common chemotherapy regimens were anthracycline and taxane-based chemotherapy regimens (N = 15; 36%) and anthracycline-based regimens (N = 14 out of 42; 33%) combinations. In addition, 52 out of 71 patients (73%) were treated with RT. At the time of analysis, 5 patients were dead, 50 still alive, and 16 were lost to follow-up.

Statistical analysis

Survival data were analyzed using Kaplan-Meier curves. χ^2 or Fisher exact tests were performed to probe the relationships between 2 categorical variables. The 2-sample *U*-test was used to study the relationship between a categorical variable and a continuous variable. LC was calculated from the initiation of RT therapy until the time of documented relapse. OS was calculated from the first day of radiation. PFS was derived from the start of RT therapy until the time of documented relapse or death. Differences were considered statistically significant at $P < .05$. Variables shown by univariate analysis to be associated with LC, PFS, or OS and $P \leq 0.1$ were entered into a Cox proportional hazards regression model for multivariate analysis. All statistical analyses were conducted with IBM SPSS Statistics 25.0 software (SPSS Inc, Chicago, IL).

Results

The RT group had more advanced stages in comparison with patients without RT (81% vs 67%, $P = .2$). The median total RT dose was 50 Gy (range, 30-60), and the median daily RT fraction was 2 Gy (range, 1.8-3) with 5 fractions a week. Only 2 patients received sequential boost irradiation with 14 Gy. Four patients (6%) in our cohort received postmastectomy hypofractionated RT (fraction dose 3 Gy \times 10 in 2 patients and 2.67 Gy \times 15 in 2

Table 1 Patient and treatment characteristics

Characteristic	Value	Percentage or range
Mean age, y	62	40-91
Tumor location		
Left breast	32	45%
Right breast	27	38%
bilateral	1	1%
unknown	11	16%
Disease stages		
Early stages		
Stage I	15	21%
Stage II	29	41%
Advanced stages		
Stage III	17	24%
Stage IV	5	7%
Unknown	5	7%
Histologic differentiation		
Grade 1	3	4%
Grade 2	50	71%
Grade 3	13	18%
Unknown	5	7%
Hormone receptors		
Estrogen receptor positive/negative	47/2	96%/4%
Progesterone receptor positive/negative	56/6	90%/10%
Surgery		
Mastectomy	64	90%
lumpectomy	4	6%
No	3	4%
Chemotherapy		
Yes	42	59%
No	26	37%
Unknown	3	4%
Hormonal therapy		
Yes	59	83%
No	5	7%
Unknown	7	10%
Treatment parameters		
Adjuvant radiation therapy	52/71	73%
Med. radiation dose (range), Gy	50	30-60
Normal fractionated	45/52	86%
Hypofractionated	4/52	8%
Unknown	3/52	6%
Med. fraction dose (range), Gy	2	1.8-3

Abbreviations: M = males; Med. = median.

patients). The most common radiation techniques were 3-dimensional conformal RT in 26 out of 52 patients (50%) and 2-dimensional technique in 25 out of 52 patients (48%). Only one patient received intensity modulated radiation therapy with 50.4 Gy of thorax wall and lymphatics. In the postoperative setting (axillary dissection N = 17 and sentinel node dissection N = 8), regional lymphatics were irradiated in 25 patients (35%). The median follow-up was 34 months (range, 2-189). During the follow-up period, 18 patients (25%) developed tumor

recurrence. The local failure rate was 3% (n = 2) for the whole cohort. A lower rate of relapses after adjuvant RT (19% vs 32%, *P* = .05) has been detected. Regarding the relapse pattern, there was no infield relapse after postoperative RT (0%), although patients without RT had a local relapse rate of 10% (*P* = .02). The most common site of distant metastasis was the bone (14 out of 18; 78%).

In the whole cohort, the 5-year LC was 95% (Fig 1A). Regarding the staging system, no significant differences in terms of LC (*P* = .6) were detected. Higher LC has been observed in patients receiving adjuvant hormonal therapy (96% vs 67%, *P* = .003), chemotherapy (100% vs 84%, *P* = .034), and RT (100% vs 75%, *P* = .004; Fig 2A). In terms of PFS, the 5-year PFS was 62% (Fig 1B). No difference in survival between different tumor grades have been detected (*P* = .5). There was a significantly longer PFS in the early stages in comparison with advanced stages (161 months vs 49 months, *P* < .001). Better 5-year PFS has been detected after adjuvant hormonal therapy (62% vs 25%, *P* = .014) and RT (67% vs 47%, *P* = .04; Fig 2B). Regarding the hormone receptors, patients with negative PR had trend toward inferior 5-year PFS in comparison with positive PR (67% vs 30%, *P* = .06). On the other hand, no significant difference in term of ER status has been observed (*P* = .7).

Regarding OS, the 5-year survival rate was 96% (Fig 1C). No difference in survival between different tumor grades have been detected (*P* = .9). There was a significantly longer OS in the early stages in comparison with advanced stages (*P* = .049). No significant difference in 5-year OS has been detected after adjuvant hormonal therapy (98% vs 67%, *P* = .2), chemotherapy (97% vs 94%, *P* = .14), and RT (95% vs 100%, *P* = .29; Fig 2C). The patients younger than 71 years old had a 94% 5-year OS in contrast to an 83% 5-year survival in older patients (*P* = .038).

In the univariate and multivariate analysis (Table 2), hormonal therapy administration was found to have a significant effect on LC and PFS. In addition, the disease stage and adjuvant RT seem to have a significant effect on PFS, although only patient age had a possible effect on OS.

In terms of postradiation acute toxicities, grade 1 and grade 2 acute toxicities were 48% and 27%, respectively. No grade 3 to 5 acute toxicities have been detected. On the other hand, the rate of chronic toxicities grade 1, grade 2, and grade 3 were 10%, 6%, and 2%, respectively. Almost all toxicities were skin-related reactions. Hypofractionated regimens were not associated with increased acute toxicity rates when no chronic toxicities have been observed.

Discussion

Postoperative radiation therapy should be offered according to guidelines developed for women with breast

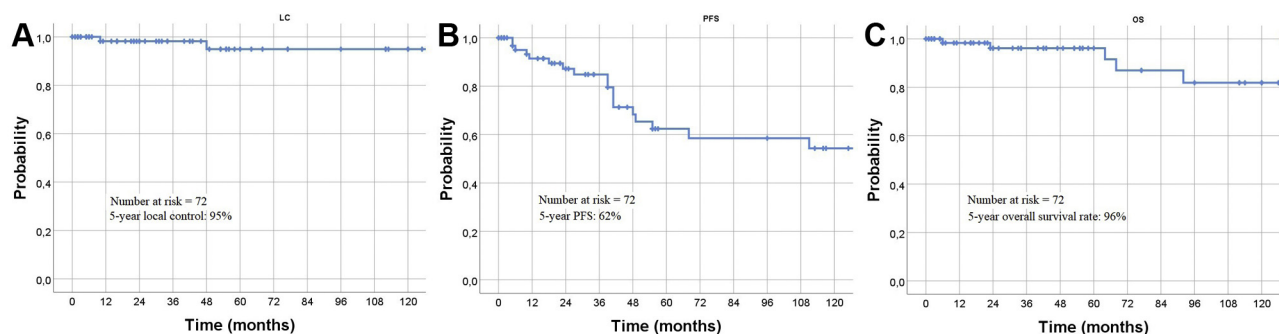


Figure 1 Kaplan-Meier curve derived estimates of local control (A), progression-free survival (PFS) (B), and overall survival (C) in all patients (N = 71).

cancer.⁸ In addition, several retrospective studies of male breast cancer demonstrate improvement in LC and survival after postoperative RT.^{4,7} Owing to advances in modern radiation therapy (RT) and treatment techniques, we could reduce exposure of normal tissues to radiation significantly.^{9,10}

In practice, postoperative RT is often underused in men with breast cancer.^{3,11} An analysis from the SEER database indicates that only 42% of men with stage I breast cancer received radiation therapy after breast-conserving surgery.¹² Although the international Male Breast Cancer Program showed that only half received adjuvant RT,¹³ several observation studies have suggested a benefit for RT in men with early stages and locally advanced stages such as node-positive breast cancer or stage III disease.^{4,14-16}

In a retrospective trial with 1933 patients, the case-matched analysis showed an improved OS at 5 years in the postmastectomy RT group (83% vs 54%). On subgroup analysis, postoperative RT was associated with improved 5-year OS in men with 1 to 3 positive nodes (79% vs 72% $P = .05$) and those with 4 + positive nodes (73% vs 53% $P < .001$).¹⁴ In addition, another study cohort with 664 patients shows that postmastectomy RT is associated with longer OS in men with stage III breast cancer (hazard ratio 0.60; 95% confidence interval, 0.41-0.88; $P = .008$).¹⁶ This trend can also be observed in our study, as only 52 out of 71 patients received RT. The toxicity profiles were minimal, and there were no infield relapses in the RT group. Although the RT group had more advanced stages in comparison with patients

without RT (81% vs 67%, $P = .2$), postoperative RT shows an improved PFS in multivariate analysis.

Four patients (6%) of our cohort received hypofractionated radiation therapy. In this group, only grade 1 and 2 acute toxicities of the skin without chronic toxicities were observed. Consistent with Wang et al, who demonstrated that hypofractionated postmastectomy radiation therapy is not inferior to conventional fractionated radiation therapy in patients with high-risk breast cancer,¹⁷ hypofractionated regimens may also be feasible in men with breast cancer.

Hormone therapy is a well-established component of adjuvant treatment, as most breast cancers in men are hormone-receptor positive. The efficacy of tamoxifen as an adjuvant treatment and in patients with metastatic disease is shown in different studies and suggests a survival benefit.^{2,18} In accordance with other studies, the multivariate model in our study shows a significant advantage in PFS for patients with adjuvant hormonal therapy ($P = .0002$).

Our study has several limitations. This retrospective study is based on only 71 patients, and therapy groups were not equal, so additional studies are necessary before a definitive conclusion can be reached. HER2/neu, ER, and PR information were not available in all patients owing to the retrospective nature of this international analysis. Some meaningful clinical results in favor of postoperative RT and other possible prognostic factors detected in this study need to be validated in randomized prospective trials.

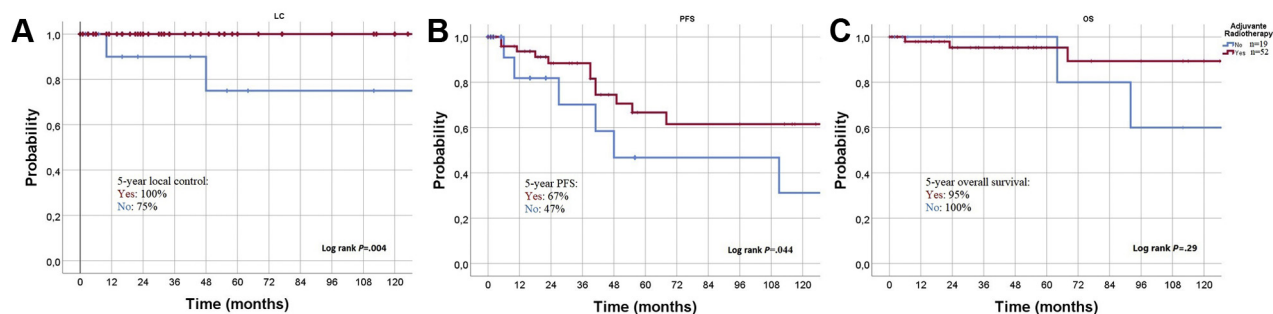


Figure 2 Kaplan-Meier curve derived estimates of local control (A), progression-free survival (PFS) (B), and overall survival (C) according to adjuvant radiation therapy (yes = 52 and no = 19).

Table 2 Univariate and multivariate analyses for local control, progression-free survival, and overall survival in patients with invasive cancer (N = 71)

Risk factor	LC		PFS		OS	
	HR	P value	HR	P value	HR	P value
Univariate model						
Age (y)	.917	.4	1.05	.2	1.14	.06
Grade (3 vs 1-2)	2000	.6	1.4	.5	1.12	.9
Stage (early vs advanced)	.027	.6	3.7	.01	.6	.6
Adjuvant hormonal therapy	.05	.03	.23	.02	.29	.26
Adjuvant chemotherapy	.005	.4	1.4	.5	.28	.1
Adjuvant radiation therapy	.001	.6	.41	.05	.4	.3
Multivariate model						
Age (y)	-	-	-	-	1.14	.06
Stage (early vs advanced)	-	-	.117	.0002	-	-
Adjuvant hormonal therapy	.05	.03	.156	.01	-	-
Adjuvant radiation therapy	-	-	.3	.05	-	-

Abbreviations: HR = hazard ratio; LC = local control; OS = overall survival; PFS = progression-free survival.

Conclusions

Postoperative RT is an effective treatment for male patients with breast cancer with minimal toxicity profiles and no infield relapses. Hormonal therapy administration was found to have a possible significant effect on LC and PFS. While the disease stage and adjuvant RT seem to have a significant effect on PFS.

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