Volume 20, No 3 | International Journal of Radiation Research, July 2022

Clinical outcomes of adjuvant radiotherapy for nodal negative T1 and T2 breast cancer

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► ***Original article***

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Received: April 2020
Final revised: December 2021
Accepted: January 2022

Int. J. Radiat. Res., July 2022; 20(3): 601-605

DOI: 10.52547/ijrr.20.3.12

Keywords: *Early-stage breast cancer, prognostic factors, radiotherapy, survival.*

ABSTRACT

***Background*:** The objective of this study was to determine the long-term results of postoperative radiotherapy (RT) in patients with node-negative T1–T2 breast cancer and the prognostic factors affecting these results. ***Materials and Methods*:** We retrospectively evaluated 382 node-negative breast cancer patients (pT1a–c, T2) treated with surgery. All patients underwent postoperative RT and 80% of patients received hormone therapy. Prognostic variables included patient characteristics, disease characteristics, and intervention factors. The primary endpoint was overall survival (OS). Survival curves were estimated using the Kaplan–Meier method. Differences in observed survival distributions among patient subgroups were evaluated using a two-sided long-rank test. We applied univariate and multivariate Cox models to evaluate predictive factors. Statistical significance was evaluated at a level of $P < 0.05$. ***Results*:** The median follow-up was 143 months. The 10-, 15-, and 20-year OS rates were 92%, 86%, and 80%, respectively. Univariate analysis showed that age (< 45, 45–65, > 65 years; $P < 0.0001$), comorbidity ($P = 0.008$), menopausal status ($P = 0.03$), and tumor stage (T1a–c, T2; $P = 0.006$) (table 1) were significant predictors of OS. Multivariate analysis showed that age (< 45, 45–65, > 65; $P = 0.01$) and tumor stage (T1a–c, T2; $P < 0.0001$) were independent predictors of OS. At age 15 years, the OS rate of patients with T1b, T1c, or T2 stage cancer was 87.5%, 81%, or 77%, respectively. ***Conclusions*:** Age and tumor stage were independent prognostic factors for women with node-negative early breast cancer.

INTRODUCTION

Breast cancer (BC) is one of the most common female cancers among women and one of the serious causes of cancer-related death in the world [(1)]. Postoperative breast irradiation using modern radiotherapy (RT) techniques following breast-conserving surgery has already been demonstrated in several randomized studies and many meta-analyses, concluding that lumpectomy provides similar survival rates to mastectomy for stages I and II BC [(2–8)]. The aim of postoperative RT is to reduce the locoregional recurrence rate (LRR). The rate of ipsilateral breast recurrence in patients who did not receive postoperative radiation therapy after breast-conserving surgery ranges from 9% to 35%. Radiotherapy given after breast-conserving surgery reduces LRR by approximately one-third [(9–11)]. In addition, randomized studies have also found a reduced risk of recurrence after breast-conserving surgery, regardless of the accrual of tumors ≤2 cm [(12)], <2.5 cm [(3)], or ≤4 cm in diameter [(2, 5, 7)] and regardless of the inclusion of either invasive or intraductal cancers in the study [(13)]. Over the past 20 years, treatment of BC has shifted towards less invasive surgical treatment methods. Many clinical studies having long-term follow-up showed that treatments after breast conserving or after mastectomy have equivalent survival rates [(14, 15)]. Patients with mastectomy and T1-T2 node-negative BC are assessed to have a low risk in terms of locoregional recurrence and do not require routine post-mastectomy RT [(16)]. Retrospective studies identified the characteristics associated with LRR as age <40, tumor size, lymphovascular invasion, and high nuclear grade an elevated LRR of up to 20% [(17, 18)]. More recently, based on 10-year results from the Canadian National Cancer Institute Clinical Research Group MA20 and European Organization for Cancer Research and Treatment randomized controlled trials found better disease-free survival rates after adding regional nodal irradiation to whole breast RT for early-stage BC in "high-risk" node-negative patients [(19, 20)]. T1 tumors, including T1a (≤5 mm), T1b (>0.5 and ≤1 cm), and T1c (>1 and ≤2 cm) tumors, it has been determined as the most frequently diagnosed invasive breast tumors in developed countries. These small tumors have cancer-specific survival rates of

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[DOI: 10.52547/ijrr.20.3.12]

5-10 years, with rates of 90% or 95% [21–24]. Considering all these, we aimed to determine the long -term results of postoperative RT in patients with node-negative T1–T2 BC and the prognostic factors affecting these results

MATERIALS AND METHODS

From the database of our institution, between 1997 and 2010, we identified 382 female patients who were diagnosed with negative lymph nodes and had undergone mastectomy or breast-conserving surgery (BCS) without any detectable distant metastases. Prognostic variables were designated as patient characteristics (age, comorbidity, use of oral contraceptive pills, family history of BC, smoking, pregnancy, menopausal status), disease characteristics (tumor, laterality, location, lymphovascular involvement, cell differentiation grade, extracapsular involvement, perineural involvement, number of removed lymph nodes, number of positive nodes, lymph node ratio, and status of hormone receptors) and interventional factors (type of surgery, safe surgical margin, chemotherapy, and hormone therapy). The clinicopathological characteristics of patients are shown in table 1. Each patient underwent postoperative RT. External RT was applied using a linear accelerator (Saturn 42, GE Healthcare) with a photon energy range of 6–12 MV. The maximum total dose was 50 Gy, given in 25 fractions at 2 Gy per fraction. Treatment was applied to the chest wall or breast for the patients who had undergone BCS or postmastectomy. Peripheral lymphatics were included in the RT field in only 10% of patients. In breast RT, a total dose of 10 Gy (2 Gy per fraction) was applied to the tumor bed via electrons or photons.

All patients were treated with three-dimensional conformal RT. Patients with positive hormone receptors (80%) had at least 5 years of adjuvant hormone therapy, among which 49% of patients received tamoxifen, 32% received aromatase inhibitors, and 19% received both. Half of the patients underwent chemotherapy regimens, among which 13% were taxane-based (anthracycline combined with taxane) and 87% anthracycline-based (anthracycline combined with cyclophosphamide, with or without fluorouracil).

Overall survival (OS) was defined as the primary end point. The follow-up time was calculated between the dates of the last RT treatment and the last follow-up or death. OS was defined as the time between the histologic diagnosis and death or last contact. Survival curves were designated using the Kaplan–Meier method. Differences in observed survival distributions among patient subgroups were tested using the two-sided long-rank test. We applied univariate and multivariate Cox models to evaluate predictive factors. Data are reported as hazard ratios (HRs) with 95% confidence intervals (Cls). "SPSS Statistics v20 software for Windows''was used for statistical tests. Statistical significance was evaluated at a level of $P<0.05$; all P values were two-sided.

Table 1. Clinicopathological characteristics of patients with breast cancer (n= 382).

Variable	No of Patients (N=382) (%)	P value
Age (year)		
Median and range	52 (26-80)	
<45 age	107 (28)	**<0.0001**
45-65 age	216 (56.5)	
>65 age	59 (15.5)	
Comorbidity		
Yes	131 (34)	**0.008**
No	251 (66)	
Oral contraceptive pills		
Yes	58 (15)	0.5
No	324 (85)	
Family History of breast cancer		
Yes	75 (20)	0.8
No	307 (80)	
Smoking		
Yes	123(32)	0.4
No	259 (68)	
Pregnancy		
No previous pregnancy	78 (21)	0.34
Previous pregnancy	304 (79)	
Menopausal status		
Postmenopausal	208 (54)	**0.03**
Premenopausal	174 (46)	
Breast		
Left	199 (52)	0.3
Right	183 (48)	
Location		
Upper lateral	202 (53)	0.18
Upper medial	52 (13)	
Lower lateral	25 (6.5)	
Lower medial	24 (6.5)	
Central portion	79 (21)	
Type of surgery		
Mastectomy	31(8)	0.9
Breast conservation surgery	351(92)	
Safely margin		
Positive	13(3)	0.32
Negative	367 (97)	
Tumor type		
Ductal	309 (81)	0.61
Lobuler	22 (6)	
Mixed	19 (5)	
Others	32 (8)	
Histological grade		
Well	63 (16)	0.61
Moderate	174 (46)	
Poorly	110 (29)	
Unknown	35 (9)	
Cerb2		
Negative	207 (54)	
Positive	78 (20)	0.72
Unknown	97 (26)	
Tumor size		
1a	8 (2)	**0.006**
1b	59 (15)	
1c	172 (45)	
2	143 (38)	
Number of removed lymph nodes		
0	13 (4)	
1-9 N	199 (51)	0.89
≥10 N	170(45)	

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Continued table 1. Clinicopathological characteristics of patients with breast cancer (n= 382).

Variable	No of Patients (N=382) (%)	P value
Lymphovasculer involvement		
No	209 (54)	0.39
Yes	138 (36)	
Unknown	52 (13)	
Perinoral involvement		
no	226 (60)	0.32
yes	86 (22)	
unknown	70(18)	
Estrogen receptor status		
Negative	100 (24)	0.62
Positive	282(76)	
Progesterone receptor status		
Negative	112 (30)	0.99
Positive	300 (70)	
Triple negative		
Yes	51(13)	0.82
No	331(87)	
Hormone therapy		
No	82(21)	0.5
Yes	300 (79)	
Chemotherapy		
No	205(54)	0.53
Yes	117 (46)	
radiotherapy break day		0.68
0-2 day	206(53)	
>2	176 (47)	

RESULTS

We evaluated patients with node-negative BC over 25 years of follow-up. The mean age at diagnosis was 52 (range 26–80 years). The clinicopathological characteristics of the patients with node-negative BC are shown in table 1. Lymph node dissection was performed in 80% of patients; the average number was 9 (range, 1–41).

The median follow-up was 12 years (0.5–25 years). The 10-, 15-, and 20-year OS rates were 92%, 86%, and 80% respectively (95% CI, 264.3–284.2). Univariate analysis showed that age (<45, 45–65, >65 years; P<0.0001), comorbidity (P = 0.008), menopausal status (P = 0.03), and tumor stage (T1a–c, T2; P = 0.006) (table 1) were significant predictors of OS. Multivariate analysis showed that age (<45, 45–65, >65; P = 0.01) and tumor stage (T1a –c, T2; P<0.0001) were independent predictors of OS. At age 15 years, the OS rate of patients with T1b, T1c, or T2 stage cancer was 87.5%, 81%, or 77%, respectively. The survival analysis according to tumor diameters and age is shown in figures 1 and 2.

Although 19% of patients show no acute side effects during RT, grade I, II, and III radiodermatitis has been observed in 50%, 30%, and 1% of patients, respectively. Radiation pneumonia was observed in 1% of patients during the acute period. Lymphedema was not observed in 95% of patients; grade III lymphedema was observed in only one patient. Good and very good cosmetic results were detected in 89% of patients who received RT after BCS; 49% of patients receiving an aromatase inhibitor had bone side effects, of which osteopenia was the most common.

Local recurrence was detected in 12 patients, after a median time of 8 years. Ten patients had cancer in the opposite breast, with a median incidence of 10 years. Metastasis developed in 30 patients (21%), of whom 10 had metastasis at more than one site, after a median time of 5 years. Seven patients developed secondary cancers (vulva in one, thyroid in one, salivary gland in one, colon in two, endometrial in one, and gastrointestinal stromal tumor in one). One patient had angiosarcoma in the RT field, and one patient had a malignant epithelial tumor. Fourteen patients (3.6%) died from causes not related to BC.

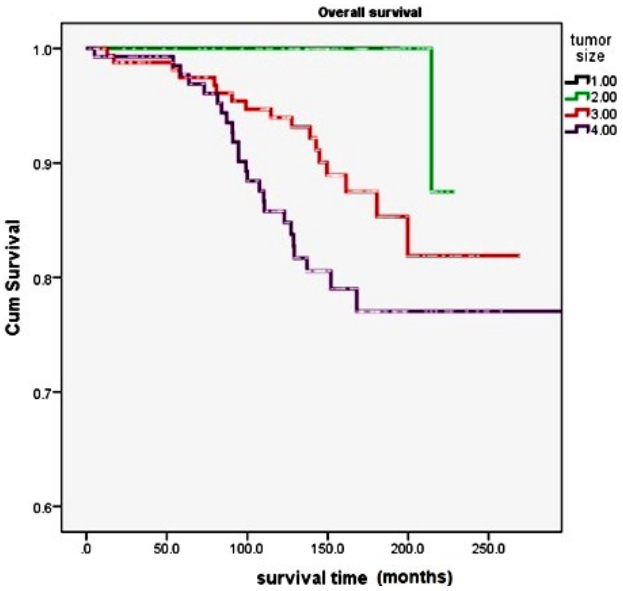


Figure 1. Survival of T1a (≤ 5 mm), T1b (> 0.5 and ≤ 1 cm), T1c (> 1 and ≤ 2 cm), T2 (>2 cm and ≤5 cm) tumors by months. Shown in the figure is 1; T1a, 2; T1b, 3; T1c, 4; T2.

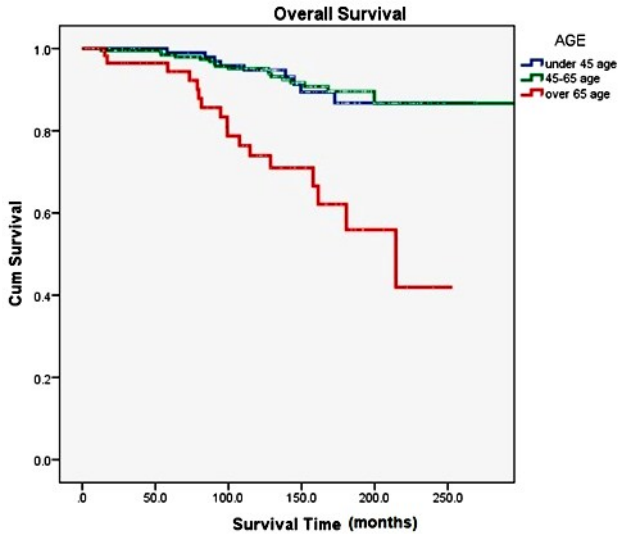


Figure 2. Survival curve by month shown as < 45, 45-65, > 65 years.

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DISCUSSION

Previous studies have shown that breast irradiation following BCS reduced the risk of local recurrence and improved survival [2–8]. In retrospective studies, features associated with LRR including age < 40, lymphovascular invasion, high nuclear grade and tumor size; these features were found in 20% of women with more than one risk factor [17, 18].

In this study, we examined the 25-year follow-up results of T1–T2 node-negative early-stage BC who treated with postoperative RT after BCS. Multivariate analysis revealed significant differences in OS depending on patient age and tumor diameter. Among all patients, 26 (7%) died from disease progression, and local recurrence was detected in 14 (4%) patients.

A previous study reported poor disease-free survival and LRR in patients with tumors > 2 cm in diameter [25]. Despite the uncertain role of tumor diameter, another study reported differences between stage T1 and T2 cancers, which require different therapeutic approaches [26]. In this study, we found that a tumor diameter > 2 cm was a significant prognostic factor for OS.

A LRR of 4.7% within 5.7 years was reported in a study of 671 patients, having T1–T2 node-negative cancer, with a significant effect of tumor diameter on the LRR [27]. In this study, the LLR was 4%, and tumor diameter was significantly linked with OS.

The benefits of postmastectomy RT in patients, having T1-T2 node-negative cancer and one or more high-risk features have been found to be controversial [17]. In this study, 34 (8%) patients underwent RT after mastectomy, but no statistical difference in survival was observed. Peripheral lymphatic irradiation was administered to 28 patients (7%) with at least one risk factor. Nodal recurrence was detected in four patients (1%).

In this study, patients aged > 65 years showed worse survival in a relatively old population (average age, 52 years). In a study of 4,836 patients aged 50–89 years with early stage BC and treated with BCS, no radiation therapy was associated with significantly higher relapse rates and worse disease-specific and all-cause survival after a median follow-up of 7.5 years; up to 26% of women aged > 74 years received no radiation, compared with only 7% of those aged 50–64.4 years [28]. In women aged > 50 years with small, node-negative BC, the addition of radiation to tamoxifen following BCS significantly decreased the risk of breast cancer or axillary recurrence compared with tamoxifen alone [29]. A randomized study assessed the contribution of radiotherapy after BCS in women over 70 years with stage I, hormone receptor positive BC who had been treated with systemic therapy with tamoxifen. After a mean follow-up for 5 years, additional radiation therapy reduced the LRR from 4% to 1%; however, no difference was found in OS and most deaths were due to comorbid diseases, not BC [30]. This patient population appears to require individualized treatment [31].

In conclusion this study reports the results of a large retrospective study of T1–T2 node-negative BC patients treated with low toxicity with very good local control and survival rates after 25 years of follow-up. Tumor stage and age were found to be independent prognostic factors among these patients.

ACKNOWLEDGEMENTS

Not applicable.

***Funding*:** None.

***Ethics approval and consent to participate*:** Ethics committee of Marmara University Faculty of Medicine approved the study (approval no. 09.2019.383).

***Author contributions*:** Study conception and design: I Alsan Cetin, SU Akay; Data collection: I Alsan Cetin, SU Akay; Analysis and Interpretation of results: I Alsan Cetin, SU Akay; Manuscript preparation: I Alsan Cetin; Manuscript editing: I Alsan Cetin, SU Akay, HBC Ozkok, M Sengöz. All authors reviewed the results and approved the final version of the manuscript

***Conflicts of interest*:** Declared none.

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