Prognostic factors for locoregional recurrence and survival in stage IIIC breast carcinoma: impact of adjuvant radiotherapy

Kuru B

ABSTRACT

Introduction: The aims of the present study were to define the prognostic factors for locoregional recurrence (LRR) and survival in stage IIIC breast carcinoma as well as to examine the impact of adjuvant radiotherapy on the outcome of the disease.

Methods: The records of 586 consecutive patients with stage IIIC breast carcinoma who underwent modified radical mastectomy were evaluated, and the prognostic factors for LRR and survival were analysed. Survival curves were generated using the Kaplan-Meier method, and multivariate analysis was performed using the Cox proportional hazard model.

Results: Five-year LRR and survival of stage IIIC breast carcinoma were 15 percent and 41.3 percent, respectively. Five-year LRR was significantly lower and five-year survival was significantly higher for all patients as well as for T1–2 patients with one to three apical node involvements who were treated with adjuvant radiotherapy. In multivariate analysis, apical node involvement, age below 35 years, T4 tumour, grade 3, extracapsular extension and lymphovascular invasion decreased survival, whereas adjuvant tamoxifen and adjuvant radiotherapy risk ratio [RR] 0.51, 95 percent confidence interval [CI] 0.39–0.67) increased survival. Adjuvant radiotherapy was the sole independent factor that was found to be significantly associated with decreased LRR (RR 0.25, 95 percent CI 0.16–0.38).

Conclusion: Radiotherapy decreased LRR and increased survival significantly in all stage IIIC patients and in the subgroup of T1–2 patients with one to three apical node involvements. Thus, it should be considered in the treatment of stage IIIC breast carcinoma.

Keywords: adjuvant radiotherapy, apex axillary invasion, one to three positive axillary nodes, stage IIIC breast carcinoma

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INTRODUCTION

The American Joint Committee on Cancer (AJCC) revised the staging system for breast cancer in 2002 and introduced a new stage IIIC breast carcinoma.[1] According to the current AJCC staging system, any positive nodes at apex axilla (level III) and/or ten or more positive axillary lymph nodes are classified as pN3 (pathological lymph node status 3) and any TN3M0 are categorised as stage IIIC. Patients with apex metastasis or ten or more positive nodes have decreased survival rates.[2-5] The grave survival outcome for stage IIIC has also been demonstrated in a previous study.[4] We are unaware of any published study that has analysed prognostic factors for locoregional recurrence (LRR) and survival in stage IIIC breast carcinoma. The impact of adjuvant radiotherapy (RT) on its locoregional treatment is also unclear. The indication for adjuvant RT in patients with four or more metastatic nodes has been established;[6] however, there is no consensus for its use in patients with one to three positive nodes.[7-9] Adjuvant RT is also known to affect locoregional failure and survival,[10-14] and apex metastasis has been suggested to be a prognostic factor for locoregional metastasis[15] and survival in node-positive breast carcinomas.[2-4] To date, however, the effect of adjuvant RT has not been addressed in stage IIIC breast carcinoma. We aimed to define the prognostic factors for LRR and overall survival for stage IIIC breast carcinoma as well as to determine whether adjuvant RT is effective for decreasing LRR and promoting survival.

METHODS

We reviewed the records of 1,483 consecutive female patients (at our hospital) with T1–3 and non-inflammatory T4 tumour, who underwent modified radical mastectomy (MRM) with level I–III axillary dissection and who had positive axillary lymph node(s) in 1993–2002. 21 patients were not eligible for the study, as their records

Ondokuz Mayıs Üniversitesi Tıp Fakültesi, Genel Cerrahi Anabilim Dalı, Kurupelit 055100, Samsun, Turkey

Kuru B, MD, FACS
Associate Professor

Correspondence to:
Dr Bekir Kuru
Tel: (90) 532 775 5668
Fax: (90) 362 457 6041
Email: bekirkuru@yahoo.com

Table I. Comparison of radiotherapy treatment according to prognostic and treatment-related factors.

Variable	No. (%)			p-value
	Total	No radiotherapy	Received treatment	
Age (yrs)				
< 35	115 (20)	24 (23)	91 (19)	0.42
≥ 35	471 (80)	82 (77)	389 (81)	
Pathological tumour size (cm)				
≤ 2	37 (6)	2 (2)	35 (7)	0.44
2.1–5	247 (42)	46 (44)	201 (42)	
> 5	161 (28)	47 (44)	114 (24)	
T4	141 (24)	11 (10)	130 (27)	
Number of positive nodes				
1–3	100 (17)	38 (36)	62 (13)	< 0.001
4–9	185 (32)	33 (31)	152 (32)	
≥10	301 (51)	35 (33)	266 (55)	
Level of invasion				
Level 1–2	44 (7.5)	5 (5)	39 (8)	0.31
Level 3 (± level 1–2)	542 (92.5)	101 (75)	441 (92)	
Grade				
1	74 (12)	8 (7)	66 (14)	0.16
2	303 (52)	57 (54)	246 (51)	
3	209 (36)	41 (39)	168 (35)	
Lymphovascular invasion				
Absent	158 (27)	25 (24)	133 (28)	0.47
Present	428 (73)	81 (76)	347 (72)	
ER status				
Negative	240 (41)	58 (75)	182 (66)	0.17
Positive	111 (19)	19 (25)	92 (34)	
Unknown	235 (40)			
Extracapsular extension				
No	242 (41)	62 (58)	180 (38)	< 0.001
Yes	344 (59)	44 (42)	300 (62)	
Chemotherapy				
No	7 (1)	3 (3)	4 (1)	0.11
Yes	579 (99)	103 (97)	476 (99)	
Tamoxifen treatment				
No	434 (74)	85 (76)	349 (73)	0.14
Yes	152 (26)	21 (24)	131 (27)	

ER: oestrogen receptor

for the number of positive axillary nodes and/or the distribution of the nodes (by levels) were unavailable. Of the remainder, 586 patients who had ten or more positive nodes and/or apex axillary invasion that were classified as stage IIIC breast carcinoma were the subjects of the current study. The study design was approved by the institutional review board of our hospital.

Ten patients who developed metachronous contralateral breast carcinoma and six patients who developed secondary cancer after MRM, and who were still alive were included in the study. All patients had histologically confirmed invasive breast carcinoma and metastatic axillary lymph nodes, and underwent level I, II or III axillary dissection. After the axillary dissection, the three berg levels were marked with silk sutures for identification by pathological examination. The median follow-up time for patients who were still alive was 74 (range 60–120) months at the follow-up cut-off date. No patient was lost to follow-up for the first six years; by ten years, 13 patients who had been lost to follow-up were censored. Two deaths from traffic accidents were also deemed as censored observations; whereas ten deaths from diseases other than breast carcinoma were included in the overall survival analysis.

Pathological lymph node classification and tumour staging were performed according to the current AJCC staging system; any positive lymph node at apex axilla (level III) and/or ≥ 10 positive axillary nodes were categorised as pN3 (pathological lymph node status) (stage IIIC). All patients received adjuvant systemic treatment with tamoxifen or chemotherapy. Seven (1%) patients were treated with tamoxifen alone, while 434 (74%) were treated with chemotherapy alone and 145 (25%), were treated with both tamoxifen and chemotherapy. Of the 579 patients treated with chemotherapy, 410 received cyclophosphamide/methotrexate/5-fluorouracil (CMF)

Table II. Comparison of radiotherapy treatment according to prognostic and treatment-related factors among T1–2 patients with one to three apical node involvements.

Variable	No. (%)			p-value
	Total	No radiotherapy	Received treatment	
Age (yrs)				
< 35	16 (24)	6 (17)	10 (29)	0.39
≥ 35	50 (76)	26 (83)	24 (71)	
Pathological tumour size (cm)				
≤ 2	7 (10)	1 (3)	6 (18)	0.106
2.1–5	59 (90)	31 (97)	28 (82)	
Grade				
1	6 (9)	1 (3)	5 (15)	0.14
2	33 (50)	16 (50)	17 (50)	
3	27 (41)	15 (47)	12 (35)	
Lymphovascular invasion				
Absent	5 (8)	3 (9)	2 (6)	0.66
Present	61 (92)	29 (91)	32 (94)	
ER status				
Negative	29 (44)	15 (75)	14 (70)	0.1
Positive	11 (17)	5 (25)	6 (30)	
Unknown	26 (39)			
Extracapsular extension				
No	32 (48)	32 (100)	0 (0)	< 0.0001
Yes	34 (52)	0 (0)	34 (100)	
Chemotherapy				
No	1 (1.5)	0 (0)	1 (3)	0.1
Yes	65 (98.5)	32 (100)	33 (97)	
Tamoxifen treatment				
No	50 (76)	22 (69)	28 (82)	0.25
Yes	16 (24)	10 (31)	6 (18)	

ER: oestrogen receptor

and 169 received either 5-fluorouracil/doxorubicin/cyclophosphamide (FAC) or 5-fluorouracil/epirubicin/cyclophosphamide (FEC).

Patients with T1–3 tumour underwent six cycles of adjuvant chemotherapy. 141 patients with non-inflammatory T4 tumours underwent surgery following downstaging by 3–6 cycles of neoadjuvant CMF, FAC or FEC chemotherapy, and had 3–6 cycles of adjuvant chemotherapy, completing a total of nine cycles of chemotherapy. 480 (82%) patients received adjuvant RT to the chest wall, while three received RT to the axillary nodal levels, the supraclavicular region and the internal mammary nodal region within three months of surgery. RT was indicated for patients who met one of the following criteria: ≥ 4 positive axillary nodes; extracapsular extension; or T3–4 tumour. A total of 50 Gy were given in 25 fractions over five weeks using 2 Gy per fraction. Radiation was delivered with Cobalt-60 and linear accelerators using 6 MV photons or a 12-MeV electron beam. The chest wall was treated with medial and lateral tangents using photons designed to include the entire chest wall. The supraclavicular fossa and axillary nodal levels were treated with photon fields. A combination of 20 Gy anterior photon fields and 30 Gy anterior electron fields was used against the internal mammary region. Tissue-equivalent bolus material (0.5 cm) was applied to the chest wall during the first two weeks of RT treatment. Radiation was scheduled between chemotherapy cycles. A group of patients for whom RT was indicated did not receive RT either due to refusal or socioeconomic reasons.

Histological grade was assessed using the Elston-Ellis modification of Bloom-Richardson grading method.[16] Oestrogen receptor (ER) status was defined by immunohistochemistry, and staining of 10% of the tumour cells was accepted as ER positivity. ER status was known in 60% of the patients, and those with unknown ER status were included in the study so as to avoid selection bias. However, the results would not have changed when patients with unknown ER status were not included in the multivariate survival analysis. Each lymph node was sectioned into four slides and stained with haematoxylin and eosin, and pathological assessment was performed by two experienced staff pathologists. Investigations such as physical examination, abdominal and pelvic ultrasonography (USG), chest radiograph and bone scintigraphy were carried out to rule out distant metastasis before the surgery. Computed tomography

Table III. Univariate analysis for overall survival and locoregional recurrence according to patient and tumour characteristics and treatment-related factors.

Variable	5-year LRR rate (%)	p-value	5-year OS rate (%)	p-value
Age (yrs)				
< 35	13	0.55	23	< 0.0001
≥ 35	15		46	
Pathological tumour size (cm)				
≤ 2	8	0.0011	47	< 0.0001
2.1–5	10		47	
> 5	20		48	
T4	24		25	
Number of positive nodes				
1–3	16	0.99	42	0.92
4–9	15		42	
≥10	15		41	
Level of invasion				
Level 1–2	16	0.26	55	0.0067
Level 3 (± Level 1–2)	15		40	
Grade				
1	13	0.0001	67	< 0.0001
2	13		47	
3	22		23	
Lymphovascular invasion				
Absent	13	0.90	51	0.0006
Present	18		38	
ER status				
Negative	15	0.36	30	< 0.0001
Positive	19		57	
Unknown				
Extracapsular extension				
No	15	0.86	52	< 0.0001
Yes	15		34	
Chemotherapy				
No	14	0.89	57	0.28
Yes	15		41	
Tamoxifen treatment				
No	13	0.84	35	< 0.0001
Yes	19		62	
Radiotherapy				
No	42	< 0.0001	21	< 0.0001
Yes	10		47	

LRR: locoregional recurrence; OS: overall survival; ER: oestrogen receptor

(CT) and correlation radiography were performed, if necessary. Patients underwent follow-up examinations every three months post surgery for the first two years, every four months in the third year, every six months in the fourth year, and annually thereafter. Blood chemistry analyses, including full blood counts, were tested at every examination. Chest radiograph and abdominal and pelvic USG were performed every six months, and bone scintigraphy and mammography were performed annually. If the patients had any complaints or signs of disease, and/or whenever the physician required blood analysis or imaging modalities, radiographs of the bone, CT imaging, magnetic resonance (MR) imaging and bone scintigraphy were performed.

Information regarding adjuvant treatment, follow-up and prognostic indicators, including age, the number of metastatic lymph nodes, metastatic nodes by levels, pathological tumour size, histological grade, presence of peritumoural lymphovascular invasion (LVI), extracapsular extension (ECE) and ER status, were obtained from the medical records of the patients. The follow-up interval was calculated in months and was defined as the time between the date of surgery and the date of LRR, death or last follow-up.

The endpoints of the present study were LRR and overall survival. LRR was defined as invasive breast carcinoma, consistent with the primary breast cancer that was detected in the ipsilateral chest wall, supraclavicular fossa or axilla. When LRR emerged subsequent to distant metastasis, it was not included in the incident analysis. Survival analysis was performed using the Kaplan-Meier method, and the log-rank test was used for comparisons. The stepwise Cox proportional hazard model was used to calculate hazard ratios and 95% confidence interval

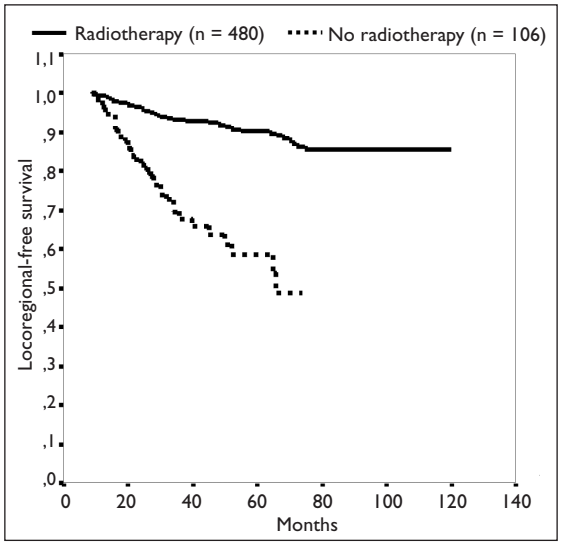

Fig. 1 Graph shows locoregional-free survival in patients with and without radiotherapy treatment ($p < 0.0001$).

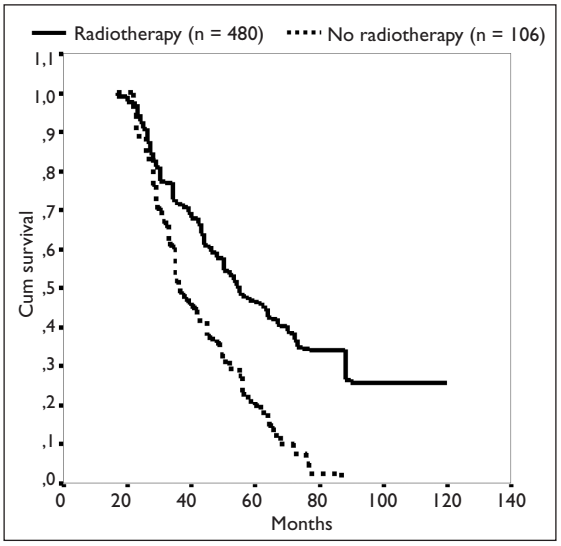

Fig. 2 Graph shows the overall survival of patients with and without radiotherapy treatment ($p < 0.0001$).

(CI), for the risk of LRR from breast cancer and the risk of dying.[17,18] Comparisons of RT with cardiac deaths and potential prognostic and treatment-related factors were made using the χ^2 or Fisher's exact test. Statistical analyses were performed using the Statistical Package for the Social Sciences version 10.05 (SPSS Inc, Chicago, IL, USA). A p-value ≤ 0.05 was considered to be statistically significant.

RESULTS

The median age of the subjects was 44 (24–70) years. The five-year LRR was 15%, and the five-year overall survival (OS) was 41.3%. A median of 19 (range 7–51) lymph nodes were identified. Patients who were treated with RT were comparable to those who were untreated with respect to age, pathological tumour size, level of invasion, grade, lymphovascular invasion, ER status, and chemotherapy and tamoxifen treatment. However, they differed with respect to the number of positive nodes and ECE. Comparison of RT treatment by prognostic and treatment-related factors showed that significantly more patients with adverse prognostic factors were treated with RT (Table I). Among the 66 T1–2 patients with 1–3 apical node involvements, those who received RT and those with did not were found to possess a similar profile. Patients treated with RT differed from untreated patients only with respect to ECE. However, comparison of RT treatment by ECE showed that all patients with ECE which was an adverse prognostic factor, were treated with RT (Table II).

The five-year LRR and OS by patient, tumour characteristics and treatment-related factors are shown in Table II. Of the 82 LRR, 61 were at the chest wall or surgical scar and 21 were in the supraclavicular area. Of the 425 deaths, 12 were from causes other than breast carcinoma. Two patients died in traffic accidents, seven had cardiac failure and three had myocardial infarction (MI). The two patients who died of MI had distant metastasis. Four of the seven patients who died of cardiac failure had bone metastasis, while the other three had liver and lung metastases. Three patients with cardiac failure were diagnosed with cardiomyopathy due to second-line FAC chemotherapy after distant metastasis. All patients who died of cardiac failure or MI had RT as well. Five patients with cardiac failure had left-sided breast carcinoma. Three of the patients who died of cardiac events had received adjuvant CMF, whereas seven had received FAC or FEC chemotherapy. Among patients who died from cardiac causes, no significant difference was observed between patients who underwent RT and those who did not ($p = 0.22$).

In univariate analyses, the level of invasion, age, tumour size, grade, ER status, ECE, LVI, adjuvant tamoxifen and RT treatment correlated with OS (Table III). Tumour size, grade and RT correlated with LRR (Table II). The five-year LRR for patients with 1–3 and ≥ 4 positive nodes were 16% and 15%, respectively. The five-year LRR was significantly lower (42% vs. 12%, $p < 0.0001$) (Fig. 1) and the five-year OS was significantly higher (47% vs. 21%, $p < 0.0001$) (Fig. 2) for patients who were treated with adjuvant RT. RT was also associated with decreased LRR in patients with 1–3 positive axillary nodes (34% vs. 7%, $p = 0.0017$) (Fig. 3) and ≥ 4 positive nodes (47% vs. 13%, $p < 0.0001$) (Fig. 4).

The five-year LRR and OS was found to be 16% and 42.4%, respectively, for 66 T1–2 patients with 1–3 apex

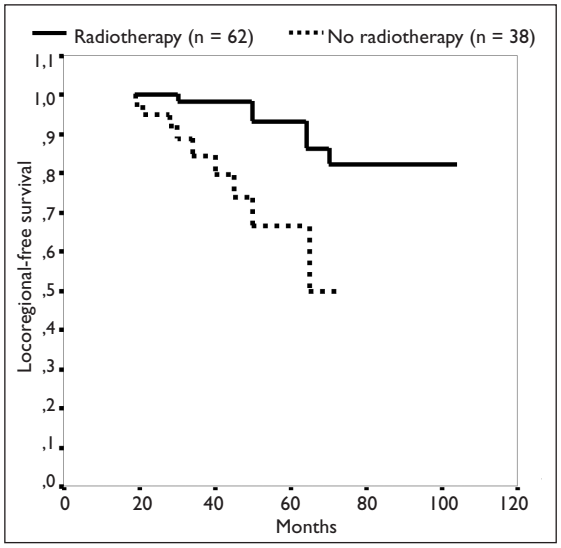

Fig. 3 Graph shows locoregional-free survival according to radiotherapy treatment in patients with 1–3 positive lymph nodes (66% vs. 93%, p = 0.0017).

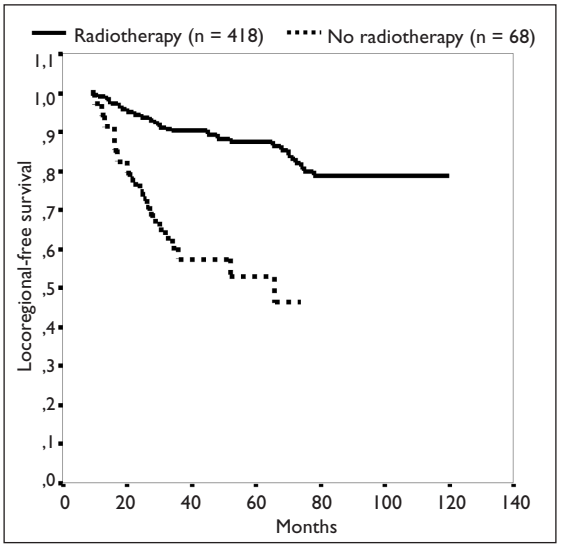

Fig. 4 Graph shows locoregional-free survival according to radiotherapy therapy in patients with ≥ 4 positive lymph nodes (53% vs. 87%, p < 0.0001).

axillary node involvements. The former was significantly lower (0% vs. 36%, p = 0.0002) (Fig. 5), but the latter was significantly higher (47% vs. 31%, p = 0.0009) (Fig. 6) in the above patients treated with adjuvant RT. The eight-year survival was 35% for patients treated with RT, whereas none of the untreated patients survived. The two-thirds reduction in LRR with RT was precisely the magnitude of benefit observed in the overview analyses, and it indicates that radiation was effective in improving locoregional control.[10,11]

When the variables (as categorised and listed in Table I) and RT treatment were entered into the multivariate analysis, invasion of level III axillary nodes, age < 35 years, T4 tumour, grade 3, ECE and LVI were found to be independent and detrimental factors for OS. Adjuvant tamoxifen treatment and RT (risk ratio [RR] 0.51, 95% confidence interval [CI] 0.39–0.67) contributed significantly to OS. Adjuvant RT was the sole independent factor that was significantly associated with decreased LRR (RR 0.25, 95% CI 0.16– 0.38, p < 0.001) (Table IV).

DISCUSSION

Our findings indicate that stage IIIC breast carcinoma has a poor outcome. The five-year LRR is high (15%) and the OS is low (41%). While we have identified age < 35 years, apical invasion, T4 size, grade 3, ECE and LVI to be prognostic factors for OS, we were unable to identify any prognostic factor for LRR. Our study has demonstrated that stage IIIC patients carry a high risk for LRR. The LRR risk is high for all subgroups in our series. Multivariate analysis revealed that only RT was significantly associated with a decreased LRR. The current study has also demonstrated that RT was associated both with decreased LRR and increased survival.

Avoidance of LRR is of utmost importance following mastectomy not only because LRR is a distressing event, but also because it is very difficult to treat.[19] Randomised studies have consistently shown a highly significant two-thirds reduction in LRR with the addition of postmastectomy RT (PMRT).[10,11] Recent analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has also shown that avoidance of LRR improves survival.[20] While consensus has been reached concerning the indications for patients with ≥ 4 positive nodes and T3–4 tumours,[6] the indication for adjuvant RT in patients with 1–3 positive nodes is still debatable.[7-9] At the core of the debate is the identification of subgroups that carry a high LRR risk and the magnitude of absolute reduction in LRR by RT.[7-9,21] Olivotto suggested a ten-year LRR risk exceeding 20% as an indication for PMRT.[21] The ten-year LRR rates have been reported to be 13%–20% [22-24] in T1–3 patients with 1–3 positive nodes who were treated with chemotherapy or tamoxifen but not RT. Furthermore, T2 tumour size, ECE ≥ 2 mm, LVI and high grade were identified as risk factors for an increased risk of LRR over 20%.[23-25] In our series, the five-year LRR for 1–3 positive nodes, 4–9 positive nodes, and ≥ 10 positive nodes were 16%, 15% and 15%, respectively, and they did not differ according to the number of positive axillary nodes.

In our study, the five-year LRR without RT was 42%

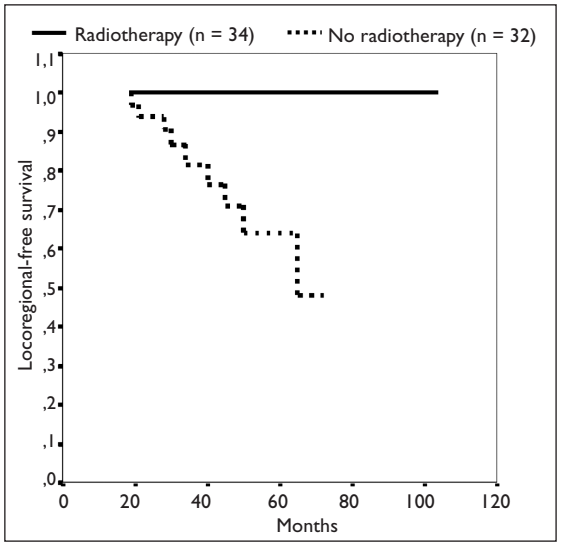

Fig. 5 Graph shows locoregional-free survival according to radiotherapy treatment in T1–2 patients with 1–3 positive apex axillary lymph nodes (100% vs. 64%, p = 0.0002).

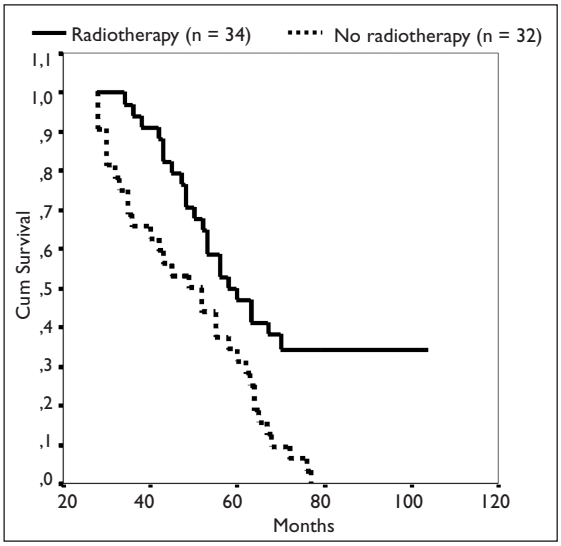

Fig. 6 Graph shows overall survival according to radiotherapy treatment in T1–2 patients with 1–3 positive apex axillary lymph nodes (47% vs. 31%, p = 0.0009).

for all patients, 34% for patients with 1–3 positive nodes and 47% for those with ≥ 4 positive nodes. Moreover, RT reduced LRR by more than two-thirds for all patients, and for patients with either 1–3 positive nodes or ≥ 4 positive nodes, as well as for T1–2 patients with 1–3 apical node involvements. This suggests that all patients with stage IIIC breast carcinoma are candidates for adjuvant RT. The five-year LRR rate in patients with ≥ 10 positive nodes was 14% with RT and 36% without RT in our series. Similarly, in other series, the five-year LRR was reported to be 10%–13% with RT,[26,27] and the ten-year LRR was reported to be 13% with RT[29] and 32%–36% without RT in patients with ≥ 10 positive nodes.[23-25]

We were unable to identify any subgroup where LRR was low. In the current study, the five-year LRR risk in patients with 1–3 positive nodes and apex invasion was 16%. Moreover, patients with 1–3 positive nodes who had not received RT had a significantly higher LRR compared to those who underwent RT (34% vs. 7%). It could be argued that many patients with 1–3 apical node involvements may also have T3–4 tumour, and it is well established that they would receive RT. Therefore, the question is whether adjuvant therapy should be indicated in T1–2 patients with 1–3 apical node involvements. In the current study, among these patients, those who received RT had a significantly lower five-year LRR compared with those who did not (0% vs. 36%). These findings could help discriminate patients with high LRR risk from among those with 1–3 positive nodes. We suggest that patients with apical invasion should receive adjuvant RT, regardless of whether they have T1–2 or T3–4 tumour.

We concur with Griem et al's findings that adjuvant RT administered after chemotherapy significantly reduces LRR (20% without RT vs. 6% with RT) in patients with ≥ 4 nodes or with at least one positive node in the axillary apex (level III); such patients should be considered to be at high risk for LRR and should thus receive RT.[28] We have also demonstrated in our previous study, which consisted of 539 cases of T1–3 invasive breast carcinoma, that apex axillary invasion is an independent prognostic factor for LRR (hazard ratio 2.6, 95% CI 1.29–5.35), and that patients with apical invasion who did not receive RT had a higher five-year LRR (42%) compared to patients without apical invasion (4%).[15] Our findings could aid in decision-making for adjuvant RT indication among patients with 1–3 positive nodes.

There is mounting evidence from randomised clinical trials that support a link between local control and OS in breast cancer.[29] Therefore, prevention of LRR is very important for improved survival. The recent EBCTCG meta-analysis showed that local treatments that had more than 10% absolute reduction in the five-year risk of LRR increased the 15-year breast cancer survival by 5%.[20] In the current trial, RT resulted in a 30% decrease in LRR and a 26% increase in survival. The EBCTCG analysis also implies that in order to indicate RT as a survival advantage, an absolute reduction of at least 10% in LRR should be expected.[20] Therefore, given the two-thirds reduction in LRR produced by RT,[10,11] the five-year LRR risk without RT should be over 15% in order to expect a survival advantage.[30] Five-year LRR was 15% in the current study, and RT reduced LRR from 42% to 12% for all patients and from 34% to 7% in patients with 1–3

Table IV. Prognostic and treatment-related factors for locoregional recurrence and overall survival in multivariate analysis.

Variable	Overall survival		Locoregional recurrence	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yrs)				
≥ 35	1*			
< 35	2.1 (1.68–2.79)	< 0.001	-	-
Pathological tumour size (cm)				
≤ 2	1*			
T4	1.7 (1.07–2.74)	0.026	-	-
Level of invasion				
Level 1–2	1*			
Level 3 (± Level 1–2)	1.8 (1.14–2.75)	0.0011	-	-
Grade				
1	1*			
3	2.2 (1.51–3.13)	< 0.001	-	-
Lymphovascular invasion				
Absent	1*			
Present	1.6 (1.21–2.17)	0.001	-	-
Extracapsular extension				
No	1*			
Yes	1.4 (1.16–1.78)	0.001	-	-
Tamoxifen treatment				
No	1*			
Yes	0.73 (0.57–0.94)	0.016	-	-
Radiotherapy				
No	1*		1*	
Yes	0.51 (0.39–0.67)	< 0.001	0.25 (0.16–0.38)	< 0.001

* Reference group
HR: hazard ratio; CI: confidence interval

positive lymph nodes. This represents a greater than two-thirds reduction both groups of patients. Furthermore, our results are similar to the findings of Diab et al,[5] who found the LRR to be 13% in patients who had undergone RT compared to 38% in those who did not, and that RT decreased LRR and increased survival in T1–3 patients with ≥ 10 positive nodes.

In the present study, we have identified age < 35 years, T4 tumour, grade 3, invasion of level III axillary nodes, LVI and ECE as adverse risk factors for OS. Tamoxifen treatment and RT were associated with improved OS. The survival effect of RT is independent from the number of metastatic axillary nodes, i.e. from 1–3 or ≥ 4 positive axillary nodes, and other risk factors. RT also increased survival in the subgroup of T1–2 patients with 1–3 apical node involvements. The current data supports the conclusion of previous studies that found that apical invasion is an independent detrimental prognostic factor for survival and disease-free survival (DFS) in node-positive breast cancers.[2-4,15,31] We also demonstrated in our previous study that the five-year survival of stage IIIC breast cancer patients was 38.2%, making it the worst of the stages.[4] Borger et al reported a five-year LRR and survival of 37% and 40%, respectively, in T1–3 patients with biopsy-proven apex axillary invasion treated by primary RT and chemotherapy (40%).[32] Diab et al reported that tumour size, number of metastatic nodes (≥ 10 vs. ≥ 15), ER status, age < 40 years and RT were independent predictors of survival in T1–3 patients with ≥ 10 positive nodes.[5] The survival rate of these patients in our series was 46%, whereas it was 47% in Diab et al's study.[5] In Schmoor et al's study, the five-year OS was cited as 39% in T1–3 patients with ≥ 10 positive nodes who were treated by adjuvant CMF and RT.[33] Duraker et al recently reported that the presence of a T4 tumour was a detrimental factor for DFS in patients with ≥ 10 positive axillary nodes.[34]

Our findings are in accord with the results of the Danish Breast Cancer Cooperative Group and British Columbia trials, which reported that PMRT increased survival in node-positive patients who have systemic therapy.[12-14] Our findings are also similar to Whelan et al's study, which reported that in patients whose probable distant micrometastases were reduced with chemotherapy, the effect of radiation therapy on preventing LRR and the resulting secondary systemic recurrence may be more evident.[35] We also agree with the EBCTCG analysis, which demonstrated that PMRT increased survival in patients who had an absolute reduction of over 10% in LRR as a result of RT.[20] RT has also been shown to increase OS among patients with ≥ 10 positive axillary nodes.[5] Overgaard has noted that RT was more effective

in patients who had their distant micrometastasis controlled by adjuvant systemic therapy.[36] Many women in whom isolated LRR was prevented did not develop recurrence. This substantial improvement in local disease control must have been largely or wholly responsible for the substantial reduction in breast cancer mortality.[20] We agree with this view and suggest that if RT had also been given to patients with apical invasion and to those for whom RT was indicated but could not undergo it, their LRR would have been further reduced and OS would thus have been further improved in these patients. The Stockholm trial also showed that locoregional RT in node-positive patients decreases the risk of systemic metastases and increases OS. This finding suggests that the decrease in distant metastases was related to the prevention of local recurrence.[37]

In the current study, PMRT had been indicated primarily for patients with ≥ 4 positive nodes, a tumour stage of T3–4 and ECE. However, apical invasion had not been considered for PMRT. Therefore, we suggest that apex axillary invasion cases should also be considered for adjuvant RT. If a level I or II axillary dissection was planned, the status of level III axillary nodes could be defined by axillary USG, an approach that has been successfully demonstrated by Newman et al.[38] Patients with apical invasion detected by preoperative USG would then have the option to undergo level III axillary dissection. Patients with a level III invasion detected by USG could also be treated by surgery with neoadjuvant[38] or adjuvant chemotherapy and RT; such patients could have a decreased LRR and increased survival, as the prognosis of a patient with level III invasion is poor without combined treatment by surgery, chemotherapy, RT and/or hormonotherapy.[2,3,32]

Although this retrospective study has some potential limitations (e.g. selection bias and short follow-up), our findings suggest that PMRT was associated with decreased LRR and improved OS in stage IIIC breast cancer patients, as well as in the subgroup of T1–2 patients with 1–3 apical node involvements. The five-year LRR is high and survival is low for stage IIIC patients. RT was the only independent factor associated with a decreased LRR, and it was also associated with increased survival. Thus, we recommend that stage IIIC patients should receive adjuvant RT.

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