Original Articles

Prognosis and role of postmastectomy radiotherapy in patients with T1-T2 breast cancer with one to three positive axillary nodes

Z. Chen[1], J. Hao[1], H. Zhuang[1], J. Yu[2]

[1]Department of Radiotherapy, Tianjin Cancer Institute and Hospital; Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education; Key Laboratory of Cancer Prevention and Therapy, Tianjin
[2]Department of Radiotherapy, Shandong Cancer Institute and Hospital, Jinan (China)

Summary

Purpose: To evaluate the prognosis and role of postmastectomy radiotherapy (PMRT) in T1-T2 breast cancer with one to three positive axillary nodes. *Methods:* The 10-year Kaplan-Meier locoregional recurrence (LRR), distant recurrence (DR), disease-free survival (DFS) and overall survival (OS) were compared between the N0 and 1-3N+ cohorts. The role of PMRT was evaluated in the 1-3N+ cohort. Results: The 10-year LRR, DR, DFS, OS rates in N0 and the 1-3N+ cohorts were as follows: LRR 7.5% vs 19.4% (p = 0.011); DR 14.4% vs 23.0% (p = 0.029); DFS 71.3% vs 51.2% (p = 0.001) and OS 77.0% vs 58.7% (p = 0.001). Of the 192 1-3N+ patients not treated and treated with PMRT, the outcomes were: LRR 20.1% vs 18.4% (p = 0.047); DR 26.4% vs 21.5% (p = 0.743); DFS 40.2% vs 55.4% (p = 0.260) and OS 40.7% vs 66.0% (p = 0.344), respectively. *Conclusion:* PMRT reduces the 10-year LRR rate for such patients, but further examination is needed.

Key words: Postmastectomy radiotherapy; Breast cancer; Positive axillary nodes.

Introduction

It is well known that postmastectomy radiotherapy (PMRT) is indicated for patients with advanced primary tumors of > 5 cm or with four or more positive axillary nodes. Adjuvant PMRT is used in patients with breast carcinoma chiefly to reduce the risks of locoregional recurrence [1-5]. However, the role of PMRT in patients with tumors ≤ 5 cm with one to three positive axillary nodes is controversial; the use of PMRT in node-negative patients with tumor size < 5 cm has also not been widely accepted and the long-term effect on overall survival of local tumor control improved by adjuvant PMRT continues to be debated [4, 6]. This retrospective study aimed to evaluate locoregional recurrence (LRR), distant recurrence (DR), disease-free survival (DFS) and overall survival (OS) in patients with T1-T2 breast cancer with one to three positive nodes in comparison with patients with node-negative disease, and to discuss the role of PMRT in such patients.

Methods and Materials

Patients

The charts and final pathologic reports of female patients with T1-T2 breast cancer with zero to three positive axillary lymph nodes (0-3N) who underwent mastectomy between May 1997 and March 2002 at Tianjin Cancer Hospital were reviewed retrospectively after approval by the institutional review board. Patients with established indications for PMRT, including pT3-4 tumors and/or four or more positive nodes, patients presenting with distant metastasis and patients with unknown pTN stage were excluded. The remaining 540 Chinese women with stage T1-T2 breast cancer with zero to three positive axillary nodes (0-3N+) formed the cohort for this analysis.

Treatments

Of the 540 patients, 512 underwent a modified radical mastectomy – that is, removal of the breast plus level I+II+III axillary dissection; 28 patients underwent radical mastectomy. Before surgery, no patients had distant metastasis, and no tumors were present at the margins of excision as confirmed by postoperative pathology.

Before surgery, 119 patients had received chemotherapy (79 of N0 patients and 40 of 1-3N+ patients): cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2 (CMF regimen) on either day 1 and day 8 every four weeks or day 1 every three weeks. Of these patients, 63 received one cycle of chemotherapy; 30 patients received two cycles; 20 patients received three cycles and 6 patients received four to six cycles. After surgery, 504 patients received chemotherapy (323 of N0 patients and 181 of 1-3N + patients): 493 received the CMF regimen (162 patients received one to five cycles; 194 patients received six cycles; 112 patients received seven cycles and 25 patients received eight to nineteen cycles); 9 patients received a CAF (cyclophosphamide, adriamycin and fluorouracil) regimen and 2 patients received NF treatment (navelbine and fluorouracil).

Radiation therapy was followed by mastectomy and chemotherapy. A total of 275 patients underwent radiation therapy after four to six cycles of CMF chemotherapy (140 of N0 patients and 135 of 1-3N + patients). One hundred and sixty-two patients were given postmastectomy radiation therapy that included axillary apex/supraclavicular fossa and internal mammary lymph nodes; 84 patients received radiation treat-

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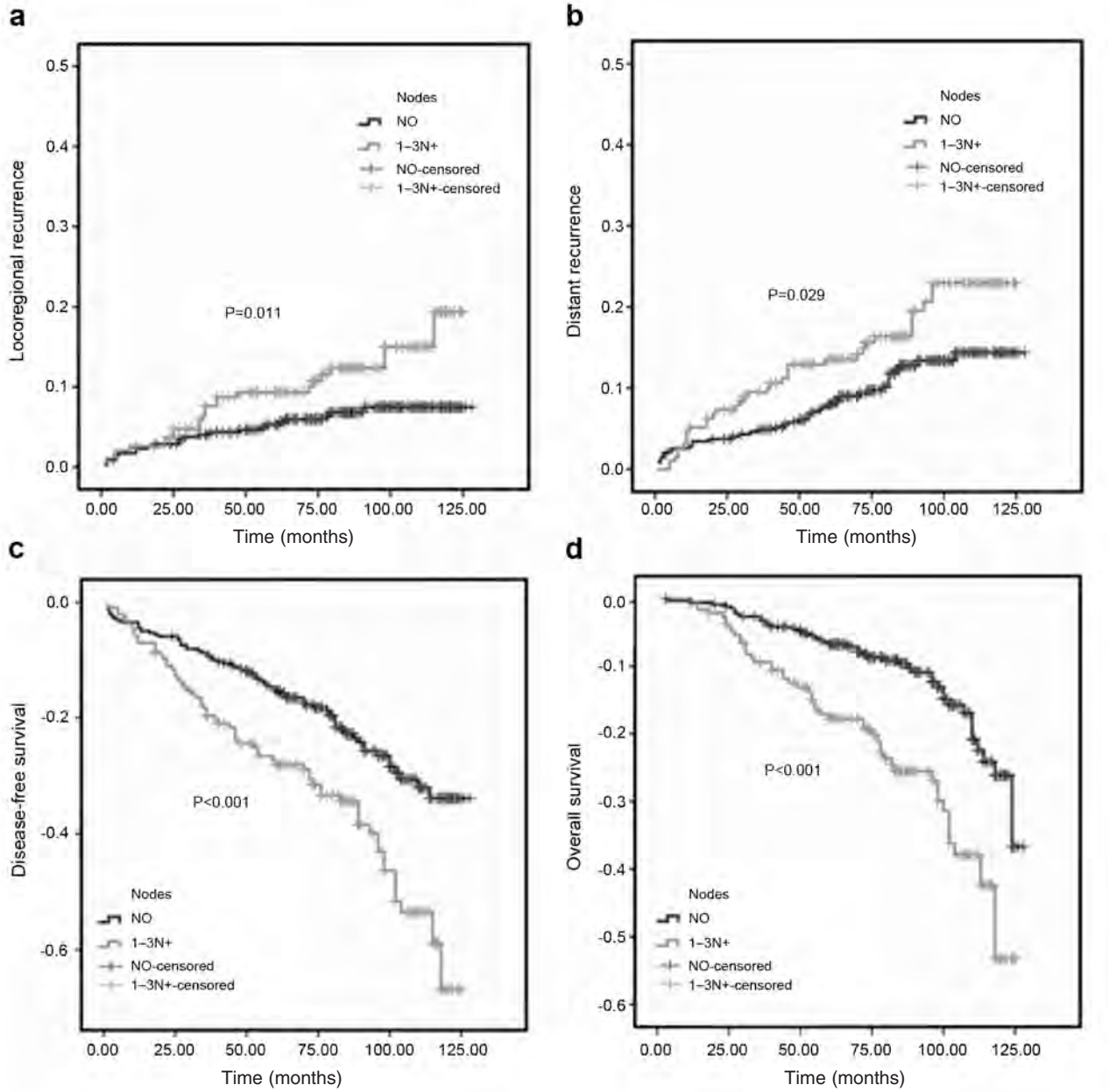

Figure 1. — Comparisons of (a) locoregional recurrence (b) distant recurrence (c) disease-free survival and (d) overall survival between patients with node-negative and node 1–3-positive axillary lymph nodes.

ment of the chest wall only and 29 patients received radiation of the chest wall, axillary apex/supraclavicular fossa and internal mammary lymph node areas. All areas received a total dose of 50 Gy in 25 portions over five weeks. Photon energy of 6 MvX was delivered to the axillary apex/supraclavicular fossa and internal mammary lymph node areas for three weeks (30 Gy total dose), then changed to 9 Mevβ or 12 Mevβ electron energy according to the thickness of the patient's skin. Electron energy of 6 Mevβ was delivered to the chest wall. A 3-5 mm bolus was delivered to the chest wall every day for three weeks, then discontinued.

In addition to radiotherapy, hormonal therapy was indicated for 235 patients with estrogen receptor (ER)- or progesterone receptor (PR)-positive breast cancer (159 of N0 patients and 76 of 1-3N + patients). Tamoxifen was given to premenopausal patients, and aromatase inhibitor to postmenopausal women.

Study assessments

The primary outcomes were LRR and DR, and the secondary end points were DFS and OS. LRR was defined as the first site at which a tumor recurred involving the ipsilateral chest wall and/or axillary, supraclavicular, infraclavicular and internal mammary nodes. LRR events occurring > 1 month after DR were not recorded. DFS was computed from the date of the diagnosis to the first recurrence of all types or breast cancer-related death by the end of follow-up. OS was estimated from the date of diagnosis to the date of breast carcinoma-related death.

Pathologic lymph node classification and tumor staging were according to the American Joint Committee on Cancer criteria (2002) [7]. Histologic grading was carried out according to the criteria of Bloom and Richardson [8]. ER and PR status were determined by immunohistochemical studies on paraffin-embedded tissue and results were considered positive if > 10% of tumor cells showed staining. The presence of lymphatic vascular invasion was not analyzed owing to incomplete data in the pathology report. Patients were split into two groups according to age < 50 vs ≥ 50 years. The tumor factors analyzed were histologic features (ductal, lobular, other); T stage (T1, T2); tumor location (medial, central, lateral); histologic grade (1, 2, 3); ER and PR status (positive, negative, unknown). Nodal factors analyzed included the number of positive axillary nodes (0-3), percentage of positive nodes (≤ 20% positive nodes, > 20% positive nodes).

Statistical analysis

Tumor and treatment characteristics of N0 and 1-3N+ patients with breast cancer were compared using chi-square tests. Ten-year rates of LRR, DR, DFS and OS of the N0 and 1-3N+ cohorts were computed by the Kaplan-Meier method and the log-rank test. Ten-year rates of LRR, DR, DFS and OS in the 1-3N+ cohort were compared for those undergoing and not undergoing PMRT.

Results

Clinicopathologic characteristics

The median follow-up time was 7.2 years (range 0.25-10.7 years), median age 48 years (range 25-83 years) and median tumor size 3.0 cm (range 0.3-5.0 cm). The median number of lymph nodes in dissected tissue was 19 (range 2-44). In comparison with N0 patients, patients with 1-3N+ were older (71% vs 46% aged ≥ 50), had more T2 disease (89% vs 62%), more lateral tumors (60% vs 51%) and a greater proportion underwent radiotherapy (70% vs 40%) (Table 1).

Comparisons of 10-year LRR, DR, DFS, OS rates in N0 and 1-3N+ groups

The 10-year Kaplan-Meier LRR and DR rates were higher in 1-3N+ than in N0 patients: LRR 19.4% vs 7.5% ($p = 0.011$); DR 23.0% vs 14.4% ($p = 0.029$); and the 10-year Kaplan-Meier DFS and OS rates were lower in 1-3N+ than in N0 patients: DFS 51.2% vs 71.3% ($p = 0.001$); OS 58.7% vs 77.0% ($p = 0.001$). Of 48 LRRs, 25 (52.1%) involved the chest wall, 16 (33.3%) the clavicular nodes and seven (14.6%) the axillary nodes. DR occurred in 76 (14.1%) of the two groups (Table 2, Figure 1).

Comparisons of 10-year LRR, DR, DFS and OS rates in the 1-3N+ cohort treated and not treated with PMRT

The 10-year Kaplan-Meier LRR and DR rates were lower in 1-3N+ patients who underwent radiotherapy than in those who did not, and the 10-year KM DFS and OS rates in the 1-3N+ cohort who underwent radiotherapy were higher than in those who did not (Table 3, Figure 2). However, only the comparison of the 10-year Kaplan-Meier LRR rate had statistical significance.

Table 1. — *Clinicopathologic characteristics of the entire cohort and comparisons between N0 and 1-3N+ patients with breast cancer.*

Characteristic	Entire cohort (n = 540)	N0 (n = 348)	1-3N+ (n = 192)	*p*
Age (y)				< 0.001
< 50	244 (45)	189 (54)	55 (29)	
≥ 50	296 (55)	159 (46)	137 (71)	
Tumor size (pT)				< 0.001
1a	5 (1)	4 (1)	1 (0)	
1b	30 (5)	27 (8)	3 (2)	
1c	118 (22)	101 (29)	17 (9)	
2	387 (72)	216 (62)	171 (89)	
Tumor location				< 0.001
Medial	123 (23)	87 (25)	36 (19)	
Central	125 (23)	84 (24)	41 (21)	
Lateral	292 (54)	177 (51)	115 (60)	
Histology				0.56
Ductal	434 (81)	275 (79)	159 (83)	
Lobular	3 (0)	2 (1)	1 (0)	
Other	103 (19)	71 (20)	32 (17)	
Histological grade				0.10
Grade 1	240 (44)	146 (42)	94 (49)	
Grade 2	53 (10)	41 (12)	12 (6)	
Grade 3	247 (46)	161 (46)	86 (45)	
Estrogen receptor status				0.19
Positive	203 (38)	133 (38)	70 (36)	
Negative	183 (34)	109 (31)	74 (39)	
Unknown	154 (28)	106 (31)	48 (25)	
Progesterone receptor status			0.18	
Positive	196 (36)	126 (36)	70 (36)	
Negative	200 (37)	121 (35)	79 (41)	
Unknown	144 (27)	101 (29)	43 (23)	
Positive nodes (%)				0.001
≤ 20	533 (99)	348 (100)	185 (96)	
> 20	7 (1)	0 (0)	7 (4)	
Nodes removed (n)				0.51
≤ 5	4 (1)	3 (1)	1 (0)	
6-10	22 (4)	13 (4)	9 (5)	
11-15	110 (20)	77 (22)	33 (17)	
≥ 16	404 (75)	255 (73)	149 (78)	
Radiotherapy				< 0.001
Yes	275 (51)	140 (40)	135 (70)	
No	265 (49)	208 (60)	57 (30)	
Systemic therapy				0.11
Chemotherapy alone	286 (53)	179 (51)	107 (56)	
Hormonal therapy alone	17 (3)	15 (4)	2 (0)	
Both	218 (40)	144 (41)	74 (39)	
None	19 (4)	10 (4)	9 (5)	

Results are shown as number (%).

Table 2. — *Crude rates and 10-year Kaplan-Meier rates of LRR, DR, DFS and OS in patients between N0 and 1-3N+ patients with breast cancer.*

	N0 (n = 348)		1-3N+ (n = 192)		Log-rank
	Crude rate N (%)	10-year KM rate (%)	Crude rate N (%)	10-year KM rate (%)	*p*
LRR	23 (6.6)	7.5	25 (13.0)	19.4	0.011
DR	41 (11.8)	14.4	35 (18.2)	23.0	0.029
DFS	272 (78.2)	71.3	123 (64.1)	51.2	0.001
OS	303 (87.1)	77.0	140 (72.9)	58.7	0.001

LRR = locoregional recurrence; DR = distant recurrence; DFS = disease-free survival; OS = overall survival.

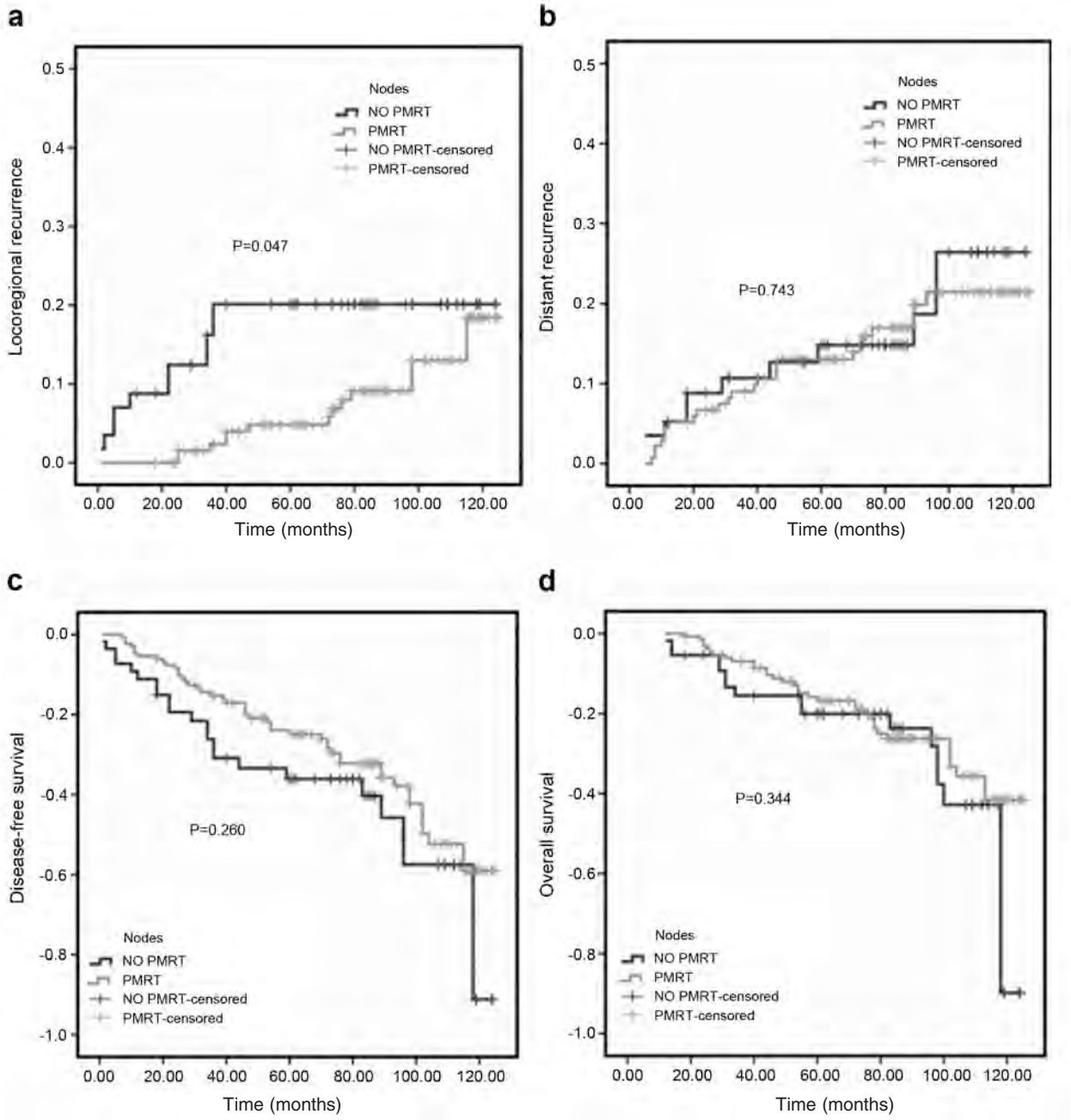

Figure 2. — Ten-year (a) locoregional recurrence, (b) distant recurrence, (c) disease-free survival and (d) overall survival in 1-3N+ patients treated and not treated with postmastectomy radiotherapy (PMRT).

Table 3. — *Crude rates and 10-year Kaplan-Meier rates of LRR, DR, DFS and OS in 1-3N+ patients between with radiotherapy and without radiotherapy.*

	RT (n = 135)		No RT (n = 57)		Log-rank
	Crude rate N (%)	10-year KM rate (%)	Crude rate N (%)	10-year KM rate (%)	*p*
LRR	14 (10.4)	18.4	11 (19.3)	20.1	0.047
DR	24 (17.8)	21.5	11 (19.3)	26.4	0.743
DFS	89 (65.9)	55.4	34 (59.6)	40.2	0.260
OS	101 (74.8)	66.0	39 (68.4)	40.7	0.344

LRR = locoregional recurrence; DR = distant recurrence; DFS = disease-free survival; OS = overall survival.

Discussion

As expected, patients with T1-T2 breast cancer with one to three positive axillary lymph nodes had higher 10-year LRR and DR rates and lower 10-year DFS and OS rates than patients with negative nodes. Differences in the 10-year LRR, DR, DFS and OS rates between the two groups were statistically significant. It is well known that nodal status is one of the strongest predictors of overall survival and metastasis and also a strong predictor of postmastectomy chest wall relapse when radiation is not used [2, 9, 10]. Although outcomes will continually

improve as systemic therapies advance, data from previous National Surgical Adjuvant Breast and Bowel Project (NSABP) trials, in which local regional therapy alone was mostly used, showed 5-year survival rates of 82.8% for node negative patients and 73% for those with 1-3 positive nodes [11]. In our study, we also found that patients with T1-T2 breast cancer with one to three axillary lymph nodes have worse prognosis than patients with negative axillary lymph nodes.

Also, as expected, PMRT reduced the 10-year LRR and DR rates and improved the 10-year DFS and OS rates in patients with T1-T2 breast cancer with one to three positive axillary lymph nodes in comparison with patients without PMRT. However, contrary to our expectations, only the 10-year Kaplan-Meier LRR rate was significantly different between the two groups.

PMRT improves not only locoregional control, but also disease-free and overall survival, possibly because when distant micrometastasis is controlled by systemic therapy and the locoregional tumor burden is reduced by radiation therapy, the effects combine to enhance disease control and survival [12]. The differences of 10-year DR, DFS and OS rates between the groups treated or not treated with PMRT did not reach statistical significance, possibly owing to the small number of patients with T1-T2 breast cancer with one to three positive nodes enrolled in this retrospective trial.

As in our study, many trials have shown that in women receiving systemic therapy, PMRT improves not only LRR but also disease-free and overall survival [13]. In the Danish Breast Cancer Cooperative Group 82b and 82c trials, 3,083 high-risk patients with breast cancer were followed-up for 18 years. The 18-year probability of LRR (with or without distant metastasis (DM)) was 49% and 14% ($p < 0.001$) after no RT and RT, respectively; the 18-year probability of DM subsequent to LRR was 35% and 6% ($p < 0.001$) after no RT and RT, respectively, whereas the probability of any DM was 64% and 53% ($p < 0.001$) after no RT versus RT, respectively. The trials suggested that RT not only improves local control rate but also reduces the DM rate [14]. Regrettably, no randomized trial designed to study the role of PMRT in patients with breast cancer with one to three positive nodes has yet been carried out [15]. Thus the role of PMRT in women with breast cancer with one to three positive nodes is currently undefined, but possibly our study may shed some light on its role in such patients.

As with other retrospective analyses, our study was subject to biases in patient and treatment selection. However, the clinical outcomes obtained strongly suggest that PMRT combined with systemic therapy is important in controlling local recurrence and potentially reduces distant recurrence and improves disease-free and overall survival. Further investigation with randomized trials and a greater number of patients is needed.

Conclusion

Patients with T1-T2 breast cancer with one to three axillary lymph nodes have a worse prognosis than patients with negative lymph nodes. PMRT reduces the 10-year LRR rate for such patients, but its influence on 10-year DR, DFS and OS rates needs further observation.

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Address reprint requests to:
J. YU, M.D.
Department of Radiotherapy
Shandong Cancer Institute and Hospital
No. 440, Jiyan Road
Jinan 250117 (China)
e-mail: 652361261@qq.com