·Clinical Research·

The value of radiotherapy in patients with T1 and T2 breast cancer with one to three positive nodes after modified radical mastectomy

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[Abstract] Background and Objective: The role of adjuvant radiotherapy to the regional nodes in women with T1 to T2 breast cancer and one to three positive nodes is controversial. This study compared and analyzed the prognosis of patients with T1-T2 breast cancer with one to three positive nodes after modified radical mastectomy with or without postoperative radiotherapy. **Methods:** The cases of 434 women patients with T1 to T2 breast cancer with one to three positive lymph nodes after modified radical mastectomy were reviewed, of which 196 patients received postoperative radiotherapy and 238 patients did not. The ipsilateral chest wall and supraclavicular fossa were irradiated with doses of 46–50 Gy in 23–25 fractions. **Results:** For all patients, the 3- and 5-year rates of overall survival (OS) were 94.7% and 85.7% respectively, local control (LC) 96.5% and 95.6%;, and disease-free survival (DFS) 89.3% and 82.3% respectively. The 3- and 5-year OS rates for patients without radiotherapy were 92.7% and 97.1% and for those with radiotherapy were 82.4% and 89.2%, both with significant differences (P = 0.039). The 3- and 5-year LC rates for patients without radiotherapy were 94.8% and 98.4% and for those with radiotherapy were 93.6% and 97.7%, again with significant differences (P = 0.041). The 3- and 5-year DFS rates for patients without radiotherapy were 87.8% and 91.3% and for patients with radiotherapy were 78.5% vs 86.1% (P = 0.047). **Conclusions:** Postoperative radiotherapy confers better rates of OS, LC, and DFS in patients with T1 to T2 breast cancer with one to three positive nodes after modified radical mastectomy.

Key words: Breast cancer, modified radical mastectomy, postoperative radiotherapy, positive nodes, prognosis

Currently it is generally accepted that for stage T1-T2 breast cancer, patients with at least four positive axillary nodes should receive postoperative radiotherapy of the chest wall and lymphatic drainage area, and patients with negative axillary nodes need no radiotherapy after mastectomy [1-2]. However, whether patents with one to three positive axillary nodes need postoperative radiotherapy after mastectomy has been controversial [3-7]. In this study, we analyzed the effect of radiotherapy on the prognosis of patients with stage T1-T2 breast cancer with one to three positive axillary nodes after mastectomy to explore the value of radiotherapy in these patients.

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Patients and Methods

Clinical information

Between January 2001 to September 2006, 565 patients with pathologically confirmed stage T1-T2 breast cancer and one to three positive axillary nodes after mastectomy were treated in the department of general surgery (1), the Fourth Hospital, Hebei Medical University, accounting for 17.82% (565/3170) of the patients with breast cancer admitted in the same period. Enrollment criteria included: (1) female; (2) the number of dissected axillary lymph nodes was equal to or more than 10; (3) lymph node metastasis rate less than 20%; (4) stage pT1-T2N1M0 confirmed by pathology according to the 2003 International Union Against Cancer (UICC) Breast Cancer Tumor Node Metastasis (TNM) staging system. A total of 434 patients met the above criteria with a median age of 48 years (range 23–80 years). The number of patients with one, two, or three positive axillary nodes was 267, 128, and 39, respectively, and the median number of dissected axillary nodes was 14 (range 10–37). A total of 196 patients received postoperative

radiotherapy (group with radiotherapy), and 238 patients did not receive postoperative radiotherapy (group without radiotherapy). The clinical data of the two groups are shown in Table 1.

Treatment

Surgery All patients underwent modified radical mastectomy and axillary lymph node dissection, which included first- and second-level lymph nodes, with clear pathologic diagnosis.

Radiotherapy The irradiation area included the ipsilateral chest wall plus the ipsilateral supraclavicular field, with a total dose of 46–50 Gy, each 2 Gy, once daily, 5 times a week. The chest wall received 6 MV x-ray tangential irradiation or 5–7 MeV β-ray perpendicular irradiation (30 Gy with a tissue compensator of 0.5 cm and 20 Gy without a tissue compensator), and the supraclavicular area received cobalt-60 γ-ray or 6 MV X-ray radiation.

Chemotherapy and endocrine therapy Chemotherapy with either CAF (cyclophosphamide + adriamycin + 5 - fluorourafcil) or CMF (cyclophosphamide + MTX + 5 - fluorouracil) regimen was carried out for 4–6 cycles in sequential or sandwich order with radiotherapy. Endocrine therapy with tamoxifen or aromatase inhibitors was used for patients positive for estrogen receptor (ER-positive), progesterone receptor (PR-positive), or both, for 3–5 years.

Evaluation criteria

Evaluation criteria included rates of overall survival (OS), local control (LC), and disease-free survival (DFS). Locoregional recurrence was defined as postoperative recurrence in the ipsilateral chest wall, axilla, supraclavicular area, and internal breast lymph nodes, with or without distant metastasis. DFS was defined as the time from surgery to the onset of either locoregional recurrence or distant metastasis. OS time was defined as the time from surgery to either death or censored follow-up.

Follow-up and statistical methods

Follow-up included outpatient review, telephone follow-up, questionnaires by mail, and home visits. SPSS version 15.0 was used for statistical analysis. A χ^2 test was used for clinical and pathologic features of each group, and a *t* test was used for measurement data. OS, LC, and DFS were calculated by the Kaplan-Meier method and tested by log-rank test. $P < 0.05$ was considered statistically significant.

Results

OS, LC, and DFS in the whole group

The follow-up time of all patients ranged from 16.1–100.2 months with a median time of 44.8 months. The 3- and 5-year OS rates were 94.7% and 85.7%, respectively (Figure 1), with a median OS time of 44.8 months. The 3- and 5-year LC rates were 96.5% and 95.6%, respectively (Figure 2), with a median LC time of 42.4 months. The 3- and 5-year DFS rates were 89.3% and 82.3% , respectively, with median DFS at 40.8 months.

Comparisons of OS, LC, and DFS in the two groups

The 3- and 5-year OS rates for patients without radiotherapy were 92.7% vs 97.1% , respectively, and for those with radiotherapy were 82.4% vs 89.2%, respectively (Figure 3). The median OS times were 39.5 months vs 52.0 months in the two groups, with a significant difference ($\chi^2 = 4.268$, $P = 0.039$). The 3- and 5-year LC rates for patients without radiotherapy were 94.8% and 98.4% , respectively, and for patients with radiotherapy were 93.6% and 97.7% , respectively (Figure 4). The median LC times were 38.7 months and 52.0 months in the two groups, with a significant difference ($\chi^2 = 4.177$, $P = 0.041$). The 3- and 5-year DFS rates for patients without radiotherapy were 87.8% and 91.3% , respectively, and for patients with radiotherapy were 78.5% and 86.1% , respectively (Figure 5). The median DFS times were 37.9 months and 48.9 months, with a significant difference between the groups ($\chi^2 = 3.963$, $P = 0.047$).

Analysis of treatment failure after first treatment

With regard to locoregional recurrence, for patients without radiotherapy, 7 had recurrence in the chest wall and 7 had supraclavicular lymph node recurrence. For patients that received radiotherapy, 3 had recurrence in the chest wall. No patients had axillary and internal breast lymph node recurrence, and the locoregional recurrence rates were 5.9% vs 1.5% with significant differences between the two groups ($P = 0.020$). For all patients, 51 had distant metastasis in lung, bone, liver, brain, mediastinum, pleura, ovary, abdominal cavity, or choroid, including lung metastases in 28 patients (54.9%), bone metastases in 28 patients (54.9%), liver metastases in 10 patients (19.6%), and brain metastases in 4 patients (7.8%). In patients without radiotherapy, 31 patients had distant metastasis and the rate of metastasis was 13.0% . In patients with radiotherapy, 20 patients had distant metastasis and the rate of metastasis was 10.2%, which was lower by 2.8% compared with the patients without radiotherapy but was not statistically significant ($P = 0.364$) (Table 2).

Discussion

Adjuvant radiotherapy after radical surgery can reduce the locoregional recurrence rate of breast cancer by about two-thirds. However, with the widespread use of chemotherapy and endocrine treatment, adjuvant radiotherapy is mainly applied in patients with at least four positive axillary nodes and at stages higher than T3 who have high risk of locoregional recurrence.8 The value of adjuvant radiotherapy in patients with T1-T2 breast cancer and one to three positive nodes after modified radical mastectomy has not yet reached consensus. In patients with T1-T2N1 breast cancer that did not receive postoperative adjuvant radiotherapy, the local recurrence rate is 8% to 23%[9-11]. Some researchers believe that in patients with breast cancer that have one to three positive axillary nodes, after effective postoperative systemic adjuvant therapy, the local recurrence rate is about 10%, and conventional radiotherapy is not needed[12]. Wang *et al.*[13] reported that for patients with breast cancer with one to three positive axillary nodes, the 10-year locoregional recurrence, OS, and DFS rates for patients that received adjuvant radiotherapy had no significant difference from patients

Table 1 Clinicopathologic characteristics in the two groups with or without radiotherapy

Characteristic	Entire cohort [cases(%)]	No postoperative radiotherapy [cases(%)]	Postoperative radiotherapy [cases(%)]	*P*
Patients	434	238	196	
Age (years)				< 0.001
⩽ 50	260 (59.9)	122 (51.3)	138 (70.4)	
> 50	174 (40.1)	116 (48.7)	58 (29.6)	
Menstrual status				0.079
Pre-/perimenopausal	376 (86.6)	200 (84.0)	176 (89.8)	
Postmenopausal	58 (13.4)	38 (16.0)	20 (10.2)	
Primary tumor location				0.102
Outer quadrant	230 (53.0)	135 (56.7)	95 (48.5)	
Inner quadrant	108 (24.9)	50 (21.0)	58 (29.6)	
Center	96 (22.1)	53 (22.3)	43 (21.9)	
T stage				0.987
T1	84 (19.4)	46 (19.3)	38 (19.4)	
T2	350 (80.6)	192 (80.7)	158 (80.6)	
Histologic type				0.255
Invasive ductal	255 (58.8)	138 (58.0)	117 (59.7)	
Invasive lobular	136 (31.3)	75 (31.5)	61 (31.1)	
Medullary carcinoma	17 (3.9)	13 (5.5)	4 (2.0)	
Other	26 (6.0)	12 (5.0)	14 (7.2)	
Involved lymph nodes (*n*)				< 0.001
1	267 (61.5)	163 (68.5)	104 (53.1)	
2	128 (29.5)	64 (26.9)	64 (32.6)	
3	39 (9.0)	11 (4.6)	28 (14.3)	
ER status				0.574
Unknown	71 (16.4)	42 (17.6)	29 (14.8)	
Positive	281 (64.7)	149 (62.6)	132 (67.3)	
Negative	82 (18.9)	47 (19.8)	35 (17.9)	
PR status				0.576
Unknown	90 (20.7)	52 (21.8)	38 (19.4)	
Positive	236 (54.4)	124 (52.1)	112 (57.1)	
Negative	108 (24.9)	62 (26.1)	46 (23.5)	
Her-2/neu				0.817
Unknown	119 (27.4)	66 (27.7)	53 (27.0)	
Positive	230 (53.0)	128 (53.8)	102 (52.0)	
Negative	85 (19.6)	44 (18.5)	41 (20.9)	

ER, estrogen receptor; PR, progesterone receptor

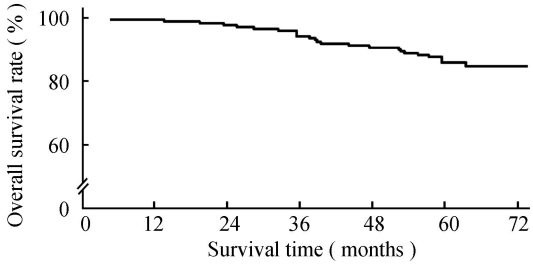

Figure 1 Overall survival of the entire cohort

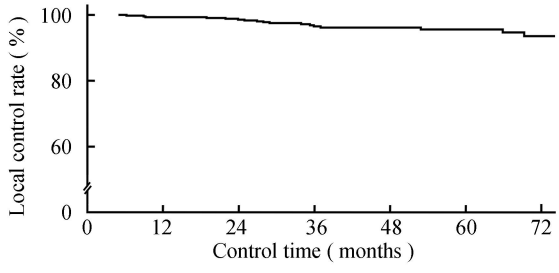

Figure 2 Local control survival of the entire cohort

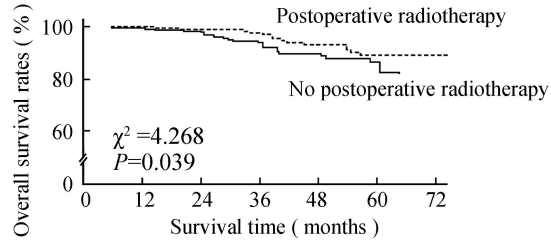

Figure 3 Overall survival in the two groups

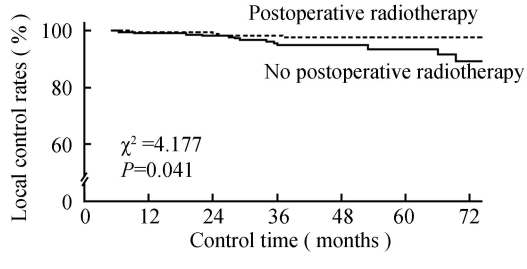

Figure 4 Local control in the two groups

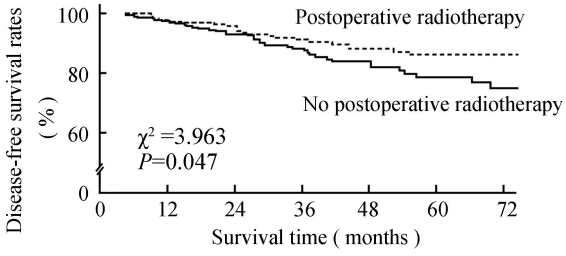

Figure 5 Disease-free survival in the two groups

that did not receive radiotherapy. Shikama *et al.*[14] supported this viewpoint. Overgaard *et al.*[15] thought that the number of positive nodes (> 4) might not be a suitable cutoff for postoperative adjuvant radiotherapy. More and more evidence has indicated that adjuvant radiotherapy is necessary for patients with breast cancer that have positive axillary nodes[16]. van der Hage *et al.*[17] suggested that postoperative radiotherapy might have the greatest gain in patients with one to three axillary positive nodes. Buchholz *et al.*[18] showed that radiotherapy could improve the survival and LC rates in patients with stage T1–T2 disease and

Table 2 The first failures in the two groups with or without radiotherapy

Failure pattern	No postoperative radiotherapy (Patient No. (%))	Postoperative radiotherapy(Patient No. (%))
Local recurrence	6 (2.5)	2 (1.0)
Regional recurrence	3 (1.3)	0
Locoregional recurrence and distant metastases	5 (2.1)	1 (0.5)
Distant metastases	26 (10.9)	19 (9.7)

one to three positive nodes.

Incomplete dissection and detection of axillary lymph nodes underestimates the extent of axillary lymph node metastasis, and the locoregional recurrence rate in patients with less than 10 axillary lymph nodes dissected is significantly higher than the patients with 10 or more axillary lymph nodes dissected[19]. The number of dissected axillary lymph nodes should be at least 10 to be used in accurately determining axillary lymph node metastasis. For patients in this study, the number of axillary lymph nodes was more than 10, with a rate of lymph node metastasis < 20%. Young patients have a significantly low rate of survival and high rates of recurrence and distal metastasis, and the multivariate analysis of OS and progression-free survival shows that age is an independent factor for poor prognosis[20]. Through multiple regression analysis, Truong *et al.*[21] showed that the risk in patients younger than 50 years was 1.58 times greater than in patients older than 50 years. With the increase of the number of positive nodes, the recurrence rate increases and survival rate decreases[19]. In this study, patients with radiotherapy had significant differences in age and number of positive nodes compared with patients without radiotherapy, and the former had more younger patients and more with three positive nodes. Although with more adverse prognostic factors, patients that received radiotherapy had significantly better 3- and 5-year LC, OS, and DFS rates compared to patients that did not receive radiotherapy. The rates of locoregional recurrence were 5.9% vs 1.5% in patients without radiotherapy and with radiotherapy, respectively, and the difference was also significant (P = 0.020). Although without a significant difference, the rate of metastasis in patients with radiotherapy reduced by 2.8% compared to patients without radiotherapy. These results indicate that patients with T1–T2 breast cancer with one to three positive nodes could benefit from postoperative radiotherapy.

In patients with four or more positive axillary nodes, chest wall and supraclavicular lymph node irradiation has the trend of reducing the rate of recurrence in the chest wall and can significantly reduce the rate of recurrence in supraclavicular lymph nodes, but axillary and internal breast lymph node recurrence is rare[1]. In this study, patients with T1–T2 breast cancer with one to three positive nodes after modified radical mastectomy were studied. The radiotherapy field included the ipsilateral chest wall and the supraclavicular area. Locoregional recurrence in all patients included chest wall recurrence and supraclavicular lymph node metastasis. Axillary and internal breast lymph node metastasis was not found, which supports the idea that ipsilateral axillary and internal breast lymph nodes might not receive irradiation routinely at a certain extent.

Our results suggest that in patients with T1–T2 breast cancer that have one to three positive nodes after modified radical mastectomy, chest wall and ipsilateral supraclavicular area irradiation can improve rates of LC, OS, and DFS. Since this study was a retrospective analysis, further confirmation is needed by prospective randomized studies.

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