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Prognostic and Predictive Factors of Early Breast Cancer

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OBJECTIVE To identify risk factors for relapse and death in patients with T1 to T2 breast cancer with 0-3 positive axillary lymph nodes.
METHODS The case files of 540 breast cancer patients with T1-T2 tumors with 0-3 positive nodes were reviewed retrospectively. Ten-year locoregional recurrence (LRR), distant recurrence (DR), disease-free survival (DFS) and overall survival (OS) of the patients were analyzed. Univariate statistical analysis and Cox proportional hazards models were carried out with SPSS software v.16.0.
RESULTS The median follow-up of all the patients was 7.2 years. On multivariate analysis, > 20% positive axillary nodes was the only variable that influenced LRR adversely (hazard ratio[HR], 12.816; 95% confidence interval, 4.657-35.266, $P < 0.001$); > 20% positive axillary nodes and ductal carcinoma were variables that influenced DR adversely (HR, 11.088, 95% confidence interval, 3.807-32.297, $P < 0.001$; HR, 0.390, 95% confidence interval, 0.179-0.851, $P = 0.018$); 1-3 positive axillary nodes and > 20% positive axillary nodes were the only variables that had negative effect on 10-year OS (HR, 2.110, 95% confidence interval, 1.364-3.264, $P = 0.001$; HR, 10.244, 95% confidence interval, 3.497-30.011, $P < 0.001$) and they were also adverse prognostic variables on 10-year DFS (HR, 1.634, 95% confidence interval, 1.171-2.279, $P = 0.004$; HR, 7.339, 95% confidence interval, 2.906-18.530, $P < 0.001$).
CONCLUSION Axillary lymph nodal status is the only risk factor with a significant impact on 10-year LRR, DR, OS and DFS. Patients with T1-T2 breast cancer with 0-3 positive lymph nodes have the LRR and DR of over 10 years, and the OS and DFS of less than 10 years, compared to patients with negative lymph nodes. Histology in primary tumors is a significant prognostic factor for the 10-year DR.

KEY WORDS: breast neoplasms, recurrence, death, prognosis, lymph nodes.

Introduction

It is known that the College of American Pathologists presented a Consensus Statement in 1999 summarizing prognostic factors in breast cancer. Category I of the prognostic factors included tumor

size, lymph node status, micrometastasis, histologic grade, mitotic count, and hormonal receptor status. Of them, tumor size and nodal status are clearly among the strongest predictors of overall survival and metastasis and are also strong predictors of postmastectomy chest wall relapse when radiation is not used[1,2]. However, the outcomes of numerous studies correlating clinical and pathologic features of the primary tumor and/or nodal disease with prognosis have not been uniformly reported[3-11]. For example, the presence of multicentric disease is strongly associated with other risk factors for local-regional recurrence, such as tumor size and nodal involvement, but in patients with stage II disease with 0-3 positive lymph nodes, multicentric disease does not seem to elevate the risk of local-regional recurrence[12]. Another investigation suggested that radiation use led to a 15% to 20% relative reduction in breast cancer mortality, but this reduction only became significant in a multivariate analysis of patients with 7 or more positive lymph nodes[13].

The aim of the present study was to identify factors for relapse and death in patients with T1 to T2 breast cancer with 0-3 positive lymph nodes. It may be useful for clinicians and patients when making decisions about treatment.

Materials and Methods

Patients

The charts and final pathologic reports of female patients with T1-T2 breast cancer with 0-3 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 4 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 0-3 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 a 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 both day 1 and day 8 every 4 weeks or day 1 every 3 weeks. Of these patients, 63 received 1 cycle of chemotherapy; 30 patients received 2 cycles; 20 patients received 3 cycles and 6 patients received 4-6 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 1-5 cycles; 194 patients received 6 cycles; 112 patients received 7 cycles and 25 patients received 8-19 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 4-6 cycles of CMF chemotherapy (140 of N0 patients and 135 of 1-3N+ patients), 162 patients were given post mastectomy radiation therapy that included axillary apex/supraclavicular fossa and internal mammary lymph nodes; 84 patients received radiation treatment 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 5 weeks. Photon energy of 6 MvX was delivered to the axillary apex/supraclavicular fossa and internal mammary lymph node areas for 3 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 3 weeks, and 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 patients.

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). Histologic grading was carried out according to the criteria of Bloom and Richardson. 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 2 groups according to age < 50 *vs.* ≥ 50 years. The tumor fac-

tors analyzed were histologic features (ductal, lobular, other); T stage (T1, T2); tumor location (medial, central, lateral); histologic grade (I, II, III); ER and PR status (positive, negative, unknown). The nodal factors analyzed included the number of positive axillary nodes (0-3), percentage of positive nodes (≤ 20% positive nodes, > 20% positive nodes).

Statistical analysis

The univariate statistical analysis was performed with chi-square test, Kaplan-Meier survival analysis and log-rank test. Multivariate analysis was performed with Cox model, the Cox proportional regression hazard model was used to identify on 10-year LRR, DR, DFS, and OS. All variables with a P value of ≤ 0.1 in the univariate analysis were included in the stepwise regression procedures. All P-values were two sided, and $P < 0.05$ was considered to indicate a statistically significant difference. All statistical analyses were carried out with SPSS software v.16.0.

Results

Patients and disease characteristics

The median follow-up time was 7.2 years (range, 0.25-10.7 years). The median age was 48 years (range, 25-83 years), and the median tumor size was 3.0 cm (range, 0.3-5.0 cm). The median number of lymph nodes in dissection materials was 19 (range, 2-44) (Table 1).

Analysis of the influence of prognostic variables on 10-year LRR and DR

The unadjusted analysis of the impact of various variables on 10-year LRR shows that 1-3 positive axillary nodes and > 20% positive axillary nodes were adverse prognostic variables on LRR. Multivariate analysis shows that > 20% positive axillary nodes was the only variable that influenced LRR adversely; Univariate analysis of the effect of various variables on 10-year DR suggests that 1-3 positive axillary nodes, > 20% positive axillary nodes and histology were prognostic variables on DR. Multivariate analysis suggests that > 20% positive axillary nodes and ductal carcinoma were variables that influenced DR adversely (Tables 2 and 3).

Analysis of the influence of prognostic variables on 10-year OS and 10-year DFS

Univariate analysis shows that 1-3 positive axillary nodes, > 20% positive axillary nodes, without postoperation chemotherapy and ≤ 4 cycles of postchemotherapy were adverse prognostic variables on 10-year OS. Multivariate analysis suggests that 1-3 positive axillary nodes and > 20% positive axillary nodes were the only variables that had negative effect on 10-year OS. Both univariate statistical analysis and multivariate analysis show that 1-3 positive axillary nodes and > 20% positive axillary nodes were adverse prognostic variables on 10-year DFS (Table 4, Table5).

Table1. Patients and disease characteristics.

Characteristics	No.(%)
Age, years	
< 50	308 (57)
≥ 50	232 (43)
Tumor size (pT)	
1a	5 (1)
1b	35 (6)
1c	142 (26)
2	358 (67)
Tumor location	
Medial	123 (23)
Central	125 (23)
Lateral	292 (54)
Histology	
Ductal	434 (81)
Lobular	3 (0)
Other	103 (19)
Histological grade	
Grade I	240 (44)
Grade II	53 (10)
Grade III	247 (46)
Number of positive axillary nodes	
None	348 (64)
1-3 nodes	192 (36)
Positive nodes (%)	
≤ 20%	533 (99)
> 20%	7 (1)
Estrogen receptor status	
Positive	203 (38)
Negative	183 (34)
Unknown	154 (28)
Progesterone receptor status	
Positive	196 (36)
Negative	200 (37)
Unknown	144 (27)
Preoperation chemotherapy	
Yes	119 (22)
No	421 (78)
Postoperation chemotherapy	
Yes	504 (93)
No	36 (7)
Cycles of postoperation chemotherapy	
≤ 4	365 (72)
> 4	139 (28)
Radiotherapy	
Yes	275 (51)
No	265 (49)
Hormonal therapy	
Yes	235 (44)
No	305 (56)

Table 2. Unadjusted analysis of the effect of variables on 10-year locoregional recurrence (LRR) and distant recurrence (DR).

Characteristics	LRR No. (%)	*P*	DR No. (%)	*P*
Age, years		0.83		0.22
< 50	28 (9)		38 (12)	
≥ 50	20 (9)		38 (16)	
Tumor size (pT)		0.81		0.11
T1	16 (9)		20 (11)	
T2	32 (9)		56 (16)	
Tumor location		0.21		0.13
Medial	9 (7)		13 (11)	
Central	7 (6)		13 (10)	
Lateral	32 (11)		50 (17)	
Histology		0.84		0.01
Ductal	39 (9)		69 (16)	
Non-Ductal	9 (9)		7 (7)	
Histological grade		0.92		0.37
Grade I	24 (10)		36 (15)	
Grade II	5 (9)		4 (8)	
Grade III	19 (8)		36 (15)	
No. of positive nodes		0.01		0.03
None	23 (7)		41 (12)	
1-3 nodes	25 (13)		35 (18)	
Positive nodes (%)		< 0.001		< 0.001
≤ 20%	43 (8)		72 (14)	
> 20%	5 (71)		4 (57)	
Estrogen receptor status		0.31		0.76
Positive	13 (6)		30 (15)	
Negative	20 (11)		29 (16)	
Progesterone receptor status		0.77		0.97
Positive	17 (8)		29 (15)	
Negative	18 (9)		30 (15)	
Preoperation chemotherapy		0.10		0.78
Yes	6 (5)		16(13)	
No	42 (10)		60(14)	
Postoperation chemotherapy		0.22		0.38
Yes	47 (9)		73 (15)	
No	1 (3)		3 (8)	
Cycles of postoperation chemotherapy		0.66		0.46
≤ 4	35 (10)		18 (13)	
> 4	12 (9)		55 (15)	
Radiotherapy		0.86		0.42
Yes	23 (9)		35 (13)	
No	25 (9)		41 (16)	
Hormonal therapy		0.84		0.66
Yes	20 (9)		35 (15)	
No	28 (9)		41 (13)	

Table 3. Multivariate Cox regression analysis of 10-year LRR and DR.

	LRR		DR	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Number of positive nodes (none *vs.* 1-3 nodes)	1.643 (0.902-2.994)	0.105	1.426 (0.894-2.275)	0.137
Positive nodes (%) (≤ 20% *vs.* > 20%)	12.816 (4.657-35.266)	< 0.001	11.088 (3.807-32.297)	< 0.001
Preoperation chemotherapy (yes *vs.* no)	0.571 (0.241-1.355)	0.204	/	/
Histology (ductal *vs.*others)	/	/	0.390 (0.179-0.851)	0.018

Table 4. Unadjusted analysis of the effect of variables on 10-year overall survival (OS) and disease-free survival (DFS).

Characteristics	OS No. (%)	*P*	DFS No. (%)	*P*
Age, years		0.85		0.71
< 50	252 (82)		228 (74)	
≥ 50	191 (82)		167 (72)	
Tumor size (pT)		0.29		0.11
T1	152 (84)		140 (77)	
T2	291 (81)		255 (71)	
Tumor location		0.52		0.30
Medial	102 (83)		90 (73)	
Central	107 (86)		98 (78)	
Lateral	234 (80)		207 (71)	
Histology		0.52		0.18
Ductal	354 (82)		312 (72)	
Non-Ductal	89 (84)		83 (78)	
Histological grade		0.35		0.61
Grade I	223 (93)		199 (83)	
Grade II	42 (80)		41 (77)	
Grade III	178 (72)		155 (63)	
Number of positive nodes		< 0.001		0.001
None	303 (87)		272 (78)	
1-3 nodes	140 (73)		123 (64)	
Positive nodes (%)		< 0.001		< 0.001
≤ 20%	440 (83)		393 (74)	
> 20%	3 (43)		2 (29)	
Estrogen receptor status		0.68		0.80
Positive	161 (79)		147 (72)	
Negative	146 (80)		128 (70)	
Progesterone receptor status		0.26		0.42
Positive	166 (85)		146 (75)	
Negative	154 (77)		138 (69)	
Preoperation chemotherapy		0.28		0.67
Yes	92 (77)		88 (74)	
No	351 (83)		307 (73)	
Postoperation chemotherapy		0.04		0.39
Yes	418 (83)		371 (74)	
No	25 (69)		24 (67)	
Cycles of postoperation chemotherapy		0.056		0.11
≤ 4	296 (81)		262 (72)	
> 4	122 (88)		109 (78)	
Radiotherapy		0.46		0.73
Yes	231 (84)		204 (74)	
No	212 (80)		191 (72)	
Hormonal therapy		0.56		0.62
Yes	198 (84)		176 (75)	
No	245 (80)		219 (72)	

Table 5. Multivariate Cox regression analyis of 10-year OS and DFS.

Variables	OS		DFS	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
No. of positive nodes (none *vs*. 1-3 nodes)	2.110 (1.364-3.264)	0.001	1.634 (1.171-2.279)	0.004
Positive nodes ≤ 20% *vs*. > 20%)	12.816 (4.657-35.266)	< 0.001	7.339 (2.906-18.530)	< 0.001
Postoperation chemotherapy (yes *vs*. no)	NS	NS	/	/
Cycles of postchemotherapy (yes *vs*. no)	0.646 (0.378-1.104)	0.110	/	/

NS: non significant

Discussion

The purpose of this analysis was to identify possible risk factors for relapse and death among patients with T1-T2 breast cancer with 0-3 positive axillary lymph nodes. We found that axillary lymph nodal status is the only risk factor with a significant impact on 10-year LRR, DR, OS and DFS and that histology in primary tumors is a significant prognostic factor for 10-year DR.

As was expectated, the multivariate analysis found the percentage of positive lymph nodes to be a stronger prognostic factor for LRR. In node-positive patients treated with mastectomy, the percentage of positive/excised nodes has been reported to be a significant prognostic indicator for LRR[14]. An analysis by Fortin et al. of 1372 women with T1 to T2, node-positive breast cancer treated with breast-conserving surgery also identified the percentage of positive nodes to be significantly associated with LRR. In that series, regional radiation therapy after breast-conserving surgery improved axillary control for patients with 1-3 positive lymph nodes and less than 40% positive nodes[15]. In 990 patients with clinical stage I or II breast cancer treated with breast-conserving surgery and irradiation, Fowble et al. found that only the number of axillary lymph nodes removed at time of initial axillary dissection was a significant prognostic factor for axillary recurrence. But in the present study, although the LRR of 13% in 1-3 positive nodes patients is higher than that of 7% in negative nodes patients, number of positive nodes was not a significant prognostic factor for LRR in multivariate analysis, the reason for it might be few of such patients were actually enrolled in this study. It was known that of all prognostic factors, nodal status would be the strongest predictor of disease-free and overall survival and is the primary factor that governs breast cancer staging[16,17]. Although outcomes will continually improve as systemic therapies advance, data from previous NSABP trials treated primarily with local-regional therapy alone revealed 5-year survival rates of 82.8% for node negative, 73% for 1-3 positive nodes. In the data, the 10-year overall survival rates was 87% for node negative, 73% for 1-3 positive nodes.

In the present study, histology in primary tumors is a significant prognostic factor for DR, and invasive ductal has a higher distant recurrence, compared to other subtypes. There are many studies which suggested that the invasive ductal have a more unfavorable prognosis, compared to tubular, mucinous, and medullary subtypes[18,19]. Invasive ductal tumors appear to have a worse prognosis similar to invasive lobular tumors. In a classic analysis of 293 T2-N0 breast cancers with over 20-year follow-up treated by mastectomy, Rosen et al.[18] reported more unfavorable relapse rates in invasive ductal and invasive lobular tumors, compared to medullary, mucinous, tubular, and papillary subtypes.

Contrary to expectations, tumor size had no prognostic significance. Numerous studies suggested that the size of the primary tumor ranks among the strongest predictors of distant recurrence, disease-free, and overall survival[20,21]. In an analysis of 826 women with node-negative breast cancer treated by mastectomy at the University of Chicago with a median follow-up of 13.5 years, Quiet et al.[22] reported a 20-year disease-free survival of 79% for patients with tumors < 2 cm, compared to 64% with tumors > 2 cm. In the present study, the 10-year disease-free survival of 77% for patients with tumors < 2 cm, compared to 71% with tumors > 2 cm. The rates of 10-year DFS decreased when tumors changed from T1 to T2. Other prognostic factors, such as age, tumor location, histological grade, ER, PR, radiotherapy and systemic treatments also had no prognostic significance. Regrettably lymphatic vascular invasion was not evaluated for incomplete data in pathologic reports[23,24].

Similar to other retrospective analyses, this study was subject to biases in patients and treatment selection. But from the clinical outcomes, one point is certain -that axillary lymph nodal status is a stronger prognostic factor for 10-year LRR, DR, OS and DFS. Patients with T1-T2 breast cancer with 1-3 positive lymph nodes have higher 10-year LRR and DR, and lower 10-year OS and DFS, compared to patients with negative lymph nodes. From the above analysis, it can be strongly suggested that radiotherapy to regional lymphatics and the breast/chest wall combined with systemic treatments should be given to breast cancer patients with T1-2 with 1 to 3 positive lymph nodes[25]. Of course, ongoing trials by the National Cancer Institute of Canada and EORTC, which are randomizing high-risk node-negative and node-positive patients to treatment to the breast/chest wall alone or breast/chest wall and regional lymphatics, will give some answers for these issues.

In summary, axillary lymph nodal status is the only risk factor with a significant impact on 10-year LRR, DR, OS and DFS, patients with T1-T2 breast cancer with 1-3 positive lymph nodes have higher 10-year LRR and DR, and lower 10-year OS and DFS, compared to patients with negative lymph nodes. Also histology in primary tumors is a significant prognostic factor for 10-year DR.

Conflict of interest statement

No potential conflicts of interest were disclosed.

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