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T3N0M0 Breast cancer patients: A subgroup with favorable prognosis

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ABSTRACT

The true pathological T3N0M0 breast cancer is a rare disease with surprisingly good survival rate. In this retrospective study we tried to evaluate the possible prognostic factors in pT3N0M0 breast cancer patients and to compare them with pT3N1M0 and pT1-2N0M0 patients. Between December 1993 and December 1998, 444 patients without any distant metastases were treated at our department. A total of 194 patients were staged as pT3. Among them 40 were pT3N0 and 154 were pT3N1. One hundred patients were staged as pT1-2N0. The 3-year overall (OS) and disease free survival rates (DFS) for T3N0M0 patients with a median follow-up time of 38 months are 100% and 90%, respectively. There was no statistically significant DFS and OS difference between T1-2N0 and T3N0 patients. A significant DFS, distant metastasis free survival (DMFS) advantage was observed in T3N0 subgroup when compared to T3N1 patients. Although not significant, there was a strong trend for OS in favor of T3N0M0 patients as well (p=0.09). For T3 patients, the metastatic lymph node ratio (LNR: number of metastatic lymph nodes/total number of lymph nodes dissected) significantly affected both DFS and DMFS; however there was no significant survival difference between 0% and 1-25% LNR groups both in terms of DFS and DMFS. These results suggest that T3N0M0 breast cancer patients treated by postoperative radiotherapy and chemotherapy have a fairly good outcome comparable to T1-2N0M0 patients. A subgroup of T3N1 patients with less than 25% lymph node involvement seems to behave similarly to T3N0 patients. [Turk J Cancer 2003;33(3):144-149]

KEY WORDS:

Breast cancer, T3N0, prognosis

INTRODUCTION

Despite all the advances made in the field of early detection of breast cancer, large primary tumors continue to be a major problem in the developing countries. These tumors are frequently associated with axillary lymph node metastases and/or distant metastases. Large tumors without axillary lymph node metastases are reported to be uncommon. In a study from Finland (1), among 4190 patients with a diagnosis of breast cancer treated from 1987 to 1994, only 38 (0.9%) were classified as true pathological T3N0M0.

Patients with T3-4N0 tumors show a surprisingly good outcome, with statistically significant survival advantage when compared to lymph node positive ones (2,3). These results led the American Joint Committee on Cancer Staging in conjunction with the UICC TNM Staging Committee to down stage the T3N0M0 tumor category from stage III to stage II (4).

The true pT3N0M0 breast cancer is a rare disease and the benefit of postoperative radiotherapy in these patients has not been clearly defined yet. The aim of this retrospective study is to evaluate possible prognostic factors, to compare the outcome with T3N1 and T1-2N0 patients and to discuss the radiotherapeutic approach in pathologically staged T3N0M0 patients.

MATERIALS AND METHODS

Between December 1993 and December 1998, a total of 444 breast cancer patients without any detectable distant metastasis were referred to Hacettepe University Faculty of Medicine, Department of Radiation Oncology after mastectomy or breast conserving surgery (BCS). Forty out of 444 patients (9%) were pT3N0 whereas 154 (34.7%) were considered as pT3N1 and 100 (22.5%) as pT1-2N0.

Applied radiotherapy (XRT) protocol was to irradiate the whole breast in all patients with BCS and the chest wall after mastectomy in case of positive surgical margin, skin or fascial involvement, or a primary tumor diameter equal to or more than 4 cm in size or if the applied surgery was in the form of simple mastectomy. Supraclavicular fossa (SCF) and axillary lymph node irradiation were applied in cases with inadequate dissection (less than 10 lymph nodes removed) or when 3 or more axillary lymph nodes contain metastatic cancer. In patients with inner quadrant tumors which are equal or larger than 4 cm or with more than 50% of axillary lymph nodes involved with cancer, internal mammary XRT was also applied. A total dose of 50 Gy to the chest wall and/or peripheral lymphatics was administered with conventional daily fractions either by Co-60 or 6 MV tangential photon beams or electron beams after mastectomy. In case of BCS, a boost dose of 10 Gy with electron beams of 8-12 MeV energy was applied to the tumor bed after 50 Gy whole breast irradiation with conventional daily fractions with 6 MV photon beams.

Patients either with T3 tumors or with metastatic axillary lymph nodes or patients younger than 40 years of age and with tumors more than 1 cm received adjuvant chemotherapy in the form of intravenous CMF (Cyclophosphamide, Methotrexate, 5-Fluorouracil), FAC (Cyclophosphamide, Adriamycin, 5-Fluorouracil) or FEC (Cyclophosphamide, Epirubicine, 5- Fluorouracil) for 6 cycles. Patients with estrogen receptor positive tumors were prescribed tamoxifen therapy for 5 years.

Statistical analysis was performed using the SPSS software (SPSS Inc., Chicago, USA, 1994). The survival analyses were based on overall, disease free survival, locoregional survival and distant metastasis free survival which are defined as:

Overall survival (OS): time from the end of radiotherapy till death.

Disease free survival (DFS): time from the end of radiotherapy till time of the first local or systemic recurrence.

Locoregional relapse free survival (LRRFS): time from the end of radiotherapy till the first time locoregional recurrence is detected.

Distant metastasis free survival (DMFS): time from the end of radiotherapy till the first time systemic metastases are detected.

The OS, DFS, LRRFS and DMFS were estimated using Kaplan-Meier method and comparison between the groups was made using Log-Rank test. A p value <0.05 was considered as significant.

Patient characteristics between groups were compared using chi-square test. The comparison of the mean number of the axillary lymph nodes removed was made using one-way ANOVA test.

RESULTS

The median age at the time of the diagnosis was 48 years with a range of 22 to 85 years. Median follow-up time is 38 months (10-89 months) for the whole 444 patients and 36 months (19-78 months) for pT3N0 patients. Applied surgery in pT3N0 patients were as follows: BCS in 1 (2.5%), simple mastectomy and axillary dissection in 4 (10%), modified radical mastectomy in 33 (82.5%) and radical mastectomy in 2 (5%). All patients had undergone axillary dissection beside primary surgical intervention. The mean number of axillary lymph nodes dissected in pT3N0 patients was 18.3 ± 9.5 (range 1-47). Eight patients (20%) in the pT3N0 group had inadequate dissection according to our protocol, with less than 10 lymph nodes removed.

Patient characteristics in T3N0, T1-2N0 and T3N1 with less than 25% lymph node ratio (LNR: number of metastatic lymph nodes/total number of lymph nodes dissected) were analyzed according to histopathology, menopausal status,

median age at diagnosis, mean number of axillary lymph nodes removed and the type of surgery. All but the type of surgery were similar without any significant difference between groups. In T1-2NO patients the main type of surgery was in the form of breast conserving surgery (47%) while the remaining patients were treated by either modified or radical or simple mastectomy. For the other 2 groups the main type of surgery was modified radical mastectomy (82.5% in both groups). The mean number of axillary lymph nodes removed were 16.8±6.8 for T1-2 N0, 18.3±9.5 for T3N0 and 18.35±8.9 for T3N1 with less than 25% LNR. These were not statistically different.

All 40 patients in the pT3N0 group received chest wall or breast irradiation. Only 8 (20%) patients in this group received SCF and axillary irradiation because of inadequate axillary dissection. Of the 154 patients with pT3N1 tumors, 63 (40.9%) cases were considered as having less than 25% LNR. The median number of metastatic lymph nodes in this subgroup was 2 with a range of 1-7. Twenty-six out of 63 patients (41.3%) in this subgroup received axillary irradiation due to inadequate dissection. The other patient subgroups in pT3N1 group were as follows: 38 (24.6%) patients with 25-50% LNR and 53 (34.4%) patients with more than 50% LNR.

Seventeen patients in T1-2N0M0 group received no systemic therapy. There was a statistically significant difference between the 3 groups when adjuvant systemic therapy was considered (p<0.0001, Table 1).

Three years OS and DFS for the whole group is 94% and 74%, respectively. For pT3N0 patients, 3-year OS and DFS were found as 100% and 90%, respectively. Family history, menopausal status, benign breast disease, receptor status, age at the time of the diagnosis (≤40 years vs. >40 years) were the prognostic factors analyzed for pT3N0 patients and only age at diagnosis was found to be a statistically significant prognostic factor for DFS. Patients ≤40 years of age at diagnosis did significantly worse than patients more than 40 years of age (p=0.005).

For the 140 patients without axillary lymph node metastasis, there was no OS, DFS or DMFS difference between pT1-2N0 and pT3N0 patients (Figures 1 and 2). For T3 patients, a statistically significant DFS, DMFS advantage was observed in pT3N0 subgroup when compared to T3 node positive patients. Although not significant, there was a strong trend for OS in favor of pT3N0 patients as well (p=0.09). The LNR significantly affected both DFS and DMFS (Figures 3 and 4). The survival difference among subgroups of LNR was not significant between 0% LNR and 1-25% LNR both in terms of DFS and DMFS. Patients with more than 50% axillary lymph node involvement did worse and showed a survival difference compared to the remaining groups in terms of LRRFS (Figure 5).

Table 1

Patient distribution according to the systemic treatment in pT1, 2N0, pT3N0 and pT3N1 with less than 25% LNR (p<0.0001)

	No (%)	CMF (%)	FAC (%)	FEC (%)	TMX (%)	CMF+TMX (%)	FAC+TMX (%)	TOTAL (%)
pT1-2N0	17 (17)	53 (53)	18 (18)	4 (4)	7 (7)	1 (1)		100
pT3N0		19 (47.5)	10 (25)	8 (20)	3 (7.5)			40 (100)
PT3N1 LNR <25%		32 (50.8)	14 (22.2)	7 (11.1)	4 (6.3)	4 (6.3)	2 (3.2)	63 (100)

No: No further systemic therapy, **CMF:** Cyclophosphamide, Methotrexate, 5-Fluorouracil, **FAC:** Cyclophosphamide, Adriamycin, 5-Fluorouracil, **FEC:** Cyclophosphamide, Epirubicine, 5-Fluorouracil, **TMX:** Tamoxifen

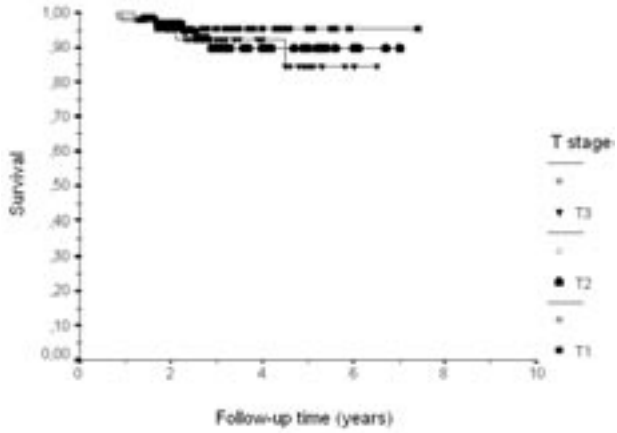

Fig 1. Disease free survival by T stage in lymph node negative patients (p: 0.69)

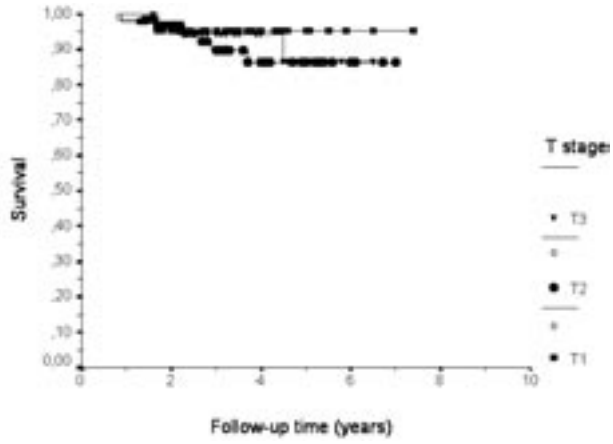

Fig 2. Distant metastasis free survival by T stage in lymph node negative patients (p: 0.66)

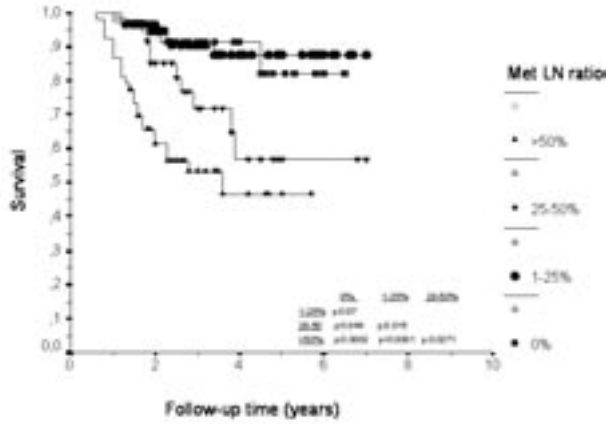

Fig 3. Disease free survival in pT3 patients by Metastatic Lymph Node Ratio (p<0.00001)

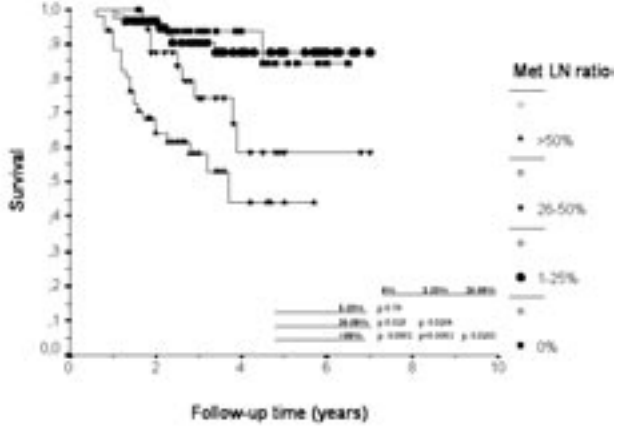

Fig 4. Distant metastasis free survival in pT3 patients by Metastatic Lymph Node Ratio (p<0.0001)

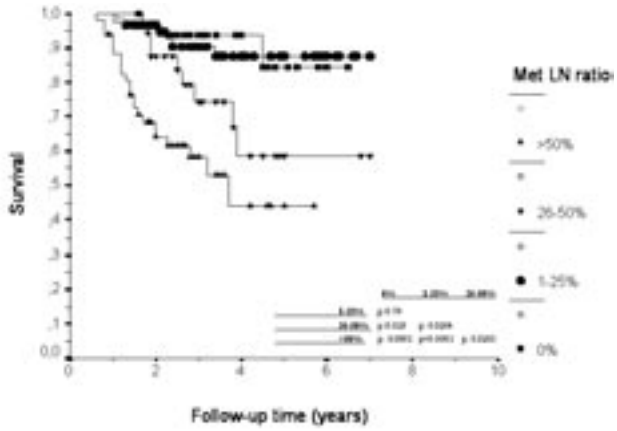

Fig 5. Locoregional relapse free survival in pT3 patients by Metastatic Lymph Node Ratio (p=0.051)

DISCUSSION

The true pT3N0 breast cancer is a fairly rare disease and studies dedicated to this special group of patients in the literature are seldom reported. In a study from Finland, Helintö et al. (1) reported the frequency of true pathological T3N0M0 patients as 0.9% among 4190 breast cancer patients. True pathological T3N0 breast cancer patients in our series is 9%. Lack of screening programs in addition to educational and social problems in our country may lead to this high frequency of patients with large tumors but all those reasons do not explain the relatively benign nature of these tumors that they are large enough to be considered as T3 tumors but without any lymph node metastasis.

The optimal treatment and the role of postmastectomy XRT in the management of resected T3 pathologically node

negative breast cancer is controversial (5). In one of the largest studies, Fracchia et al. (6) reported the 10-year outcome in 488 stage III breast cancer of which 58 were T3-4N0 patients. In that study 75% of patients with T3-4N0 tumor were alive at 10 years compared with only 21% in T3-4 patients with positive axillary lymph nodes.

Two prospective randomized trials addressed the role of postmastectomy XRT in resected T3 node negative breast cancer. In the Helsinki trial, Klefstrom et al. (2) analyzed 120 stage III patients comparing XRT alone vs. chemotherapy (CT) alone vs. combined chemoradiotherapy. Locoregional recurrence was reported in 2 of the 27 patients with T3N0 breast cancer who received postmastectomy XRT compared with 5 of 13 patients who did not. In 40 T3N0 patients in this trial, systemic recurrences were observed in 30% of the cases compared with 76% in T3N1-2 cases. In the Danish Breast Cancer Cooperative Group 82B trial, Overgaard et al. (3) reported their results in 1708 premenopausal patients of whom 135 were staged as T3N0. The 10-year overall survival of the 58 patients receiving CT+XRT was 82% with 3/58 locoregional recurrences. The remaining 77 cases with T3N0 breast cancer in the Danish trial were treated with adjuvant CT alone and 10 year survival in this group was reported to be 70% with 17/77 locoregional recurrences. There is no DFS or DMFS difference in lymph node negative patients in our series no matter what T stage the patient is (T1-2 vs T3) which may be due to relatively short follow-up time. Seventeen out of 100 patients in T1-2N0 group received no further systemic therapy after locoregional treatment. These patients were with tumors of 1 cm or less in diameter without any lymph node metastases and can be considered as a very favorable group with no need for further systemic treatment. Only 1 patient in the T3N0 group experienced locoregional recurrence located on chest wall. Since all patients in this group with T3 tumors received irradiation either to chest wall or breast, we can not make a conclusion about the possible beneficial role of postmastectomy chest wall XRT. Although we do not have phase III trials dedicated to this pT3N0 group of patients, the results of Helsinki and Danish trials in addition to our clinical experience lead us to believe that postmastectomy XRT is essential.

Breast cancer recurrence and survival rates are significantly influenced by the pathologic status of the axillary lymph nodes. The total number of the positive nodes is the major determinant of the risks of locoregional recurrence, distant metastases and breast cancer death (7-10). Commonly accepted subdivisions of node positive patients with prognostic significance include the categories of 1-3 positive nodes vs. 4 or more (11-13). For patients with 1-3 positive axillary lymph nodes, who receive adjuvant chemotherapy and/or XRT, locoregional recurrence and distant metastasis rates at 10 years are reported to be in the range of 7- 30% and 17-30%, respectively; whereas in patients having more than 3 axillary lymph nodes involved, these rates are in the range of 14-42% for locoregional recurrences and 23-46% for distant metastases (3,9,10). For patients with operable locally advanced tumors, results of a randomized trial by Eastern Cooperative Oncology Group (14) showed that the increased number of metastatic axillary lymph nodes significantly increased the patients' risk of relapse by 79% and risk of death by 66% at a median follow up time of 9.1 years. Since there is a great heterogeneity of the number of the axillary lymph nodes removed during dissection, we chose to classify the axillary lymph nodes with LNR rather than the crude number of metastatic lymph nodes in patients with adequate axillary dissection and in the analysis of pT3N1 breast cancer patients in our series, a subset of patients with less than 25% lymph node involvement showed a prognosis equally favorable as patients with pT3N0 disease in terms of DFS, DMFS and LRRFS. The median number of metastatic lymph nodes in 1-25% LNR group in our series was 2. Prognostically these patients can be accepted as having less than 4 metastatic lymph nodes and the short term results of our study, in our opinion, support the literature in terms of classifying node positive patients according to the number of metastatic axillary lymph nodes, to a better prognosis of 1-3 positive lymph nodes and unfavorable prognosis in 4 or more metastatic lymph node group.

With a median follow up time of 38 months, only 2 patients, 1/40 in pT3N0 and 1/63 in less than 25% LNR group, developed locoregional recurrence. According to our treatment protocol, XRT to chest wall was routinely applied to all T3 cases and in case of inadequate dissection or when equal or more than 3 lymph nodes contained metastatic cancer, SCF and posterior axillary fields were also irradiated. Despite the short follow-up time, the low locoregional recurrence rates suggest that chest wall XRT can be an effective adjuvant locoregional treatment after surgery in T3N0 and T3N1 with less than 25% LNR patients provided that an adequate axillary dissection has been performed.

In conclusion, the preliminary results of our study give us an impression that pT3N0 and a favorable group of T3N1 patients may have a fairly good short-term outcome that is comparable to T1-2N0 patients. Longer follow-up time of at least 5 years will answer the question whether this favorable outcome will continue or not. The need for routine postoperative chest wall irradiation in these patients, remains to be tested in a prospective randomized trial.

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