The role of post-mastectomy radiotherapy in node negative breast cancer with tumor size 5 cm or larger

Alaa Maria and Mohamed El-Shebiney.

Clinical Oncology Department, Faculty of Medicine, Tanta University, Egypt
alaamaria1@hotmail.com

Abstract: Background and purpose: It is not been established whether breast cancer patients who have a primary tumor 5 cm or larger with no axillary nodal nor distant metastases at the time of the diagnosis benefit from post mastectomy radiation therapy (PMRT) or not. **Materials and Methods:** Between January, 1997 and December, 2008, a total of 53 lymph node-negative (LNs) breast cancer patients with tumors sizes 5 cm or larger were treated with mastectomy, adjuvant systemic therapies with or without PMRT at Department of Clinical Oncology, Tanta University Hospital. Of these 53 patients, 40 (75.5%) patients had received adjuvant PMRT. We retrospectively assessed rates of cause-specific survival (CSS), locoregional–recurrence free survival (RFS) and distant-failure free survival (FFS) and risk factors for CSS in these patients. **Results:** With a median follow-up of 74.7 months (range 30-132 months), distant failure only was diagnosed in 9 patients (17%), locoregional recurrence only in 2 patients (3.78%), and 2 (3.78%) patients had both locoregional and distant failure. Three (23%) of the 13 patients who were not treated with PMRT developed locoregional recurrence (two patients had recurrence in the chest wall and one patient in the axilla) as compared with only one (2.5%) of the 40 patients who were given PMRT. The 5-year locoregional-RFS rate was 97.37% in the PMRT group vs. 76.92% in the no-PMRT group (p = 0.01). The 5-year distant FFS rate was 82.35% in the PMRT group vs. 69.23% in the no-PMRT group (p = 0.26). The 5-year CSS rate was 87.24% in the PMRT group vs. 68.38% in the no-PMRT group (p = 0.11). By the univariate analysis using Cox proportional-hazards survival regression adjusted for the prognostic variables; the tumor size, tumor grade, estrogen/progesterone (ER/PR) receptor status and adjuvant hormonal therapy had associated with statistically significant CSS rate. **Conclusion:** The CSS, locoregional-RFS and distant-FFS rates were better in LNs negative breast cancer patients with large tumor size (≥5cm) who received PMRT. Also, tumor size pT2 =5 cm, low tumor grade, hormonal receptors positive and hormonal therapy administration were associated with improved CSS. These data should be interpreted with caution because of the small number of patients and events and because pathologic features that are associated with adverse outcome, such as lymphovascular or perineural invasion and surgical margin status not available and this imbalance in prognostic factors masks a favorable impact of PMRT.
[Alaa Maria and Mohamed El-Shebiney. **The role of post-mastectomy radiotherapy in node negative breast cancer with tumor size 5 cm or larger**. Journal of American Science, 2012;8(4):27-34] http://www.americanscience.org. 4

Key words: Breast cancer, Post-mastectomy radiotherapy, node negative, tumor size.

1. Introduction

In Egypt, breast cancer is the most common cancer among women, representing 18.9% of total cancer cases (35.1% in women and 2.2% in men) among the Egyptian National Cancer Institute (NCI) series of 10,556 patients during the year 2001[(1)], with an age-adjusted rate of 41.9 per 100,000 population and peak incidence in the age 50-54.[(2)]

Patients with node-negative breast cancer and primary tumors 5 cm or larger represent less than 1% of new breast cancer patients,[(3)] and optimal management for these patients is not well defined.[(4)] Standard recommendations for these patients include systemic treatment in addition to surgery. Several randomized trials and meta-analyses have evaluated PMRT over the past several decades [(5-9)]. However, those reports typically involved a very heterogeneous patient population, radiotherapy techniques and equipment, and suboptimal systemic therapy.

The PMRT guidelines of the American Society of Clinical Oncology[(10)] provide no recommendations for T3N0 tumors because of a lack of information and conflicting data. Yet, the majority of practicing radiation oncologists recommends PMRT for these tumors. The adoption of these guidelines has been reflected in the results of a recent survey of 1,137 North American and European radiation oncologists, of whom 88% stated that they would offer PMRT to Stage pT3N0 patients.[(11)] The National Institutes of Health Consensus Development Conference at 2010 had recommended PMRT for stage pT3N0 breast cancer.[(12)]

McCammon *et al.*[(13)] using the Surveillance, Epidemiology, and End Results (SEER) database in total, 1865 T3N0 breast cancer women met the analysis criteria for overall survival (OS); cause-specific survival (CSS) data were available for 98.8% of those women. The actuarial 10-year CSS for those who received PMRT versus those who did not

receive PMRT was 81.6% versus 79.8%, respectively (*P*=0.38). PMRT was not associated with a CSS benefit in any subgroups, a finding that persisted in multivariate analyses. Women who received PMRT had an increased 10-year OS rate (70.7% vs. 58.4%; P <.001) that was confined to women aged >50 years in a subgroup analysis.. However, SEER studies are limited by the absence of information regarding LRR outcomes, margin status, lymphovascular invasion (LVI), and systemic therapy use. The potential imbalance of key prognostic and predictive factors could have significantly affected the outcome of patients and potentially masked any benefit from PMRT.

In a multi-institutional retrospective cohort of 70 patients, **Floyd *et al.*** [14] reported a 5-year cumulative LRR rate of 7.6% and a 5-year disease-free survival rate of 86%. **Goulart *et al.*** [15] reported in a prospective study included 19,846 non-metastatic breast cancer patients. Out of 100 patients had node-negative with tumors ≥5 cm, 44 (44%) had received adjuvant PMRT. The cumulative 10-year LRR rate of 2.3% in the PMRT group vs. 8.9% in the no-PMRT group (*p*=0.2). The 10-year breast cancer-specific survival rate (BCSS) was 85.8% in the PMRT group vs. 74.6% in the no-PMRT group (*p* = .2). On multivariate analysis, adjusted for the prognostic and predictive variables, PMRT did not significantly improve the LRR or BCSS.

2. Materials and Methods

According to the patient registry at Department of Clinical Oncology, Tanta University Hospital, a total of 53 non-metastatic nodes negative breast cancer patients with primary tumors of pathologic size greater than or equal to 5 cm were treated between January 1997 and December, 2008 with mastectomy, adjuvant systemic therapies and with or without radiotherapy. These patients were selected from files of 1120 total breast cancer patients. Patients who received neoadjuvant therapies and those with skin or chest wall invasion were excluded from this study.

Clinical data including; patients age, histopathological type, tumor-node-metastasis (TNM) classification, gender, ER/PR receptor status, menstrual status, tumor size, tumor grade, number of dissected LNs, type of adjuvant systemic therapies (chemotherapy and/or hormonal therapy) and PMRT. The staging examinations to conform the M0-status at diagnosis consisted of chest X-ray, liver ultrasound examination, isotope bone scan, and blood chemistry profile. There was lacking of information's about surgical margin and lymphovascular invasion (LVI) status through the pathological reports.

In all 53 patients mastectomy with axillary dissection was performed. Seven patients had a radical mastectomy and 46 patients underwent a modified radical mastectomy. The median number of pathologically examined axillary nodes was 13 (range 5-26).

Forty (75.5%) patients were treated with PMRT while 13 patients (24.5%) were not. The causes of unreceiving PMRT among our 13 patients were; 2 patients refused radiotherapy treatment, 5 patients according to discretion of the attending physicians and because of very long time gap between mastectomy and presentation in 6 patients. The target dose was 50 Gy administered in 2.0 Gy daily fractions, five times weekly. Out of the 40 patients who were treated with PMRT, the ipsilateral chest wall was only irradiated in 28 (70%) patients, and 12 patients received supraclavicular PMRT in addition to the chest wall. Radiation therapy was given with Cobalt-60 photon beam for all patients.

Forty-two (79.24%) patients received adjuvant chemotherapy, forty (75.47%) patients received adjuvant hormonal therapy (mainly tamoxifen, 20 mg daily) and 30 (56.60%) patient received both chemotherapy and hormonal therapy. Only one (1.89%) patient didn't receive any adjuvant systemic therapy.

Statistical analysis

The purpose of this study, to assess rates of CSS, locoregional-RFS and distant-FFS and risk factors for CSS in LNs negative patients with tumor size equal or larger than 5 centimeters who underwent mastectomy, either with or without adjuvant systemic therapies and PMRT.

Cause-specific survival (CSS) is ascertained by specifying breast cancer as the cause of death and was measured from the time of diagnosis until death from breast cancer. Known non-breast cancer deaths were censored and were not counted as events.

The local and regional recurrences were defined as relapse of cancer in the ipsilateral chest wall and in the regional lymphatics (ipsilateral supraclavicular, infraclavicular, axillary, or internal mammary nodes). Locoregional-RFS was defined as survival computed from the date of breast cancer diagnosis to the date of the last follow-up visit or death without a locoregional cancer recurrence irrespective of whether breast cancer had recurred outside of the locoregional region or not. Distant failure was defined as recurrence outside the ipsilateral chest wall or regional lymphatics. Distant disease-free survival was computed from the date of breast cancer diagnosis to the date of the last follow-up visit or death without distant metastases irrespective of whether breast cancer had recurred locoregionally or

not. The first site of locoregional or distant failure was the only event considered.

Univariate analysis using Cox proportional-hazards survival regression[16] was performed to evaluate the influence of risk factors (patient age, tumor size, pathological type, tumor grade, menopausal status, hormone receptors status, number of LNs sampled and systemic therapies) on CSS , locoregional–RFS and distant-FFS and 95% confidence intervals (95% CI) was reported.

Statistical analysis was performed using the Statistical Package for Social Sciences software (SPSS v-12). Survival curves will be calculated using the Kaplan-Meier method[17] and were analyzed using the log-rank test.[18]. Statistical significance was defined as p <0.05.

3. Results

The patient, tumor, and treatment characteristics of all patients are shown in Table 1. The median age at diagnosis was 47 years (range 28-67). Twenty-six (49.06%) patients were between 40-60 years old. Thirty-three (62.26%) patients were premenopausal and 37 (69.81%) patients were hormone receptors positive. Out of the 53 studied patients; 40 (75.47%) received PMRT and 13 (24.53%) did not.

Pathologic tumor sizes in this series ranged from 5 to 15 cm in largest dimension with the median tumor size 5.6 cm. Thirty-nine (73.6%) patients had 5-cm tumor size, whereas 26.4% had tumor size >5 cm (22.6% were >5-10 cm and 3.8% had large tumors >10 cm).

Table (1): Patients, tumor, and treatment characteristics of all patients (n=53 patients).

	PMRT	No PMRT	Total patients
	Patients (n=40) (75.5%)	Patients (n=13) (24.5%)	(n=53) (100%)
Age: Median (47 years)			
≤40	17 (42.5%)	0 (0%)	17 (32.07%)
>40-60	15 (37.5%)	11 (84.6%)	26 (49.06%)
>60	8 (20%)	2 (15.4%)	10 (18.87%)
Lymph nodes: Median 13 (range 5-26)			
≤5	2 (5%)	2 (15.4%)	4 (07.55%)
6-10	13 (32.5%)	0 (0%)	13 (24.53%)
>10	25 (62.5%)	11 (84.6%)	36 (67.92%)
Size (T)			
5 cm	30 (75%)	9 (69.2%)	39 (73.6%)
>5 cm	10 (25%)	4 (30.8%)	14 (26.4%)
Pathology			
IDC	35 (87.5%)	12 (92.3%)	47 (88.7%)
Others	5 (12.5%)	1 (7.7%)	6 (11.3%)
Grade			
I & II	30 (75%)	10 (76.9%)	40 (75.5%)
III	10 (25%)	3 (23.1%)	13 (24.5%)
ER/PR			
Positive	29 (72.5%)	8 (61.5%)	37 (69.8%)
Negative	11 (27.5%)	5 (38.5%)	16 (30.2%)
Menstuation			
Pre-menopause	27 (67.5%)	6 (46.2%)	33 (62.3%)
Post-menopause	13 (32.5%)	7 (53.8%)	20 (37.7%)
Chemotherapy			
Yes	34 (85%)	8 (61.5%)	42 (79.25%)
No	6 (15%)	5 (38.5%)	11 (20.75%
Hormonal therapy			
Yes	32 (80%)	8 (61.5%)	40 (75.5%)
No	8 (20%)	5 (38.5%)	13 (24.5%)

Abbreviations: LN: Lymph nodes, IDC: Intraductal carcinoma, ER: Estrogen receptors, PR: Progestron receptors, PMRT: Postmastectomy radiotherapy.

Table (2): Univariate analysis of factors affecting CSS of all patients (53 patients).

	HR (95% CI)	*p*-value
Age		0.9154
Tumor size	1.49 (0.40-5.54)	0.0213 *
LN number		0.0748
Pathologic type		0.2444
Grade	0.73 (0.19-2.81)	0.0095 *
ER/PR status	0.79 (0.21-3.02)	0.0055 *
Menstrual status		0.8760
PMRT		0.1134
Adjuvant CT		0.3155
Adjuvant Hormonal therapy	1.80 (0.48-6.81)	0.0146 *
HR (95% CI): Hazard ratio (95% Confidence interval) * P significant <0.05		

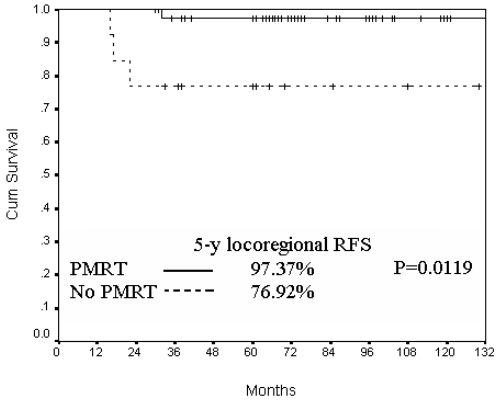

Fig. 1: Five-year loco-regional-RFS for the whole group according to radiation therapy.

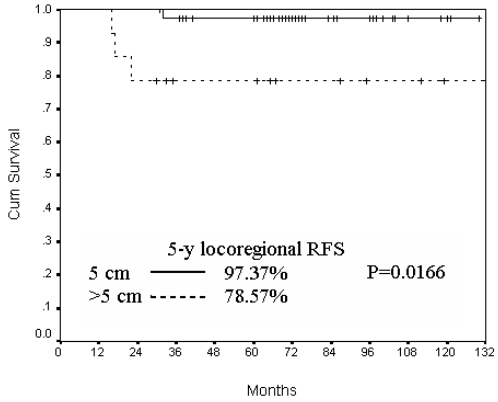

Fig. 2: Five-year loco-regional-RFS rate for the whole group according to tumor size.

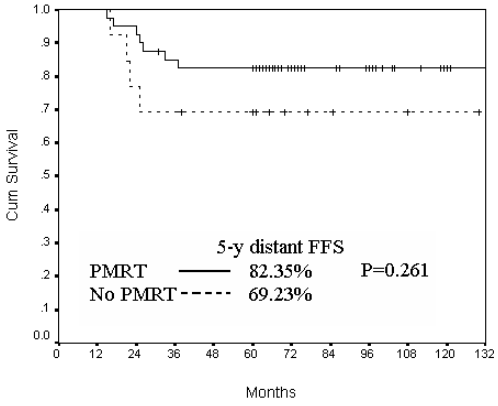

Fig. 3: Five-year distant-FFS rate for the whole group according to radiation therapy.

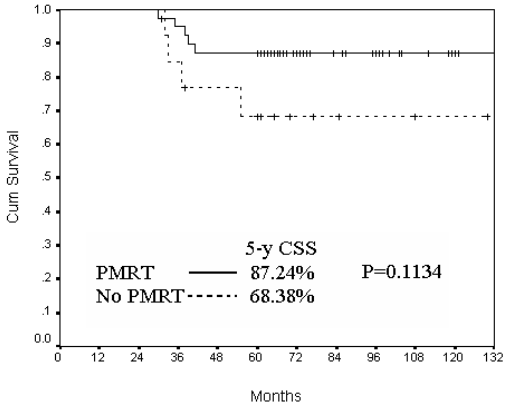

Fig. 4: Five-years CSS rate for the whole group according to radiation therapy.

The 5-year CSS, locoregional-RFS and distant-FFS rates for the whole studied patients were 82.59%, 92.37% and 79.16%, respectively.

Median lococoregional recurrence free survival was 72 months (range 16-132 months). The median time to development of locoregional recurrence was 21.8 months (range 16-32 months). Median distant failure free survival was 70.4 months (range 15-132) with the median time to development of distant metastases was 23.7 months (range 15-37 months).

At the time of cancer failure, distant failure only were diagnosed in 9 patients (17%), local recurrence only in 2 patients (3.78%), and 2 (3.78%) patients had both locoregional and distant metastases. Three

patients out of the 4 locoregional recurrences were located in the chest wall and the remaining one in the ipsilateral axilla. There was no supraclavicular nodal recurrence.

Three (23.08%) of the 13 patients who didn't receive PMRT have been developed locoregional recurrence. Two of them had recurrence in the chest wall and one in the axilla who had only 6 nodes examined at the axillary staging. On the other hand, only one out of 40 patients who received PMRT had locoregional recurrence in the chest wall. The estimated 5-year locoregional-RFS rate for no-PMRT group versus PMRT group was 76.92% versus 97.37%, the difference was statistically significant (p=0.0119). (Fig. 1)

Among 39 patients with tumor size equal to 5 cm, there is one patient had locoregional failures during the study period while the other 3 local failures had occurred in the group of patients (14 patients) with tumors size greater than 5 cm. The locoregional-RFS rate was 97.37% versus 78.57%, respectively and this differences was statistically significant (p=0.0166). (Fig. 2)

All the 4 patients with local recurrence were salvaged with surgical treatment at the time of local recurrence, three of them also received combined radiation to a dose of 50 Gy and chemotherapy and the remaining one patient treated with hormonal therapy. Among these 4 patients, two patients was locally controlled and alive without evidence of disease and the other 2 patients died with distant metastatic disease.

The estimated 5-year distant-FFS rate for no-PMRT group versus PMRT group was 69.23% versus 82.35%, the difference was not statistically significant (p=0.2610). (Fig. 3)

The median CSS was 74.7 months (range 30-132) for the all series, 77.7 months for the PMRT group, and 65.5 months for the no PMRT group. At the time of analysis 73.58% of patients recorded as alive. Fourteen (26.42%) patients were died, 9 patients from breast cancer and 5 from an intercurrent cause. The 5-year Kaplan-Meier CSS estimate was 68.38% in the no-PMRT group and 87.24% in the PMRT group, the difference was not statistically significant (p=0.1134). (Fig. 4)

A univariate analysis was performed to estimate the contribution of the patient, tumor, and treatment variables (patients age, the number of removed axillary nodes, tumor size, pathologic type, histological grade, the hormone receptor status, menstrual status, PMRT, or systemic therapy) as risk factors for CSS (Table 2). Tumor size 5 cm (p=0.0213), low tumor grade (p=0.0095), hormonal receptors positive (p=0.0055) and hormonal therapy (p=0.0146) were associated with significantly improved CSS.

4. Discussion

Large breast tumors that present without the involvement of regional LNs may be a distinct clinical and biologic entity. It is possible that the inability of these tumors to spread to regional nodes despite their ability to grow to large size may indicate a more indolent biologic nature. This clinical presentation is clear in contrast to the one in which small tumors have already spread to regional LNs and/or distant sites at the time of clinical presentation. The study of biologic differences and gene fingerprinting between these extremes of tumor presentation may help in the understanding of the nature of the invasive and metastatic potential of breast tumors and in the identification of patients who would benefit from PMRT. It is possible that the genetic characteristics of these tumors could define a benign tumor that grows locally without invasion of lymphatics.[19, 20]

Little information on the value of PMRT in breast cancer with large tumor size (≥5cm) is available in the literature. Accordingly, the existing data concerning the outcome and prognosis of patients in this category are limited, complicating evidence-based clinical decisions. The clinical situation of PMRT in pT3N0 breast cancer usually categorized together either with T4 cancers or axillary LNs positive cancers, and a very separate analysis is available.[3]

Three large clinical trials published in the late 1990s supported the use of PMRT in select, high-risk patients.[5-7]. In 2001, an American Society of Clinical Oncology (ASCO) expert panel published guidelines for the application of PMRT, and it was 'suggested' that patients with T3N0 disease receive PMRT.[10] Furthermore, guidelines published by the National Comprehensive Cancer Network (NCCN) recommend PMRT in patients with T3N0 disease.[21] In practice, nearly 90% of radiation oncologists in North America and Europe recommend PMRT in the setting of T3N0 disease.[11] Contrary to these guidelines and practice patterns, multiple retrospective series focusing on patients with T3N0 disease have suggested a high rate of locoregional control in the absence of PMRT, suggesting that large tumor size alone does not significantly increase the risk of locoregional recurrence.[3, 14, 22, 23] Furthermore, a meta-analysis performed by the Early Breast Cancer Trialists' Cooperative Group demonstrated a small local control benefit of PMRT in node negative patients, which did not translate into a CSS benefit.[24]

The study we carried out was designed to contribute to the base of clinical decision-making knowledge about the use of PMRT in node-negative patients with large tumors. We found 53 patients with tumors equal to or larger than 5 cm among 1120 patients presented to our department during the study period from January, 1997 to December, 2008, representing 4.7% of all breast cancers. The incidence of such clinical situation ranging from 0.5–4% had recorded in large published datasets of breast tumors.[3, 4, 14, 25, 26] The low incidence of large tumors sizes breast cancers is perhaps a reflection of the fact that these large datasets come from a more modern treatment era in industrialized nations where mammographic screening is commonplace. In older datasets, large breast tumors were observed more commonly, and proportionately, T3N0 tumors were better represented.[27-29]

In this study 13 patients were not given PMRT in spite of the large size of the primary tumor, and as many as 23.08% of these 13 patients developed a locoregional recurrence, whereas only 2.50% of the 40 patients who were treated with PMRT had recurred locally. Also, the estimated 5-years locoregional-RFS rate for no-PMRT group versus PMRT group was 76.92% versus 97.37%, the difference was statistically significant (p=0.0119). This suggests that patients with large tumor size (≥5cm) of breast cancer could be benefit from PMRT. This conclusion is supported by a subset data from a large number of studies. **Helinto *et al.***[3] compared 33 patients with pT3 >5 cm N0 breast cancer treated with PMRT and 5 patients treated without PMRT. The LRR rate was significantly lower in the PMRT group than in the no-PMRT group (9% vs. 40%). In another series of 70 patients with pT2 = 5 cm N0 and pT3 >5 cm N0 breast cancer treated without PMRT, **Floyd *et al.***[14] reported a 5-years cumulative LRR rate of 7.6%, with a median follow-up of 7 years. **Taghian *et al.***[22] studied a cohort of 313 patients with pT2 = 5 N0 and pT3 >5 cm N0 tumors and found a similarly low 10-year LRR rate of 7%.

In our study, 3 of 4 locoregionally recurrent patients developed a recurrence on the chest wall. **Fowble *et al.***, found that, the most common site for a locoregional recurrence was the surgical scar representing 40% of all locorecional recurrences.[30] Also, **Floyd *et al.***[14] and **Taghian *et al.***[22] had recorded that, most of the locoregional recurrences had developed on the chest wall (24/28 and 4/5 patients in both studies respectively). On the other hand, in a study by **Mignano *et al.***[23], among 101 patients with T3N0 disease, the locoregional recurrence was more likely to be in the axilla (6/11). However, as chest wall was the most common site of locoregional recurrences it may be reasonable to consider treating the chest wall only, without radiating the regional LNs, in subsets of patients thought to be at higher risk, thereby minimizing the adverse effects of PMRT.

Our results show that there was statistically significant distinction between patients with tumor size equal to 5 cm and patients with tumor size greater than 5 cm in locoregional–RFS rate (p=0.0166). (Fig. 2) All local failures occurred in the subgroup with tumors greater than 5 cm. Although the difference in locoregional–RFS rate between these two groups reaches statistical significance, we must point out that the number of patients in each of these subgroups and the total number of events was small. Larger groups of patients are needed to more thoroughly investigate the possible differences between large T2 tumors and T3 tumors.

In present study the median number of the dissected axillary LNs was 13 nodes, moreover only one patient had regional failure among all series. Axillary node dissection gives excellent regional control with axillary recurrence rates of 1–3% reported in most series in patients with node negative breast cancer.[31–33] **Vujovic *et al.***, recorded that, the number of axillary nodes removed in node negative breast cancer predicts for regional recurrence, with less than six axillary nodes removed associated with significantly higher regional nodal recurrence. **Fisher *et al.***, reported that axillary nodal recurrences are relatively uncommon after dissection of the axilla, especially when 10 or more axillary LNs have been removed. This may have clinical implications with the current practice of sentinel node biopsy replacing axillary node dissection in node negative breast cancer.[34, 35]

In the present study, univariate analysis of the previously mentioned patients, tumor, and treatment risk factors revealed that, tumor size (HR, 1.49; p=0.0213), tumor grade (HR, 0.73; p=0.0095), hormonal receptors status (HR, 0.79; p=0.0055) and hormonal therapy (HR, 1.80; p=0.0146) were associated with improved CSS rate.

Goulart *et al.*[15] reported that, by univariate analysis, tumor size >5 cm and hormonal therapy use were statistically significant variables predicting for improved BCSS. However, on multivariate analysis, only tumor size >5 cm was significant.

Two recent investigations of PMRT in T3N0 tumors had been also reported using SEER database data.[13, 36] Although SEER data does not report local recurrence; overall and cause-specific survival data are reported for patients who did or did not receive PMRT. In the study from Yale University, 1777 T3N0 patients were identified, with 568 receiving PMRT. Results for CSS and overall survival were analyzed. For overall survival, a significant increase

was observed for patients receiving radiotherapy on univariate analysis, however, this difference was not observed on multivariate analysis. Additionally, no difference was observed in CSS. Interestingly, tumor size was not a significant factor for any outcome measure. In the study from the University of Colorado, 1865 T3N0 tumors were identified from SEER data, with 623 receiving PMRT. In this study, radiotherapy had no effect on CSS, however, a statistically significant difference on overall survival was found on both univariate (71% vs. 58% $p<0.01$) and multivariate (HR 0.69, $p<0.01$) analyses.

In conclusion, the CSS, locoregional-RFS and distant-FFS rates were better in LNs negative breast cancer patients with large tumor size (≥5cm) who received PMRT. Also, tumor size pT2=5 cm, low tumor grade, hormonal receptors positive and hormonal therapy administration were associated with improved CSS.

These data should be interpreted with caution because of the small number of patients and events and because pathologic features that are associated with adverse outcome, such as lymphovascular or perineural invasion,[37] not available. Moreover, the patients files does not contain information regarding surgical margin status, this imbalance in prognostic factors masks a favorable impact of PMRT. An important factor that must be weighed in making any clinical decision about local therapy is the adequacy of LNs dissection, as this allows confidence in the determination that a tumor is truly node-negative, and therefore could fall into the rare category of large tumors with low metastatic potential described above. Complicating this determination are changes in clinical practice, as many of these patients now receive chemotherapy as initial treatment, potentially obscuring interpretation of axillary LNs status. The risk for local recurrence both in the chest wall and regional nodal areas should be assessed in light of the entirety of larger amount of data, and treatment decisions regarding irradiation of the chest wall and nodal areas must be made on an individual basis.

Corresponding author:
Alaa Mohamed Maria, MD.
Clinical Oncology Department, Faculty of Medicine, Tanta University, Al Gaish St., Tanta 11312, Gharbia, Egypt.
alaamaria1@hotmail.com

5. References

1. Elatar I. (2002): Cancer registration, NCI Egypt 2001. Cairo, Egypt, National Cancer Institute.
2. Ibrahim AS., Seif-Eldin IA., Ismail K., *et al.* (2007): Cancer in Egypt, Gharbiah: Triennial report of 2000-2002, Gharbiah population based cancer registry. Ministry of Health & Population Egypt and Middle East Cancer Consortium.
3. Helinto M., Blomqvist C., Heikkila P., *et al.* (1999): Post-mastectomy radiotherapy in pT3N0M0 breast cancer: Is it needed? Radiother Oncol., 52: 213–217.
4. Wallgren A., Bonetti M., Gelber RD., *et al.* (2003): Risk factors for locoregional recurrence among breast cancer patients: Results from International Breast Cancer Study Group trials I through VII. J Clin Oncol., 21: 1205-1213.
5. Ragaz J., Jackson SM., Le N., *et al.* (1997): Adjuvant radiotherapy and chemotherapy in node-positive women with breast cancer. N Engl J Med., 337:956-962.
6. Overgaard M., Hansen PS., Overgaard J., *et al.* (1997): Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N Engl J Med., 337: 949-955.
7. Overgaard M., Jensen MB., Overgaard J., *et al.* (1999): Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomized trial. Lancet, 353: 1641-1648.
8. Cuzick J., Stewart H., Peto R., *et al.* (1987): Overview of randomized trials comparing radical mastectomy without radiation therapy against simple mastectomy with radiation therapy in breast cancer. Cancer Treat Rep., 71: 7-14.
9. Whelan TJ., Julian J., Wright J., *et al.* (2000): Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. J Clin Oncol., 18: 1220-1229.
10. Recht A., Edge SB., Solin LJ., *et al.* (2001): Postmastectomy radiotherapy: Clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol., 19:1539–1569.
11. Ceilley E., Jagsi R., Goldberg S., *et al.* (2005): Radiotherapy for invasive breast cancer in North America and Europe: results of a survey. Int J Radiat Oncol Biol Phys., 61: 365-373.
12. Carlson RW., Anderson BO. & Burstein HJ. (2010): NCCN Breast Cancer Clinical Practice Guidelines in Oncology, version 1. Available from: http://www.nccn.org.
13. McCammon R., Finlayson C., Schwer A., *et al.* (2008): Impact of postmastectomy radiotherapy in T3N0 invasive carcinoma of the breast: A Surveillance, Epidemiology, and End Results database analysis. Cancer, 113: 683–689.
14. Floyd SR., Buchholz TA., Haffty BG., *et al.* (2006): Low local recurrence rate without postmastectomy radiation in node-negative breast

cancer patients with tumors 5 cm and larger. Int J Radiat Oncol Biol Phys., 66:358–364.
15. Goulart J., Truong P., Woods R., *et al.* (2011): Outcomes of node-negative breast cancer 5 centimeters and larger treated with and without postmastectomy radiotherapy. Int J Radiat Oncol Biol Phys., 80: 758–764.
16. Cox DR. (1972): Regression models and life-tables. J R Stat Soc., 34:187-202.
17. Kaplan EL. & Meier P. (1958): Nonparametric estimation from incomplete observations. J Am Stat Assoc., 53: 457– 481.
18. Mantel N. (1966): Evaluation of survival data and 2 new rank order statistics arising in its consideration. Cancer Chemother Rep., 50: 163-170.
19. Paik S., Shak S., Tang G., *et al.* (2004): A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med., 351: 2817-2826.
20. Floyd SR. & Taghian AG. (2009): Systematic review. Post-mastectomy radiation in large node-negative breast tumors: Does size really matter? Radiotherapy and Oncology, 91: 33–37.
21. National Comprehensive Cancer Network (2007): NCCN Guidelines, version 2. 2007. Available at: http://www.nccn.org. Accessed September 24, 2007.
22. Taghian AG., Jeong JH., Mamounas EP., *et al.* (2006): Low locoregional recurrence rate among node-negative breast cancer patients with tumors 5 cm or larger treated by mastectomy, with or without adjuvant systemic therapy and without radiotherapy: Results from five National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. J Clin Oncol., 24: 3927–3932.
23. Mignano JE., Gage I., Piantadosi S., Ye X., Henderson G. & Dooley WC. (2007): Local recurrence after mastectomy in patients with T3pN0 breast carcinoma treated without postoperative radiation therapy. Am J Clin Oncol., 30: 466-472.
24. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2000): Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomized trails. Lancet, 355: 1757-1770.
25. Katz A., Strom EA., Buchholz TA., *et al.* (2000): Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: implications for postoperative irradiation. J Clin Oncol., 18: 2817–27.
26. Trudeau ME., Pritchard KI., Chapman JA., *et al.* (2005): Prognostic factors affecting the natural history of node-negative breast cancer. Breast Cancer Res Treat., 89: 35–45.
27. Ragaz J. & Spinelli JJ. (1999): Large breast cancer tumors and radiotherapy: biology vs chronology. Radiother Oncol., 52: 203–5.
28. Klefstrom P., Grohn P., Heinonen E., *et al.* (1987): Adjuvant postoperative radiotherapy, chemotherapy, and immunotherapy in stage III breast cancer. II. 5-year results and influence of levamisole. Cancer, 60: 936–42.
29. Fracchia AA., Evans JF. & Eisenberg BL. (1980): Stage III carcinoma of the breast. A detailed analysis. Ann Surg., 192: 705–10.
30. Fowble B. (1997): Postmastectomy radiation: then and now. Oncology, 11: 213-239.
31. Fisher B., Redmond C., Fisher ER., *et al.* (1985): Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med., 312: 674–81.
32. Delouche G., Bachelot F., Premont M., *et al.* (1987): Conservative treatment of early breast cancer: long-term results and complications. Int J Radiat Oncol Biol Phys., 13: 29–34.
33. Recht A., Pierce SM., Abner A., *et al.* (1991): Regional nodal failure after conservative surgery and radiotherapy for early-stage breast carcinoma. J Clin Oncol., 9: 988–96.
34. Vujovic O., Yu E., Cherian A., *et al.* (2009): The number of axillary nodes removed as a predictor of regional recurrence in node negative breast cancer. Radiotherapy and Oncology, 91: 38–41.
35. Fisher B., Wolmark N., Bauer M., Redmond C. & Gebhardt M. (1981): The accuracy of clinical nodal staging and of limited axillary dissection as a determinant of histologic nodal status in carcinoma of the breast. Surg Gynecol Obstet., 152: 765-772.
36. Yu JB., Wilson LD., Dasgupta T., *et al.* (2008): Postmastectomy radiation therapy for lymph node-negative, locally advanced breast cancer after modified radical mastectomy: analysis of the NCI surveillance, epidemiology, and end results database. Cancer, 113: 38–47.
37. Barth A., Craig PH. & Silverstein MJ. (1997): Predictors of axillary node metastases in patients with T1 breast carcinoma. Cancer, 79: 1918-1922.

3/1/2012