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Evaluation of the Role of Postmastectomy Radiotherapy in Women with One to Three Positive Auxillary Nodes with Extracapsular Invasion

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Abstract: ***Background: There is insufficient evidence to suggest the routine use of postmastectomy radiotherapy (PMRT) in women with T1-T2 breast carcinoma and 1-3 positive lymph nodes with extracapsular invasion (ECI). Purpose: To determine whether PMRT after adjuvant chemotherapy will reduce the risk of loco-regional recurrence (LRR) and thus improve survival, in this group of patients. Patients and methods: Between May 2010 and December 2015, 64 women with pathologic T1-T2 breast carcinoma and 1-3 positive nodes with ECI, and who had undergone modified radical mastectomy and received adjuvant chemotherapy, were randomized to PMRT (group A, n=32) or no adjuvant radiotherapy (group B, n=32). Loco-regional radiotherapy schedule was 50 Gy in 25 fractions over 5 weeks. The median Follow-up period was 50 months (range, 35-66). Results: The two treatment groups were well balanced with respect to the known prognostic factors. Out of 64 patients, 53% were < 45 years, 75% had more than one positive node with ECI 56% had stage T2, 61% had lymphovascular invasion, 31% were negative estrogen receptor and 23% had histologic grade 3. LRR rates were 12.5% and 25% of patients in group A and group B, respectively (P < 0.05). The estimated 5-year disease free survival rates were 81% and 68% of patients in group A and group B, respectively (P > 0.05). The 5-year overall survival rates were 96% and 93% of patients in group A and group B, respectively (P > 0.05). Univariate analysis failed to show any impact of prognostic factors on local recurrence free survival, distant metastasis free survival or overall survival. Three patients in group A and one in group B developed grade-3 lymphedema. None of the patients have developed radiation pneumonitis, brachial plexopathy or cardiac events. Conclusion: In women with T1-T2 breast carcinoma and 1-3 positive lymph nodes with ECI, significantly lower LRR was observed with PMRT than without adjuvant radiotherapy. Further trials with a larger number of patients and longer follow-up periods are needed to optimize loco-regional control and potentially improve survival in this group of patients.***

Keywords: Breast cancer, Post-mastectomy radiotherapy, 1-3 positive nodes, Extracapsular invasion

1. Introduction

Breast cancer is the most common cancer and the leading cause of death from cancer among women worldwide **(1)**. Loco-regional recurrence (LRR) after mastectomy is not only a substantial clinical problem, but has a significant impact on the outcome **(1, 2, 3)**. Randomized trials have refined the opinion that better loco-regional control may decrease the risk of secondary dissemination and improve overall survival. PMRT has traditionally been given to selected patients considered at high risk for local-regional failure. PMRT can decrease LRR in this group, even among those patients who receive adjuvant chemotherapy. Patients at highest risk for LRR include those with four or more positive axillary nodes, large primary tumors, and very close or positive deep margins of resection of the primary tumor. Patients with one to three involved nodes without any of the previously noted risk factors are at low risk of local recurrence, and the value of routine use of PMRT in this setting has been unclear **(4, 5, 6, 7, 8)**. Extracapsular invasion (ECI) of lymph node metastases is a well known predictive and prognostic factor in many malignant solid tumors and demands additive irradiation **(9)**. The importance of ECI of axillary metastases as a risk factor for both local or distant recurrence and poorer survival in breast cancer has been suggested, but its prognostic value has not been uniformly confirmed **(10, 11, 12)**. The frequency of ECI was in accordance with the number of positive nodes: 40.9 % with one and 57.6% with two to three positive nodes. Also, ECI of 84.2% was found in lymph nodes with a diameter > 2 cm. It seems quite understandable that the frequency of ECI goes parallel to the number of involved lymph nodes ; the higher their number, the more ECI may lose its presumed independent prognostic character towards the higher number of positive lymph nodes **(12, 13, 14, 15)**. If ECI in a small number of positive lymph nodes becomes an independent prognostic factor, it is allowed to suggest that the number of involved nodes loses its independence at all against the parameter of the finding of ECI **(16, 17, 18, 19, 20, 21)**. This study was carried out at Zagazig University Hospitals and Fakous Cancer Center to determine whether PMRT after adjuvant chemotherapy will reduce the risk of LRR and thus improve survival, in women with T1-T2 breast carcinoma and 1-3 positive lymph nodes with ECI.

2. Patients and Methods

Between May 2010 and December 2015, 64 women with histologically confirmed carcinoma of the breast with primary tumor ≤ 5 cm and 1-3 positive axillary nodes with ECI, and who had undergone modified radical mastectomy and received adjuvant chemotherapy were included in this study. A minimum of 10 nodes must have been removed and pathologically examined. Patients must not have received prior chest wall or nodal radiotherapy. Pretreatment evaluation included; patient history and clinical examination, chest-x-ray, contralateral mammography, ultrasonography of the liver, bone scintigraphy, blood tests and computed tomography of the thorax. Patients were randomized into two groups:Group (A): Included 32 Patients who received 3 D Conformal PMRT. Group (B): Included 32 Patients who received no adjuvant radiotherapy. Radiotherapy started within 6 weeks of completing adjuvant chemotherapy. Radiotherapy schedule was 50 Gy in 2-Gy

fractions over 5 weeks to the chest wall, and the supraclavicular fossa with the internal mammary lymph nodes. Treatment was given by linear accelerator machine (Linac, Elekta 151204, precise plan, release 2.12, 477.08). **Radiotherapy techniques:** the patient lied comfortably on breast board with putting patient head on small head rest adjusted to small graded holes, ensured proper elevation of surface of the body in parallelism with the surface of the couch, and rotation of the head to opposite side with arm elevation, patient can catch A or B or C arms in comfortable tolerated manner as much as possible and with abduction slight rotated of the arm. Patient must be centralized on the simulator, laser alignment was applied and tattooing of the patient was done to create X, Y and Z points (references) with lead marks on them in imaging process. Measurement of tanges separation in supine position. Multislice CT every 0.3-0.5cm on same simulated position. Created CD was applied to allow reading, reconstruction and contouring saving each patient data on the computerized planning system. **Target volume definition:** the clinical target volume (CTV) comprised of the entire chest wall (skin surface to rib –soft tissue interface) extending from the anterior midline to the mid-axillary line. Superior and inferior margins to the PTV were at the sternal notch and 2 cm below the inframammary fold (or overlapping breast tissue), respectively. Posterior margins of the CTV exclude pectoralis muscles, chest wall muscles, ribs. internal mammary nodes are typically included, **Supraclavicular region**: contouring of the supraclavicular region was guided by the origin of the internal mammary artery.Cranial: Thyroid cartilage, Caudal: Clavicular head, Medial (med): Trachea, Posterior (post)-lateral (lat): Anterior scalene muscle, and Post-med: Carotid artery. **Organs at risk and DVH:**Lung: V20 <15%, V30<10%.Heart : <35 Gy to the heart. Spinal cord : <45Gy, Esophagus: maximum 40 GY in 15 cm, Larynx: <20Gy The dose reaching the heart should be minimized by shielding the heart using MLC without interference with the target coverage. Prescription isodose covered at least 95% of the planned target volume (PTV), no more than 20% should receive > 110% of the prescribed dose, no more than 1% should receive < 93% of the prescribed dose, no more than 1% of normal tissue outside the PTV should receive > 110% of the prescribed dose:. Patients were evaluated weekly during treatment, monthly for 6 months after completion of radiotherapy, every 3 months for 2 years and every 6 months thereafter. LRR was defined as any relapse in the area of surgery between the sternum and anterior axillary line, and below the infraclavicular fossa and above the 7th rib. Any tumor recurrences at one of the pectoralis muscles or at the fascias of the serratus lateralis muscle or the oblique externus muscle were also defined as local recurrence. Any relapse infiltrating the skin and/or involving the axillary lymph nodes or the metastatic infiltration of the nodules in the infra or supraclavicular fossa was considered a regional recurrence. Any tumor outside these areas was defined as distant metastasis. The overall survival, local-recurrence-free survival, distant-metastasis-free survival and disease-free survival rates were calculated from the date of surgery until the date of death or up to the last follow-up, the date of the local recurrence or up to the last follow-up, the date of the distant metastasis or up to the last follow-up, and the date of the first relapse or up to the last follow-up, respectively. Radiotherapy related toxicity was assessed according to the Radiation Therapy Oncology Group (RTOG) scoring criteria. For statistical analysis, the computer software statistical package for the social sciences 8.0 (SPSS Inc., Chicago, USA), was used. The survival analysis was estimated by the Kaplan-Meier method and using the log-rank test to compare between survival curves. The Pearson X2 test was applied in cross tables. The influence of prognostic factors (age, no. of positive nodes, tumor size, lymphovascular invasion, histologic grade, hormone receptor status and radiotherapy) on LRR and the survival rate was evaluated using the Cox regression model. Statistical significance was assumed, when the P-value of the appropriate test was less than 0.05.

3. Results

Patient characteristics in both groups are given in table (1). No significant difference could be seen between the two treatment groups regarding; age, menopausal status, no. of positive nodes with ECI, T-stage, histological grade, hormonal receptors status, tumor necrosis, and lymphovascular invasion (LVI). Out of 64 patients, 53% were 45 years, 75% had more than one positive node, 56% had stage T2, 61% had LVI, 31% were negative estrogen receptor and 23% had histologic grade 3. At a median follow-up duration of 50 months (range, 35-66), 48 patients (75%) were free of tumor recurrence. Table (2) shows the number of local, regional, and distant failures as the first event in both groups. The frequencies of isolated LRR were 12.5% (4/32) in group A and 25% (8/32) in group B with a statistical significant difference between both groups ($P < 0.05$). In group (B) one isolated local recurrence occurred in 32 patients representing 3.12% of cases and none in group (A). There was no isolated regional failure in group (A), while 3 patients in group B suffered a relapse in the axillary and subclavian regions. In PMRT group (A), 15.6% of patients developed distant metastasis versus 18.8% in group B with no statistically significant difference. The LRR rate in combination with distant metastases was 9.37% (3/32) in group A versus 12, 5% (4/32) in group B. The estimated 5-year disease free survival rates were 81% and 68% of patients in group A and group B, respectively ($P < 0.05$, Fig. 1). One patient in group A and two patients in group B died of their disease representing 3.12% and 6.25% respectively. The estimated 5-year overall survival rates were 96% and 93% of patients in group A and group B respectively ($P > 0.05$, Fig. 2). Univariate analysis failed to show any impact of prognostic factors (age, no. of positive nodes with ECI, T-stage, histologic grade, estrogen receptor status, tumor necrosis, LVI, tumor necrosis) on local recurrence free survival [LRFS), distant metastases free survival (DMFS), or overall survival (OS) (Table 3). Acute radiotherapy related toxicity was mainly skin reactions and mild to moderate in severity. Three patients in group A and one in group B developed grade 3 lymphedema.

Table 1: Patients characteristics in two treatment groups

Characteristic	Group A (n=32)		Group B (n=32)		P value
	No. %		No. %		
Age					
≤ 45	18	56.2	16	50	
>45	14	43.8	16	50	
Menopausal status					
Premenopausal	21	65.6	23	71.8	
postmenopausal	11	34.4	9	28.2	
Positive nodes with extracapsular invasion ECI					
1	7	21.9	9	28.2	
2	14	43.6	16	50	
3	11	34.4	7	21.9	
T-stage					
T1	13	40.6	17	46.9	
T2	19	59.4	15	53.1	
Tumor grade					<0.05
G1	3	9.4	6	18.8	
G2	19	59.4	21	65.6	
G3	10	31.3	5	15.6	
Receptor status					
R-	9	28.2	11	34.4	
R+	23	71.8	21	65.6	
PR-	15	46.9	18	56.2	
PR+	17	53.1	14	43.8	
Tumor necrosis					
YES	13	40.6	15	46.9	
NO	19	59.4	17	53.1	
Lymphovascular invasion LVI					
Yes	21	65.6	18	56.2	
No	11	34.4	14	43.8	

Abbreviations: ECI; extracapsular invasion, LVI; lymphovascular invasion, ER; estrogen receptors, PR; proestrogen receptors.

Table 2: Pattern of relapse as first event in the two treatment groups.

Character	Group A (n=32)		Group B (n=32)		P-value
	No. %		No. %		
Local only	0	-	1	3.12	
Locak+regional	1	3.12	0	-	
Local+regional+distant	1	3.12	2	6.25	
Local+distant	1	3.12	1	3.12	
Regional only	0	-	3	9.37	
Regional+distant	1	3.12	1	3.12	
All regional	4	12.5	8	25	<0.05
Distant only	2	6.25	2	6.25	
All distant	5	15.6	6	18.8	

Table 3: Univariate analysis for LRFS, DMFS and OS in both groups.

Parameter	*LRFS P-Value*	*DMFR P-Value*	*OS P-value*
Age(≤45 Vs >45)	0.506	0.522	0.627
T-Stage			
I	0.823	0.799	0.728
II	0.064	0.625	0.567
Positive lymph node(s)			
1	0.073	0.427	0.582
2	0.625	0.538	0.732
3	0.711	0.621	0.611
LVI(yes Vs no)	0.093	0.082	0.079
ER(+ Vs-)	0.0522	0.682	0.634
Grade (2 Vs 3)	0.413	0.318	0.421
Necrosis (yes Vs no)	0.863	0.726	0.679

LVI; Lymphatic Vessel Invasion, ER; Estrogen Receptors, LRFS; Local recurrence free survival, DMFS; Distant metastasis free survival, OS; Overall survival

Table 4: Treatment morbidity in both groups.

Morbidity	Group A No. %		Group B No. %	
Lymphedema	3	9.37	1	3.12
Erythema	8	25	-	-
Tetangectasia	-	-	-	-
Hyperpigmentation	2	6.25	-	-

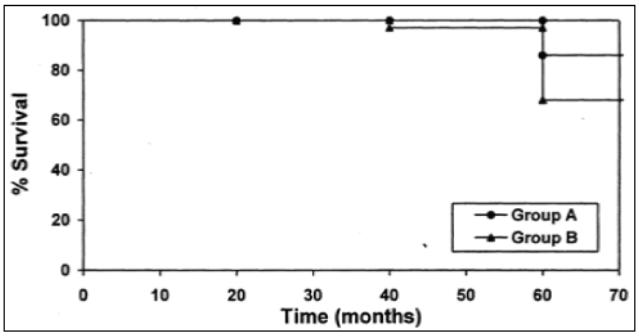

Figure 1: Local recurrence free survival (LRFS)

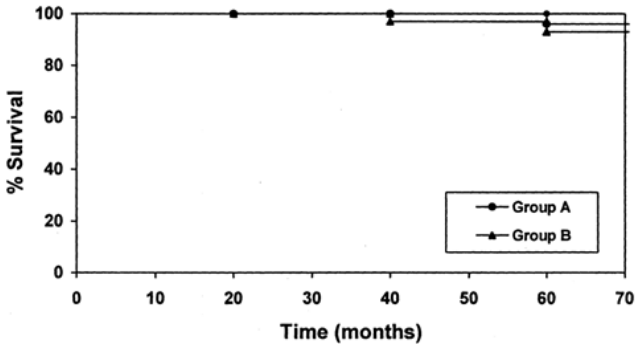

Figure 2: Overall survival in two treatment groups

4. Discussion

The finding of extra nodal invasion is frequent but is presumably dependent on the extent of examination and especially on the question of the investigator. This may explain the large differences in extracapsular invasion rates in literature **(1)**. Most series revealed extracapsular invasion rates in the rang of 24-50% **(2, 3, 4, 5). Veronesi et al. (9) R**eported on 539 patients whose 3, 259 metastatic axillary nodes were investigated prospectively and very carefully : 1, 957 (60%) showed an extracapsular invasion. The frequency of extracapsular invasion was in accordance with the number of positive lymph nodes : 40.9% with one, 57.6% with two to three, and 47.2% with more than three axillary metastases **(9)**. If extracapsular invasion in a small number of positive lymph nodes becomes an independent prognostic factor, it is allowed to suggest that the number of involved LN loses its independence at all against the parameter of the finding of extra nodal invasion **(26)**. First reports which found a correlation of extracapsular invasion with decreased

survival were published in 1976/1977 **(8, 18)**. These results have mean while been confirmed by several studies**(2, 3, 8, 23, 25)** with 50-61% OS rates in these series. While **Gruber et al. (1)** found a comparable results of OS rate of 61% at 5 years. in the study groups.Despite this knowledge of extracapsular invasion as negative prognostic factor, there is surprisingly, no prospective randomized study evaluating adjuvant therapy in the presence of this parameter. Few publications**(2, 4, 5, 8, 23, 15)** mentioned patients with extracapsular invasion treated with loco regional radiotherapy, but only, two retrospective studies **(2, 8)** compared the results of irradiated against un-irradiated patients with extra nodal invasion of their involved axillary lymph nodes. Similar to our results, there was no significant difference in the survival curves of both groups **(2, 8).** In our study the estimated 5-year overall survival was 96.6% and 93.7% for both groups A & B respectively, with no statistical significant difference. While the results of the British Columbia trial **(25)**, an absolute gain in overall survival of 20% (51% vs 31%) was reached in patients with extracapsular invasion and adjuvant CMF alone. Additional loco regional radiotherapy had its highest positive influence on the survival rate in patients with less than four axillary metastases and extracapsular invasion. In the absence of extra capsular invasion, loco regional radiotherapy failed to result in a significant improved outcome **(25)**. The Danish trials showed a 14-year OS of 35% with radiation therapy versus 22% without radiation therapy in the case of lymph node capsule invasion ($P < 0.0001$) **(12).** Univariate analysis of our results revealed no statistical significant difference regarding the number of positive lymph nodes, T-stage, LVI, hormone receptor status, age and grade of tumor. Similar results were obtained by **Gruba et al. (1)**. In this study, there was a statistical significant difference in loco regional failure between both groups 12.5% in group A versus 25% in group B, ($P = 0.045$), while DFS and DMFS showed no statistical significant difference between both groups Fig 2, table (2). A similar results were reported by I **Lknur et al. (26)**, **Gruber et al. (1), and Fodor et al.(22).** They concluded that, patients with T1 tumor and one to three positive nodes are at low risk for isolated locoregional recurrence (LRR) either with or without radiation therapy, while patients with T**2** tumor and one to three positive axillary lymph nodes are at high risk of isolated locoregional recurrence without radiotherapy. According to a consensus statement on post matectomy radiation therapy **(10)**, the chest wall should be irradiated in all patients and the inclusion of axillary apex and subclavian area is appropriate for selected node-positive cases particularly those with four or more positive nodes. We see the finding of extranodal invasion in involved axillary nodes at least of similar importance as the finding of more than three involved lymph nodes and recommend the same treatment volume (locoregional) for these patients, namely chest wall and subclavian area as for patients with more than 3 lymph node metastases.

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