Post Mastectomy Radiotherapy for High Risk T1-T2N0 Breast Cancer …. Does it Make Difference?

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Abstract:

Background: Early breast cancer cases usually have good prognosis and long-term survival. but a subgroup of them develop locoregional failure. Studying those cases have shown that they have multiple risk factors such as tumor site and size, menopausal and hormonal status, also presence or absence of lymphovascular invasion (LVI). Many radiotherapists still confused about giving adjuvant radiotherapy to that group of patients. This study seeks to document our experience about detecting the high-risk factors for local failure in T1-T2 N0 breast cancer cases after mastectomy. Also, to identify if this subgroup could have a benefit from post mastectomy radiation therapy.

Methods: This is a retrospective study of 588 cases of node-negative early (T1-2) invasive breast carcinoma. After surgery and systemic treatment and when considering adjuvant radiation therapy, 310 cases received post mastectomy radiation therapy while 278 cases did not. Risk factors were identified for all cases which include; (1) medial site tumors, (2) size more than 4 cm, (3) premenopausal status (4) positive LVI (5) triple negative cases. cases with more than 2 risk factors were also examined in both groups to assess the effect of accumulated risk factors. Time of local failure if happened and duration of disease-free survival were reported.

Results: Patients characteristics are matched between the 2 groups. At the end of the study, 18 cases (5.8%) in group 1 developed local recurrence compared with 29 cases (10.4%) in group 2 with 0.039 P value. The incidence of LRR is higher in cases presented with risk factors specially when more than 2. Considering the effect of PMRT; disease free survival was better in all risky subgroups in group 1 compared to group 2. Although P value was not significant when assessing every risk factor alone, but it was significant when there were more than 2 risk factors (mean disease-free survival was 96.28 months in group 1 compared to 82.76 months in group 2 with 0.015 P value).

Conclusion: we concluded that there are multiple risk factors for locoregional recurrence in early node-negative breast cancer patients after mastectomy. Cases presented with those factors (specially when more than 2) could have a benefit from post mastectomy radiation therapy.

Key words: early breast cancer, adjuvant radiotherapy, risk factors

Received: 22 January 2024
Accepted: 18 February 2024

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Background:

Many trials have proved that adjuvant radiotherapy after modified radical mastectomy (MRM) leads to marked reduction in the incidence of locoregional recurrence (LRR) and shows marked improvement in overall survival (OAS) (1). Early breast cancer cases (T1-T2 N0) usually have good prognosis and long-term survival. but a subgroup of them develop locoregional failure. Studying those cases have shown that they have multiple risk factors that may be the cause for developing local recurrence (2). In modern treatment system for early breast cancer, adjuvant radiotherapy is not recommended after mastectomy if with small tumor and negative lymph nodes. But positive lymph nodes is not the only risk factor for developing local recurrence. Many other factors could be considered such as tumor site and size, menopausal and hormonal status, also presence or absence of lymphovascular invasion (LVI). Several studies have revealed that the presence of that risk factors leads to marked increase in the rate of developing local recurrence even with negative lymph nodes (3). Till now post mastectomy radiotherapy in

early breast cancer is only indicated if surgical margin is positive, but with the presence of other listed risk factors, it is still a matter of debate. (4). The absolute incidence of local failure in node-negative cases with high risk factors is not well documented in recent studies. But from the low number studies tried to assess that incidence, it may range between 20% and 25% (5). Because of that debates, many radiotherapists still confused about giving adjuvant radiotherapy to that group of cases. This study seeks to document our experience about detecting the high-risk factors for local failure in T1-T2 N0 breast cancer cases after mastectomy. Also, to identify if this subgroup could have a benefit from post mastectomy radiation therapy.

Patients and Methods:

Study design:

Our study is a retrospective study of 588 cases of node-negative early (T1-2) invasive breast carcinoma who presented to our department of clinical oncology and nuclear medicine, Mansoura university hospital, faculty of medicine from Jan 2013 to Dec 2017. After surgery and systemic treatment (chemotherapy or hormonal therapy or both) and when considering adjuvant radiation therapy, group 1 including 310 cases received post mastectomy radiation therapy while Group 2 including 278 cases did not receive PORT. Inclusion criteria: the included cases were presented with early (T1-2) invasive breast cancer operated with MRM, age more than 18 and less than 70, ECOG 0 to 2 and with no contraindication for radiotherapy. Exclusion criteria: Advanced and metastatic cases and male breast cancer cases were excluded. Radiotherapy technique: radiotherapy was given with dose (40 GY /15 fractions – 5 fractions every 7 days) using three-dimensional conformal radiation therapy (3D CRT) with appropriate compensation using a field-in- field technique. Patients undergo CT simulation in the treatment position with both arms extended above their head using breast board immobilization; IV contrast is not necessary. Patients are scanned from the cricoid through 5 cm below the clinically marked inferior port edge. The entire lung was included. Chest wall was defined as CTV. A margin of 3–5 mm medially, 5–10 mm laterally, 3–5 mm posteriorly, and 5–10 mm superiorly, inferiorly, and anteriorly (to include the skin surface) was added to the CTV. LNs was not included in the plan. Dose to the lung and heart was limited to their tolerance. Follow up: All cases were examined clinically monthly and were under radiological investigation every 3 to 6 months. Patients who had suspicion for local recurrence were referred for biopsy and pathological confirmation. Time of local failure if happened, duration of survival or lost follow up till the end of the study were reported. Cases are listed in two groups, group 1 was 310 cases received post mastectomy radiotherapy, group 2 was 278 cases did not receive post mastectomy radiotherapy. The study started at JAN 2013, registration of cases continued till DEC 2017, end of follow up was at DEC 2022, duration of follow up were between 60 to 120 months (median 90 months). A number of risk factors were examined in both groups; (1) site, where inner quadrant tumors are considered risky (2) size, tumors >4cm are considered risky (3) premenopausal are more risky that postmenopausal (4) positive LVI is a risk factor (5) triple negative cases are more risky group. A subgroup of patients with more than 2 risk factors were also examined in both groups to assess the effect of accumulated risk factors.

Statistical analysis

Data was analyzed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 24). The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Qualitative data was described using number and percent. Association between categorical variables was tested using Chi-square test. Kaplan- Meier test was used for survival analysis and statistical significance of differences among curves determined by Log-Rank test. For above mentioned statistical tests, the threshold of significance is fixed at 5% level (p-value). The results were considered significant when the $p \leq 0.05$. The smaller the p-value obtained, the more significant are the results.

Results and Discussion:

Table 1 indicates patients characteristics in both groups, 94 cases (30.3%) in group 1 presented with medial side tumor compared to 88 cases (31.7%) in group 2. 110 cases (35.5%) in group 1 presented with tumor more than 4 cm compared to 107 cases (38.5%) in group 2. 152 cases (49%) were premenopausal in group 1 compared to 139 cases (50%) in group 2. As regards LVI, 140 cases (45.2%) in group 1 were positive compared to 119 cases (42.8%) in group 2. Triple negative cases in group 1 were 50 (16.1%) compared to 47 cases (16.9 %) in group 2. When considering cases who presented with more than 2 risk factors, there were 75 cases (24.2%) in group 1 compared to 68 cases (24.5%) in group 2. All the previous data were matched between the 2 groups with no statistically significant P value. At the end of the study, 18 cases (5.8%) in group 1 developed local recurrence compared with 29 cases (10.4%) in group 2. This difference in LRR rate was significant between the 2 groups with 0.039 P value.

Table 2 shows the data about the effect of risk factors on the development of local failure in group 1. Out of 18 cases who developed LRR in this group and when the tumor was presented in the inner quadrant, 8 cases out of 94 (8.5%) developed LRR compared to 10 cases out of 216 (4.6%) who presented with outer quadrant disease. when the size was more than 4 cm, 12 case out of 110 (10.9%) developed LRR compared to 6 cases out of 200 (3%) presented with tumors less than 4 cm. 16 cases out of 152 (10.5%) premenopausal women developed LRR compared to only 2 cases out of 158 (1.3%) post-menopausal cases. When presented with LVI, 17 cases out of 140 (12.1%) developed LRR compared with only one case out of 170 (0.6%) who

were negative for LVI. 9 of 50 triple negative cases (18%) developed LRR compared to 9 cases out of 260 (3.5%). 75 cases were presented with more than 2 risk factors, All the 18 cases (24%) who developed LRR were in that subgroup. In all the previous assessed factors, there is statistically significant effect of presence of risk factors in the development of LRR except the site of the disease, however the rate of LRR still lower in the non-risky site cases.

Table 3 shows the data about the effect of risk factors on the development of local failure in group 2. Out of 29 cases who developed LRR in this group and when the tumor was presented in the inner quadrant, 12 cases out of 88 (13.6%) developed LRR compared to 17 cases out of 190 (8.9%) who presented with outer quadrant disease. when the size was more than 4 cm, 20 case out of 107 (18.7%) developed LRR compared to 9 cases out of 171 (5.2%) presented with tumors less than 4 cm. 23 cases out of 139 (16.5%) premenopausal women developed LRR compared to only 6 cases out of 139 (4.3%) post-menopausal cases. When presented with LVI, 23 cases out of 119 (19.3%) developed LRR compared with only 6 cases out of 159 (3.8%) who were negative for LVI. 12 out of 47 triple negative cases (25.5%) developed LRR compared to 17 cases out of 231 (7.4%). 68 cases were presented with more than 2 risk factors, All the 29 cases (42.6%) who developed LRR were in that subgroup. In all the previous assessed factors, there is statistically significant effect of presence of risk factors in the development of LRR except the site of the disease like group 1.

The previous results in both groups confirms that the presence of risk factors including more than 4 cm tumor size, premenopausal status, positive LVI, triple negative cases and medial site tumor (although lesser effect) put the patients in considerable higher risk to develop LRR compared to cases who are negative for those risk factors either if receiving PMRT or not. This effect is more obvious when there is accumulation of risk factors more than 2.

Considering the effect of risk factors on disease free survival for group 1, table 4 illustrates that the mean disease-free survival time is better when there is no risk factor. And this was associated with significant P value for all assessed factors except the site of the disease where it was not significant but still better. When considering presence of more than 2 risk factors, Kaplan -Meier curve illustrate that the 45 months disease free survival was 76% in cases with more than 2 risk factors compared to 100% for other cases.

The same results were confirmed for group 2 as indicated in table 5 where the mean disease-free survival is better in absence of risk factors with significant P value except in the disease site (but still better). The Kaplan Meier curve also confirms the effect of accumulation of more than 2 risk factors where the 45 months disease free survival was 57.4% compared to 100% for other cases.

Table (1): **Patients characteristics in both groups**

	Group (1) (n=310)	**Group (2) (n=278)**	**Test of significance**	**P value**
Risk site				
Yes	94 (30.3%)	88 (31.7%)	χ^2 =0.122	0.727
No	216 (69.7%)	190 (68.3%)		
>4 cm size				
Yes	110 (35.5%)	107 (38.5%)	χ^2 =0.569	0.451
No	200 (64.5%)	171 (61.5%)		
Premenopausal				
Yes	152 (49.0%)	139 (50%)	χ^2 =0.055	0.815
No	158 (51.0 %)	139 (50%)		
Lymph vascular invasion				
Yes	140 (45.2%)	119 (42.8%)	χ^2 =0.330	0.566
No	170 (54.8%)	159 (57.2%)		
Triple negative				
Yes	50 (16.1%)	47 (16.9%)	χ^2 =0.064	0.800
No	260 (83.9%)	231 (83.1%)		
Loco regional recurrence				
Yes	18 (5.8%)	29 (10.4%)	χ^2 =4.26	**0.039***
No	292 (94.2%)	249 (89.6%)		
More than 2 risk factors				
Yes	75 (24.2%)	68 (24.5%)	χ^2 =0.006	0.94
No	235 (75.8%)	210 (75.5%)		

χ^2: Chi square test, *significant p≤0.05

Table (2): **Risk factors for locoregional recurrence in group 1**

	Total	Loco regional recurrence among Group (1) (n=310)		Test of significance	P value
		Yes (n=18)	No (n=292)		
Risk site					
Yes	94	8 (8.5%)	86 (91.5%)	χ^2 =1.80	0.179
No	216	10 (4.6%)	206 (95.4%)		
>4 cm size					
Yes	110	12 (10.9%)	98 (89.1%)	χ^2 =8.12	**0.004***
No	200	6 (3.0%)	194 (97.01%)		
Premenopausal					
Yes	152	16 (10.5%)	136 (89.5%)	χ^2 =12.15	**≤0.001***
No	158	2 (1.3%)	156 (98.7%)		
Lymph vascular invasion				χ^2 =18.74	**≤0.001***
Yes	140	17 (12.1%)	123 (87.9%)		
No	170	1 (0.6%)	169 (99.4%)		
Triple negative					
Yes	50	9 (18.0%)	41 (82.0%)	χ^2 =16.21	**≤0.001***
No	260	9 (3.5%)	251 (96.5%)		
More than 2 risk factors					
Yes	75	18 (24.0 %)	57 (76.0%)	χ^2 =59.88	**≤0.001***
No	235	0 (0 %)	235 (100%)		

Table (3): **Risk factor for locoregional recurrence in group 2**

	Total	Loco regional recurrence Group (2) (n=278)		Test of significance	P value
		Yes	No		
Risk site					
Yes	88	12 (13.6%)	76 (86.4%) 173	χ^2 =1.41	0.234
No	190	17 (8.9%)	(91.1%)		
>4 cm size					
Yes	107	20 (18.7%)	87 (82.3%) 162	χ^2 =12.70	**≤0.001***
No	171	9 (5.2%)	(94.8%)		
Premenopausal					
Yes	139	23 (16.5%)	116 (83.5%)	χ^2 =11.12	**0.001***
No	139	6 (4.3%)	133 (95.7%)		
Lymph vascular invasion				χ^2 =17.62	**≤0.001***
Yes	119	23 (19.3%)	96 (80.7%) 153		
No	159	6 (3.8%)	(96.2%)		
Triple negative					
Yes	47	12 (25.5%)	35 (74.5%) 214	χ^2 =13.80	**≤0.001***
No	231	17 (7.4%)	(92.6%)		
More than 2 risk factors					
Yes	68	29 (42.6 %)	39 (57.4%) 210	χ^2 =99.98	**≤0.001***
No	210	0 (0 %)	(100%)		

Table (4): Disease free survival among group 1

	Disease free survival				
	Mean Survival time	**Std. Error**	**95% CI**	**Log Rank test**	**P – value**
Risk site					
Yes	112.84	2.42	108.1-117.6	1.73	0.188
No	115.93	1.25	113.5-118.4		
>4 cm size					
Yes	110.564	2.577	105.5-115.4	8.23	**0.004***
No	117.435	1.034	115.6-119.5		
Premenopausal					
Yes	110.941	2.148	106.7-115.1	12.11	**0.001***
No	118.899	.774	117.4-120.4		
Lymph vascular invasion					
Yes	109.5	2.38	104.8-114.2	18.83	**≤0.001***
No	119.5	.493	118.5-120.4		
Triple negative					
Yes	103.600	4.662	94.4-112.7	17.07	**≤0.001***
No	117.031	0.974	115.1-118.9		
Overall DFS	114.99	1.15	112.7-117.2		

Log Rank (Mantel-Cox) was used, CI: confidence interval

Kaplan- Meier curve for disease free survival in group 1 when there is more than 2 risk factors

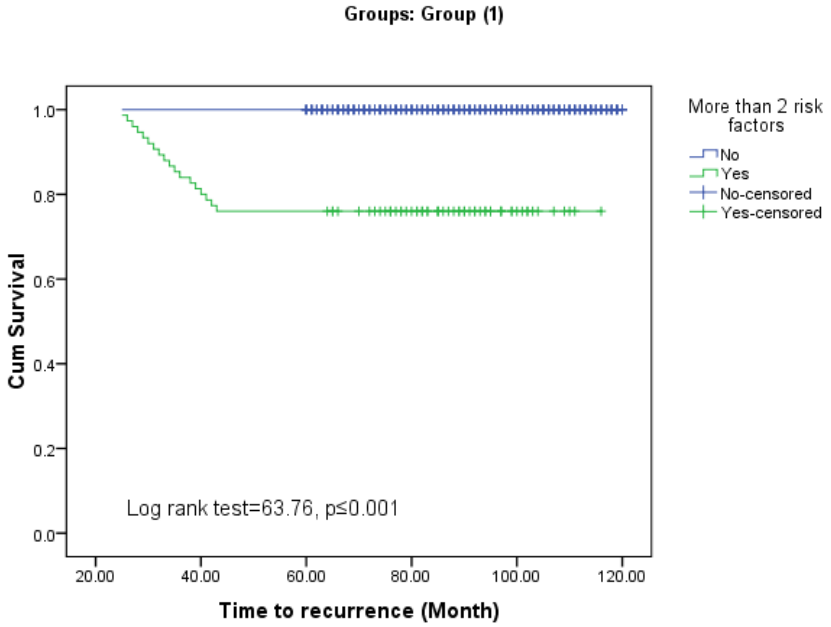


Table (5): Disease free survival among group 2

	Overall Disease survival				
	Mean Survival time	**Std. Error**	**95% CI**	**Log Rank test**	**P - value**
Risk site					
Yes	108.37	3.12	102.2-114.5	1.26	0.261
No	112.058	1.84	108.4-115.6		
>4 cm size					
Yes	103.654	3.303	97.1-110.1	12.90	**≤0.001***
No	115.421	1.488	112.5-118.3		
Premenopausal					
Yes	105.36	2.793	99.8-110.8	11.49	**0.001***
No	116.417	1.432	113.6-119.2		
Lymph vascular invasion					
Yes	102.28	3.13	96.1-108.4	17.89	**≤0.001***
No	116.73	1.31	114.1-119.3		
Triple negative					**≤0.001***
Yes	97.511	5.364	86.9-108	13.58	
No	113.463	1.529	110.4-116.4		
DFS	110.89	1.60	107.7-114.0		

Kaplan- Meier curve for disease free survival in group 2 when there is more than 2 risk factors

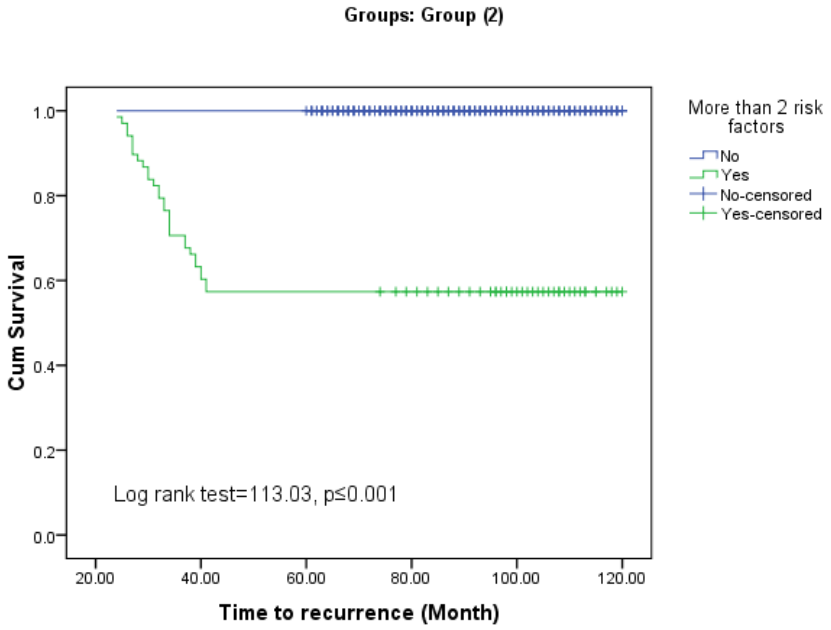
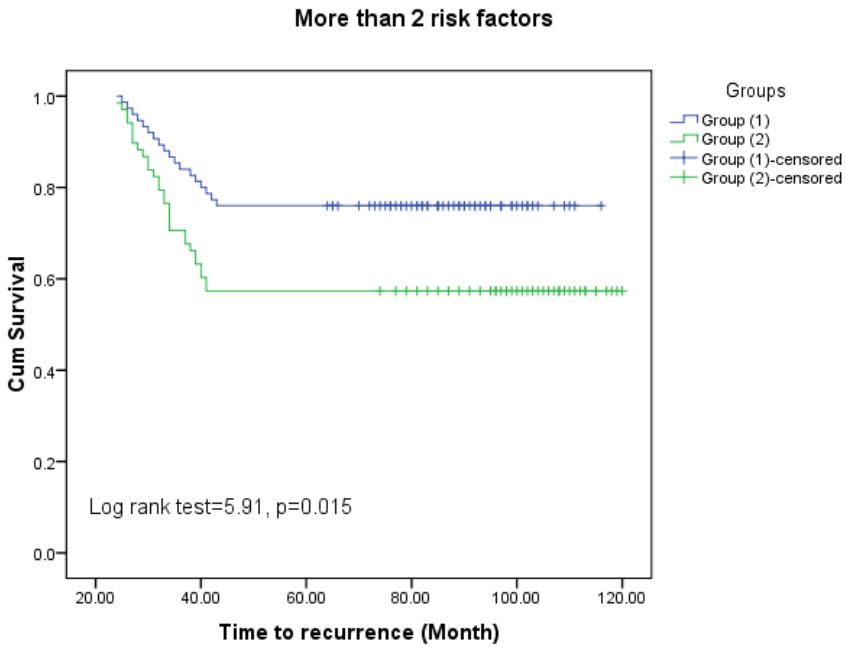


Table (6): Disease free survival for risky subgroups in group 1 and 2

	Overall Disease survival				
	Mean Survival time	**Std. Error**	**95% CI**	**Log Rank test**	**P - value**
Risk site					
Group (1)	112.84	2.42	108.1-117.5	1.26	0.262
Group (2)	108.37	3.12	102.3-114.5		
>4 cm size					
Group (1)	110.56	2.57	105.5-115.6	2.64	0.104
Group (2)	103.65	3.30	97.2-110.1		
Premenopausal					
Group (1)	110.94	2.14	106.7-115.2	2.41	0.121
Group (2)	105.36	2.79	99.8-110.8		
Lymph vascular invasion					
Group (1)	109.52	2.38	104.84-114.2	2.63	0.105
Group (2)	102.28	3.13	96.13-108.4		
Triple negative					
Group (1)	103.60	4.66	94.4-112.7	0.697	0.404
Group (2)	97.51	5.36	86.9-108		
More than 2 risk factors					
Group (1)	96.28	4.06	88.3-104.2	5.91	**0.015***
Group (2)	82.76	5.25	72.4-93.1		

Kaplan- Meier curve for disease free survival in both groups when there is more than 2 risk factors



To study the effect of giving PMRT in risky cases, we compared the mean disease-free survival of risky subgroups in both group 1 and 2. it was found that group 1 who received post mastectomy RTH showed better survival than group 2 who did not. Considering the risky site, it was 112.84 months in group 1 compared to 108.37 months in group 2. When the tumor is more than 4 cm, it was 110.56 months when giving PMRT compared to 103.65 months when not giving PMRT. In premenopausal cases, it was 110.94 months in group 1 compared to 105.36 months in group 2. In cases with positive LVI it was 109.52 months in group 1 compared to 102.28 in group 2. In triple negative cases, also giving PMRT improve the mean disease-free survival (103.6 months in group 1) compared to (97.51 months in group 2). Although P value was not significant when assessing every risk factor alone, but it was with significant P value when there were more than 2 risk factors (mean disease-free survival was 96.28 months in group 1 compared to 82.76 months in group 2) as illustrated in table 6 and the Kaplan Meier curves.

This study was done trying to demonstrate the effect of giving adjuvant radiotherapy for early breast cancer cases with high risk factors. Those risk factors include (1) Tumour site (Tumours of the inner breast quadrant are more risky) (2) Tumour size (Tumours > 4 cm are more risky) (3) menopausal status (Tumours in premenopausal females are more risky) (4) LVI status (Tumours with LVI are more risky) (5) Hormonal and HER2 status (triple negative cases are more risky). A subgroup of patients with more than 2 risk factors was also examined in the study to assess the effect of accumulated risk factors.

Our results confirm that the presence of the above-mentioned risk factors is associated with considerable higher risk to develop LRR. This effect is more obvious when there are accumulated factors (more than 2). Giving adjuvant radiotherapy markedly improve the disease-free survival for that group of patients. Although the difference was not significant when assessing every risk factor alone, but it was with significant P value when there were more than 2 risk factors.

The effect of adjuvant radiotherapy is obvious to decrease LRR in early breast cancer with low burden positive lymph nodes as illustrated by many studies which showed a considerably significant reduction in local recurrence for early cases when compared to advanced disease (6.7% vs 19.6%, P < .001) (6). But considering node negative disease, a few trials aimed to study that subgroups of patients and to determine specific risk factors for higher of LRR (4). Our study was planned to aim to solve this debate.

Kyubo Kim et al tried also to solve that debate. They concluded that LRR rate was very low in node-negative breast cancer with tumor size more than 5 cm treated with mastectomy even if not receive adjuvant radiotherapy (7). This is not matched with our results, but this could be explained by that the named study assessed the whole cases and not put in consideration the effect of risk factors rather than the size.

The larger the size of the tumor, the higher the possibility of developing LRR. Katz et al (8) reported that when the tumor is more than 4 cm, the10-year LRR risk was >20%. Similar results were found in our study where higher incidence of LRR was documented in cases with tumor size > 4cm.

Young age is one of the most adverse factors in breast cancer in general. Jwa et al (9) reported more than 300 patients with early disease and when studied the effect of age, they found that LRR is more in cases <50 years (11.4 times as high as those ≥50 years). Sharma et al (10) investigated 1019 patients also with early disease and they found age as the only independent adverse factor when comparing cases less than 40 years to cases with more than 40 (HR = 2.41, 95% CI = 1.28–3.56, P = .004). our study showed also that young age is a strong risk factor for recurrence.

When studying the site of the disease, we found that medial tumours were associated with high risk of LRR (even P value was not significant). This was the same as the results of the study done by Sarp S et al which found that lower inner tumor site is an important prognostic factor for development of local recurrence (11).

Triple negative breast cancer cases were identified to be very risky subgroup even in early stage disease. W. Eiermann1 et al have done a study on that group and found that 10% of patients developed locoregional failure after about 7 years follow up and the only independent factor associated with the development of local recurrence is not giving adjuvant radiotherapy after mastectomy (HR 2.53, 95% CI 1.12–5.75, P = 0.0264) (12). That is matched with our study which confirmed that triple negative biology is a strong adverse factor in developing LRR in early breast cancer cases.

Considering the effect of accumulated risk factors in early breast cancer cases, few studies were done to investigate that (13). Our study was aimed to assess the value of every risk factor alone and also the effect of presence of more than one risk factor and we concluded that the presence of more than 2 risk factors carry a high risk of developing local recurrence and so we strongly recommend giving adjuvant radiotherapy for that subgroup of patients.

Gongling et al investigate the effect of presence of more than one risk factors and They found that the accumulation of 2 or more of adverse prognostic factors including young age, positive LVI, high grade, HER-2 positive, and positive surgical margins have an increased probability of developing local failure. This result put the light on the effect of accumulated risk factors in early stage cases in developing LRR (14).

Conclusion:

Our study concluded that there is multiple risk factor for locoregional recurrence in early node-negative breast cancer patients after mastectomy including tumor site and size, menopausal status, LV invasion and triple negative cases. Those subgroups of patients could have a benefit from post mastectomy

radiation therapy. We strongly recommend giving post mastectomy radiotherapy specially in cases presented with more than 2 risk factors.

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