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The role of clinicopathologic and molecular prognostic factors in the post-mastectomy radiotherapy (PMRT): a retrospective analysis of 912 patients

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Abstract. – OBJECTIVE: To assess the association of clinicopathologic and molecular features with loco-regional recurrence (LRR) in post-mastectomy breast cancer patients with or without adjuvant radiotherapy (PMRT).

PATIENTS AND METHODS: We retrospectively reviewed data of patients undergone to mastectomy followed or not by PMRT between January 2004 and June 2013. The patients were divided according to clinicopathologic and molecular sub-classification features. LRR and Cancer Specific Survival (CSS) were calculated using the Kaplan-Meier method; the prognostic factors were compared using long-rank tests and Cox regression model.

RESULTS: A total of 912 patients underwent to mastectomy of whom 269 (29.5%) followed by PMRT and 643 (70.5%) not; among the PMRT group, 77 underwent to the chest wall (CW) and 202 to the chest wall and lymphatic drainage (CWLD) irradiation. The median follow-up was 54 months (range, 3-118).

No significant difference in terms of LRR and CSS was found between non-PMRT and PMRT group (p=0.175; and p=0.628). The multivariate analysis of LRR for patients who did not undergo PMRT showed a significant correlation with the presence of extracapsular extension (ECE) (p=0.049), Ki-67>30% (p=0.048) and triple negative status (p=0.001). In the PMRT group, triple negative status resulted as the only variable significantly correlated to LRR (p=0.006) at the multivariate analysis and T-stage also showed a trend to significance (p=0.073). Finally, no difference in LRR control was shown between CW and CWLD-PMRT (p=0.078).

CONCLUSIONS: After mastectomy ECE, a cut off of Ki-67>30% and triple negative status were strictly correlated with LRR regardless of clinicopathologic stage. PMRT has a positive impact in decreasing LRR in patients with this molecular profile. Besides, CW might represent a valid option for patients with one to three positive nodes.

Key Words:
Post-mastectomy radiotherapy, Locoregional recurrence, Clinicopathological factors.

Introduction

The role of conservative surgery has already been well established by many studies as it represents the milestone of treatment for early breast cancer despite mastectomy remains a validated therapeutic option[1-8]. Data resulting by the National Surgical Quality Improvement Program database on 85401 breast cancer showed an increase incidence of mastectomy over breast-conserving surgery from 2005 to 2011, starting at 40% and peaking to 51% (p<0.001), probably due to the more bilateral resection, immediate reconstruction, and prophylactic operations[9].

The role of radiotherapy after mastectomy (PMRT) has also been defined by several large randomized trials and meta-analysis showing a benefit in terms of locoregional control and overall survival in patients affected by local advanced disease[10-14]. The American Society of Clinical (ASCO) and the American Society of Therapeutic Radiology and Oncology (ASTRO) recommended the use PMRT for patients whose primary tumors

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are larger than 5 cm (T3 disease) and those with four or more positive nodes. Recently, an Early Breast Cancer Trialists' Collaborative Group meta-analysis showed that patients with 1-3 positive axillary nodes benefited from PMRT, even in combination with systemic therapy[15]. Instead, a randomized clinical study by the European Organization for Research and Treatment of Cancer (EORTC) showed that the same group of women did not have a clear survival benefit[16]. That being so, several doubts remain regarding the role of PMRT and selection of patients.

Various clinicopathologic features (i.e. age <40 years; lymphovascular invasion) have been studied regardless of the T and N stage[17-27]. Furthermore, a general consensus regarding the PMRT volumes has not yet been reached[28]. In fact, despite the chest wall (CW) is recognized as the area at greatest risk of recurrences after mastectomy, most data recommend to extend RT field to the regional lymphatic drainage (CWLD-PMRT), such as apex axilla and supraclavicular nodes regardless nodal status. This is likely because existing data support an extended treatment in more advanced disease whereas the role of CW-PMRT in the intermediate stage has been poorly investigated yet[28,29].

The purpose of this study was to associate clinicopathologic and molecular features with loco-regional recurrences (LRRs) in a large cohort of patients undergone to mastectomy with or without PMRT. Secondarily, we analyzed and compared the pattern of LRR between CW and CWLD-PMRT in the PMRT group.

Patients and Methods

Enrollment Criteria

The cases of breast cancer patients who were diagnosed and treated at University Hospital of Pisa between January 2004 and June 2013 were retrospectively reviewed. This study was approved by institutional Review Boards and carried out as a collaboration of Breast Surgery, Radiation Oncology and Medical Oncology Departments.

We reviewed data of patients who underwent a total mastectomy followed by sentinel node examination ± axillary dissection.

Mastectomy was performed in the presence of one or more of the following clinical situations:

1. Retroareolar tumor location
2. Multicentricity
3. Local advanced disease (cT3-4 and/or cN2-3)
4. Inflammatory breast cancer
5. Unfavorable tumor size/breast volume ratio

In patients affected by inflammatory breast cancer, mastectomy was always performed after primary chemotherapy and combined with axillary dissection[30].

According to the literature data, patients underwent to CW or to CWLD-PMRT depending on the pathological nodal status[31,32].

Salvage mastectomy for local recurrence after a previous conservative surgery and RT, as well as presence of systemic disease at diagnosis, was considered exclusion criteria of the study. All patients provided written consent for storage and research use of their medical information.

Clinicopathologic and Molecular Features

Classification of histologic type (ductal carcinoma not otherwise specified, lobular carcinomas or other types), histologic grade, measurement of size, invasion of the tumor into the skin or the deep fascia and number of removed and positive axillary nodes were evaluated and reported. We used the histologic tumor grade obtained by pathology review and estrogen and progesterone receptors (ER and PgR) and Her2 status extracted from pathology reports. Her2 was considered positive if immunohistochemical stains were reported 3+ and/or if Her 2 FISH showed gene amplification. Ki-67 was assessed immunohistochemically. The percentage of positive cells (nuclear immunoreactivity) among 2000 randomly selected tumors cells viewed at 400x at the periphery of the tumor, was calculated; Ki-67 was categorized as low (<30%) or high (≥30%).

Adjuvant Treatment Details

When performed, RT was delivered by a linear accelerator with a tridimensional conformal (3DCRT) or static IMRT technique. The prescribed dose was 50 Gy delivered in 25 fractions adding a boost of 20 Gy and 14-16 Gy for positive and close (<2 mm) surgical margins, respectively.

Adjuvant chemotherapy was mostly performed using CMF or FEC scheme followed by weekly taxol; PMRT was always deferred until the completion of chemotherapy.

Tamoxifen, alone or combined with LHRH agonist (for post and pre-menopausal patients respectively), as well as aromatase inhibitors or switch regimen (Tamoxifen for 3 years followed by aromatase inhibitors for 2 years) was used in hormone responsive tumors. Finally, trastuzumab was administered in all patients with Her-2/neu overexpression or FISH amplification, concomi-

tant to taxanes based chemotherapy regimens or sequential to chemotherapy as monotherapy.

Follow-up

According to our protocol, we evaluated patients at 3-month intervals for 2 years and every 6 months thereafter for a total of 5 years. All the patients analyzed for the study received at least two follow-up visits. Evaluations consisted of physical examination, complete blood cell counts and blood chemistry exams including CEA and Ca15.3 level at every follow-up visit, mammography scan and/or liver ultrasound after six months and then annually.

LRR was defined as the time interval between the date of mastectomy and recurrence (confirmed histologically) or the last follow-up contact with the patient and was distinguished into local (chest wall) and/or regional relapses (axilla, supra-clavicular, internal mammary nodes). Distant metastasis was defined as failure beyond the local or regional area. Cancer specific survival (CSS) was defined as the time interval between the date of diagnosis and the date of cancer-related death or the last follow-up contact.

Statistical Analysis

Survival curves were calculated using the Kaplan-Meier method, and the log-rank test was used to evaluate the differences among the curves.

Eight prognostic factors were assessed: T stage (T1-T2 *vs.* T3-T4), N stage (N0-N1 *vs.* N2-N3), extracapsular extension; lymphatic vascular invasion; triple negative profile; Her2/neu status; Ki-67 (≤30% *vs.* >30%); grading (G1-2 *vs.* G3).

Univariate survival analysis was performed including each variable in a Cox regression model and calculating related *p*-value by Wald test. All variables significantly influencing survival in the univariate analysis were analyzed together in a Cox regression model as multivariate analysis, with the aim of studying the independent contribution of each variable in explaining survivorship.

Five different variables were tested as independent prognostic factors: age (≤40 *vs.* >40); receptor expression; focality (unifocal *vs.* multifocal/multicentric disease); neoadjuvant chemotherapy; adjuvant chemotherapy.

Furthermore, the proportional hazard was always verified by the use of log(-log) curves. The results of the Cox regression were expressed using hazard ratios with related confidence intervals and related *p*-value. Differences were considered significant at $p<0.05$ and analyses were performed using SPSS 22 (SPSS Inc., Chicago, IL, USA) technology.

Results

Overall, 912 patients underwent a total mastectomy followed or not by PMRT and were analyzed. Patients, tumor characteristics and treatment details are shown in Table I. For the entire study population, the median follow-up was 54 months (range, 3-118).

Table I. Patients characteristics, biological tumor factors and systemic treatment details.

	No PMRT	PMRT
Total patients	643 (70.5%)	269 (29.5%)
Age		
Median	54	56
≤ 40	46 (7.2%)	21 (7.4%)
> 40	597 (92.8%)	249 (92.6%)
Extra capsular extension		
Yes	19 (2.9%)	90 (33.4%)
No	542 (84.2%)	174 (64.7%)
Unknown	82 (12.9%)	5 (1.9%)
Lymphatic vascular invasion		
Yes	63 (90.2%)	82 (30.5%)
No	580 (19.8%)	187 (69.5%)
Triple negative		
Yes	35 (5.5%)	14 (5.3%)
No	548 (85.2%)	239 (88.8%)
Unknown	60 (9.3%)	16 (5.9%)
HER2/neu status		
Negative	492 (76.5%)	204 (75.8%)
Positive	79 (12.3%)	44 (16.3%)
Unknown	72 (11.2%)	21 (7.9%)
Mib 1		
≤ 30%	433 (67.3%)	191 (71%)
> 30%	143 (22.2%)	59 (21.9%)
Unknown	67 (10.5%)	19 (7.1%)
Grading		
G1-2	226 (35.1%)	67 (24.9%)
G3	280 (43.5%)	150 (55.8%)
Unknown	137 (21.4%)	52 (19.3%)
T-stage		
T1-T2	534 (83%)	168 (62.4%)
T3-T4	40 (6.3%)	83 (30.8%)
Unknown	69 (10.7%)	18 (6.8%)
N-stage		
N0-N1	555 (86.3%)	106 (39.4%)
N2-N3	6 (1%)	158 (58.7%)
Unknown	82 (12.7%)	5 (1.9%)
Neoadiuvant chemotherapy		
Yes	66 (10.3%)	95 (35.3%)
No	577 (89.7%)	174 (64.7%)
Adiuvant chemotherapy		
Yes	367 (57%)	202 (75.1%)
No	276 (43%)	67 (24.9%)
Hormonotherapy		
Yes	473 (73.6%)	222 (82.5%)
No	170 (26.4%)	47 (17.5%)

Abbreviations: PMRT = post mastectomy radiotherapy; ECE=Extracapsular extension; LVI=Lymphatic vascular invasion.

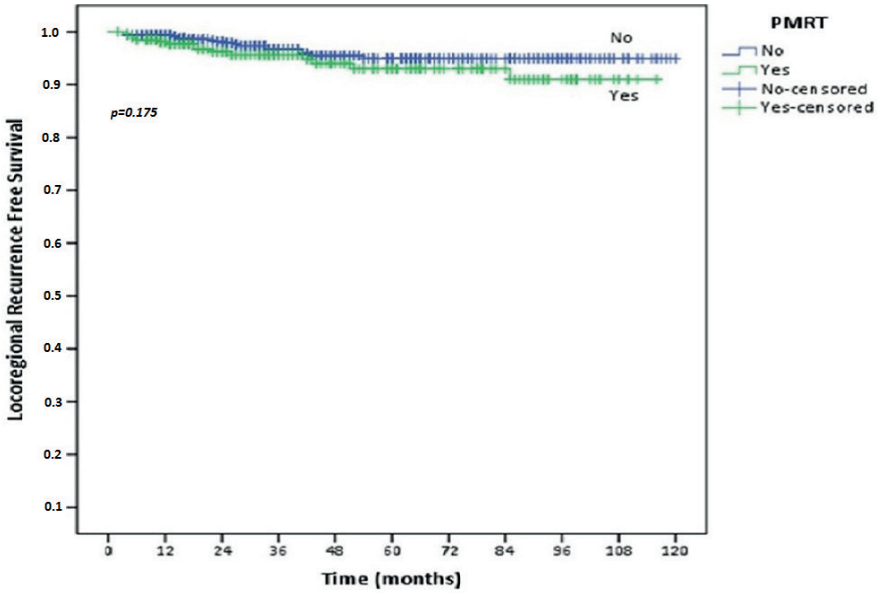

Figure 1. Comparison of locoregional recurrence free survival for PMRT and no-PMRT group of patients.

Distribution of Clinicopathologic Features Among Different Molecular Subtypes

The percentage of T1-2 stage was 77% (702/912) against 13% (123/912) of T3-4. Among T1-2 patients 55% (386/702) were affected by a multifocal or multicenter disease and 45% (317/702) by a unifocal disease. Additionally, 692 patients (76%) were affected by a receptor expressing disease, 123 patients (13%) by a Her-2 positive disease and 49 patients (5%) by a triple negative disease, whereas 57/123 patients (46%) were affected by a Her-2 positive non-luminal disease.

Adjuvant and Neoadjuvant Treatment

Overall 161/912 patients (18%) underwent neoadjuvant chemotherapy, and 11/161 (6.83%) were affected by an inflammatory breast cancer disease. Moreover, in the neoadjuvant chemotherapy group 11/161 (6.83%) patients also experienced a complete pathological remission both on T and N, and 15/161 (9.3%) the residual of single or multiple *in situ* foci. RT was delivered postoperatively in 269 patients of whom 77 underwent to CW-PMRT and 202 to CWLD-PMRT.

Distant Metastases, Cancer-Specific Survival (CSS) and Tumor Recurrences

For the entire study population, the 5-10 year locoregional free survival (LRFS) rates were 94% and 93%; the 5-10 year CSS and OS rates were 93%, 80% and 92%, 71,5%, respectively. Of the 46 locoregional recurred patients, 22 (48.5%) also experienced a subsequent distant progression; additionally, among the 22 patients who experienced locoregional recurrence and distant progression disease 15 (68%) died due to cancer.

The median time between the time of recurrence and distant progression was 6 months (range, 2-25 months) and between distant progression and death was 10 months (range, 1-61 months).

Overall, 31/643 (4.8%) in non-PMRT group experienced a locoregional relapses against 15/269 (5.5%) in PMRT group; specifically, 19 were local, 7 regional and 5 both local and regional in non-PMRT group whereas 9 local, 4 regional and 2 both local and regional in PMRT group.

Stratified Analysis of Tumor Recurrence

The patients' clinicopathologic characteristics are shown in Table I according to the treatment received. No differences were found between patients with or without PMRT for LRR (p=0.175; HR=1.613; CI95%=0.808-3.219); this comparison is reported in Figure 1.

The univariate analysis of LRR for patients not undergone PMRT showed a significant correlation with the presence of ECE (p=0.031), Ki-67>30% (p=0.010), triple negative status (p<0.0001), T stage (p=0.009) and N stage (p=0.001); at the subsequent multivariate analysis ECE, Ki-67>30% and triple negative status maintained a statistical significant value (p=0.049 for

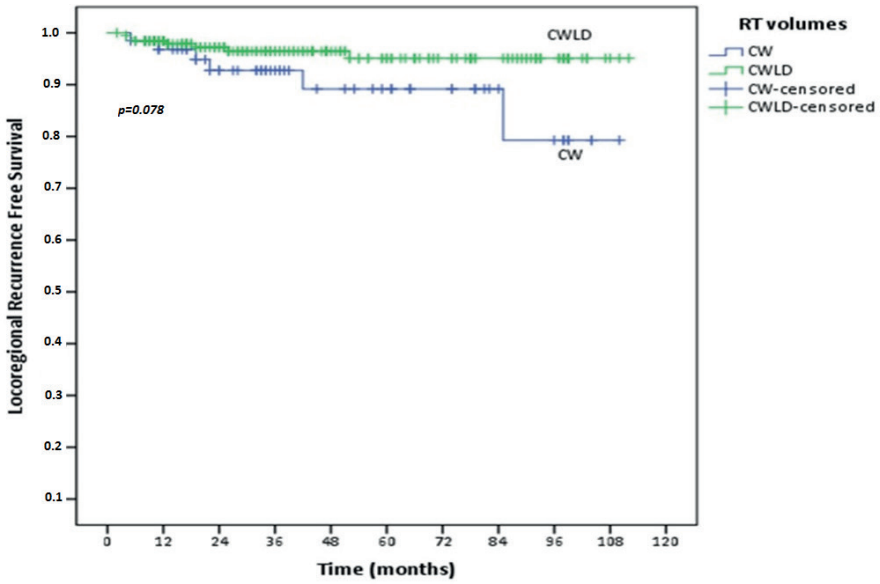

Figure 2. Comparison of locoregional recurrence free survival for CW and CWLD group of patients.

ECE; p=0.048 for Ki-67>30% and p=0.001 for triple negative). No correlation was found in the non-PMRT group with age (p=0.636) and focality (p=0.880), a trend to significance resulted for neoadjuvant (p=0.067) and adjuvant chemotherapy (p=0.073), whereas a statistical correlation was found with receptor expression (p<0.0001; HR=0.172; CI=0.064-0.461).

Differently, in the PMRT group only the triple negative status and T stage resulted significantly correlated to LRR (p<0.0001 and p=0.008, respectively) at the univariate analysis; at the subsequent multivariate analysis the triple negative maintained a significant value (p=0.006) whereas the T stage showed a trend to significance (p=0.073). These results are clearly shown in Table II.

No correlation was found with age (p=0.280), focality (p=0,734), neoadjuvant (p=0.100) and adjuvant chemotherapy (p=0.195), whereas a statistical correlation was found with receptor expression (p<0.0001; HR=0.105;CI=0.034-0.319).

CW-PMRT and CWLD-PMRT

Among 269 PMRT patients, 77 underwent to CW-PMRT and 202 to CWLD-PMRT.

As reported in Figure 2, no statistical significant difference was shown for CWLD against CW-PMRT for LRR (p=0.078; HR=0.375; CI95%= 0.126-1.116).

In detail, in the CWLD group 8/198 (4%) patients experienced LRR; 3 patients reported local, 3 regional and 2 both local and regional relapses whereas in the CW group 7/67 (10.5%) patients experienced LRR relapses of whom 6 patients reported local and only one an isolated regional relapse.

Among the CW-PMRT relapses, 2 were pN1 (one with 2/15 and the other with 2/9 positive nodes) and 5 patients were pN0 (among which the only one who experienced isolated regional failure).

Moreover, two patients had a T4 and T3 disease at the primary diagnosis and underwent neoadjuvant chemotherapy before mastectomy and PMRT.

On the contrary, among the CWLD-PMRT relapsed patients, 2 were affected by an inflammatory breast cancer disease and 3 by a T3 disease whereas 4 patients were N3 and 4 patients were N2 at the initial diagnosis; all patients with T4 and/or N3 underwent to neoadjuvant chemotherapy.

Of the 3 regional relapses, two patients were N3 and one patient was N2 whereas of the 2 combined local and regional relapses, one was T4d N2 and the other was T1cN2.

Finally, of the 3 local relapses, one patient was affected by a T3N2, one patient by a T2 N3 and another one by a T3 N3 disease.

Discussion

Long time ago, molecular typing became a standard assessment in clinical practice for the guidance of chemotherapy and endocrine therapy in patients with breast cancer[33,34]. On the contrary, few studies

Table II. Univariate and multivariate (Cox model) analysis of the LRR prognostic factors.

LRR	Univariate Analysis			Multivariate Analysis		
				No PMRT		
Prognostic factors	*p*	HR	CI 95%	*p*	HR	CI 95%
ECE						
(0) no; (1) yes	**0.031**	3.503	1.050-15.45	**0.049**	3.481	1.196-27.95
LVI						
(0) no; (1) yes	0.206	2.039	0.675-6.153			
Triple negative						
(0) no; (1) yes	**<0.0001**	8.809	3.030-25.61	**0.001**	8.427	2.328-30.50
HER2/neu status						
(0) negative; (1) positive	0.740	0.778	0.177-3.425			
Ki-67						
(0) ≤30%; (1)>30%	**0.010**	3.692	1.375-9.915	**0.048**	3.310	1.009-10.86
Grading						
(0) G1-2; (1) G3	0.254	1.836	0.647-5.214			
T-stage						
(0) T1-T2; (1) T3-T4	**0.009**	5.666	1.555-20.64	0.697	1.547	0.172-13.89
N-stage						
(0) N0-N1; (1) N2-N3	**0.001**	11.13	2.527-28,98	0.246	5.174	0.321-29.83
				PMRT		
ECE						
(0) no; (1) yes	0.197	0.430	0.120-1.550			
LVI						
(0) no; (1) yes	0.169	2.089	0.732-5.962			
Triple negative						
(0) no; (1) yes	**<0.0001**	12.27	3.022-49.78	**0.006**	9.259	1.899-27.14
HER2/neu status						
(0) negative; (1) positive	0.322	1.817	0.557-5.929			
Ki-67						
(0) ≤30%; (1)>30%	0.072	2.721	0.914-8.101			
Grading						
(0) G1-2; (1) G3	0.250	37.96	0.077-99.80			
T-stage						
(0) T1-T2; (1) T3-T4	**0.008**	4.483	1.446-13.90	0.073	3.064	0.900-10.43
N-stage						
(0) N0-N1; (1) N2-N3	0.148	0.458	0.159-1.321			

Abbreviations: LRR=Locoregional recurrence; PMRT=post-mastectomy radiotherapy; ECE=extracapsular extension; LVI=Lymphatic vascular invasion.

have analyzed the utility of molecular typing in RT, especially to guide decisions regarding PMRT.

Eight clinicopathologic variables (ECE; LVI; Triple negative; Her2 neu; Ki-67; Grading; T-stage and N-stage) were analyzed in patients treated or not with PMRT. In no PMRT group, the presence of ECE, triple negative status and Ki-67>30% resulted as independent prognostic factors of LRR. In detail, the role of ECE has been poorly investigated as prognostic factors in breast cancer and the few available literature data identified a significant correlation of this factor with a lower probability of disease-free survival. The retrospective study by Hetelekidis et al[35] was undertaken to investigate whether ECE of axillary node metastases was a predictive factor of disease or regional recurrence-free survival in early breast cancer. At first, patients with ECE were more likely to have a lower oncologic outcome as the 5 year disease free survival rates resulted 67% for patients without ECE and 57% for patients with ECE (p=0.05). However, ECE failed to maintain a significant prognostic value when combined with the other prognostic factors (such as T stage, LVI, number of positive nodes, etc.) in a proportional hazard model (p=0.64 for disease-free survival in the multimodel regression). Moreover, as reported by several other studies after mastectomy[36-38], authors specified that the prognostic value of ECE is strictly correlated to the number of positive nodes so that in the multivariate analysis, ECE was correlated with a decreased survival,

although with less importance than the number of involved nodes (p=0.054 and 0.003, respectively). Thus, we believe that our findings are consistent with results reported by the few prior studies and probably reinforce the prognostic value of ECE because it was maintained at the multivariate analysis.

The role of the cancer cell proliferation has been well acknowledged and validated in a large number of studies and several meta-analyses[39-44]. A recent retrospective study by Pathmanathan et al[45] on 203 node negative patients treated with breast conserving surgery and adjuvant radiation without systemic therapy, found out an independent prognostic role of value >14% (p=0.005) together with the presence of LVI (p=0.003) for breast cancer specific survival. Of note, authors reported a striking difference in the 15-year mortality rate between low and high group (97% compared to 78%; p=0.0003). Our results confirm the prognostic value of this factor for locoregional control rather than cancer specific survival reporting a cut off of 30% for Ki-67 to be prognostically discriminative across the entire cohort of patients.

It is important to note that the two prognostic variables failed to maintain the significance in the group of women treated with PMRT. In fact, at the multivariate analysis in the PMRT group, only the triple negative status resulted in a significant prognostic variable.

The benefit of PMRT in the triple negative subset of breast cancer patients has not already been definitely established tough a general agreement exists regarding the higher risk of locoregional recurrence compared to other molecular subtypes[45]. Several retrospective studies[46] showed that PMRT was associated with a lower local recurrence rate in triple negative patients even in early stage (T1-2 N0). Interestingly, in the multicentre prospective trial by Wang et al[47] on 681 early stage triple negative patients randomized to receive adjuvant chemotherapy with or without radiotherapy, a longer disease, and overall survival was observed in the radiotherapy group. Similarly, a recent retrospective analysis by Chen et al[9] reported a benefit in terms of locoregional control and disease-free survival in intermediate (T1-2 N1) and high risk (T3-4 and/or N2-3) triple negative patients. Differently, data reported by a subgroup analysis from the Danish Breast Cancer Cooperative Group (DBCTCG 82b and c) showed that triple negative patients received a lower benefit from PMRT than patients with luminal subtypes as an higher LRR risk was observed in both randomization arms (32% against 15% locoregional relapses at 15 years)[48]. Therefore, it is likely to suggest a radioresistant phenotype of triple negative cancer.

In our study, the triple negative status was the only variable to maintain a clear statistically significance at the multivariate analysis.

Even so, despite the low sample size of triple negative in our cohort of patients (5.3%) did not make possible a direct comparison of the two groups, our results seem to show a poor benefit of radiotherapy in this subset of patients (5/35 locoregional recurrences in non PMRT group against 3/14 in the PMRT group; p=0.863) probably supporting the radioresistance hypothesis.

A surprising result of this study endorsed the positive role of PMRT in patients with high-risk clinicopathologic features and molecular subclassification. The lack of statistical significant difference for LRR between PMRT and no PMRT groups of patients (p=0.175) emphasizes the role of radiotherapy in women after mastectomy.

Finally, in the analysis of patients who underwent radiotherapy a lack of significant difference in terms of locoregional relapses between CW and CWLD was found. Whether limit the radiation field to the chest wall or extend to the lymphatic drainage in less advanced disease has been addressed by several studies but is still largely unresolved due to the retrospective nature and a small number of patients. Briefly, most data report the chest wall as the highest risk site of local recurrence[35,36,49] as well as a very low rate of regional failure after mastectomy in intermediate breast cancer disease[38,49-51]. Thus, in this subset of patients, the irradiation of lymphatic areas might be avoided with a consequent reduction of potentially side effects. Stranzl et al[50] firstly reported data on RT limited to the CW on 37 patients who underwent mastectomy concluding that treatment was enough for patients with the T1-3 N1 disease. A more recent retrospective experience by Mac Donald et al[28] on 238 stage II (one to three nodes) patients who underwent mastectomy showed a benefit of PMRT in terms of LRR and disease free survival (p=0.02 and 0.03) that was similar for those treated to the CW alone or to the CW and lymphatic drainages.

In our work, as previously reported, all recurred CW-PMRT patients were N0-1 whereas CWLD-PMRT patients were T3-4 and/or N2-3; no differences in the site of relapses was observed in the CWLD group (3 local, 3 regional and 2 both local and regional) whereas 6 of the 7 relapses in the CW group were local and only one regional.

Conclusions

Besides the retrospective nature of this study, we do believe that our findings have a clinical relevance as they further consolidate the positive impact of radiotherapy in breast cancer despite radical surgery and bring out the possible prognostic value of ECE and Ki-67 that might be wrongly undervalued in clinical practice. Furthermore, our results seem to suggest that CW irradiation might represent a reasonable option in certain circumstances of T1-2 N1 disease after mastectomy.

Prospective studies are needed to properly validate these results.

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Conflict of interest

The authors declare no conflicts of interest.

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