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Validation of a prognostic scoring system for postmastectomy locoregional recurrence in breast cancer☆

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ABSTRACT

Background: To date, it remains unclear which patients with breast cancer (BC) benefit from post-mastectomy radiotherapy (PMRT). Cheng et al. developed and validated a scoring system based on 4 prognostic factors for locoregional recurrence (LRR) to identify patients in need for PMRT. These factors include age, estrogen receptor status, lymphovascular status and number of affected axillary lymph nodes.

Purpose: To validate the scoring system for LRR in BC developed by Cheng et al. by using an independent BC database.

Methods and materials: We retrospectively identified 1989 BC cases, treated with mastectomy (ME) with or without PMRT at the University Hospitals Leuven between 2000 and 2007. The primary endpoint was 5-year locoregional control rate with and without PMRT, according to the LRR score.

Results: Median follow-up time was 11.4 years. After excluding patients with missing variables 1103 patients were classified using the LRR scoring system: 688 (62.38%) patients were at low risk of recurrence (LRR score 0–1), 335 (30.37%) patients were at intermediate risk of recurrence (LRR score 2–3) and 80 (7.25%) patients were at high risk of recurrence (LRR score $\geq$4). 5-year locoregional control rates with and without PMRT were 99.20% versus 99.21% ($p = 0.43$) in the low-risk group; 98.24% versus 85.74% ($p < 0.0001$) in the intermediate-risk group and 96.87% versus 85.71% ($p = 0.10$) in the high-risk group respectively.

Conclusion: Our validation of the LRR scoring system suggests it can be used to point out patients that would benefit from PMRT. We recommend further validation of this scoring system by other independent institutions before application in clinical practice.

1. Introduction

Breast cancer (BC) continues to be the most common malignancy and the main cause of cancer death among women worldwide; although in Europe, BC mortality continues to decline [1,2]. With the current treatment options in the Western world BC already has a relatively good prognosis, therefore one of the remaining challenges in the treatment of BC is to move towards a more personalized approach where strategies of de-escalation need to be explored to avoid side-effects [3]. On the other hand subgroups of patients in need of extensive treatment need to be defined more specifically. One of these remaining issues in the treatment of BC is defining selection criteria for patients to undergo post-mastectomy radiotherapy (PMRT). In this matter, current international guidelines state that PMRT is recommended for high-risk patients only, including involved resection margins, at least four involved axillary lymph nodes (LN), and T3-T4 tumours independent of the nodal

Abbreviations: BC, breast cancer; CT, chemotherapy; ECE, extracapsular extension; ER, estrogen receptor; HT, hormonal therapy; LN, lymph nodes; LRC, locoregional control; LRR, locoregional recurrence; LVI, lymphovascular invasion; ME, mastectomy; PMRT, post-mastectomy radiotherapy; RT, radiotherapy.

☆ Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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status [4]. Nevertheless, several more recent studies suggest we should also consider the use of PMRT in intermediate-risk patients with 1–3 positive axillary LN [5,6].

To date, guidelines and nomograms help us in the clinical decision-making to personalize the treatment of BC. In this respect, the group of Cheng et al. developed a clinical prognostic scoring system in 2006 for 5-year locoregional recurrence (LRR) based on 1010 BC patients treated between 1990 and 2001 to identify patients most in need of PMRT. This scoring system incorporated four risk factors for LRR: young age, lymphovascular invasion (LVI), estrogen receptor (ER) negativity, and the number of involved axillary LN [7]. The scoring system is presented in Table 1.

This model has been tested and adjusted by the group of Cheng after examining a new dataset of 1545 patients treated between 2002 and 2007 [8]. To conclude, Cheng et al. recommends PMRT in 1–3 node-positive patients with a LRR score of 2 or more [8].

To apply a prognostic scoring model in clinical use it needs to be evaluated, adjusted and finally validated in different independent cohort analyses. The TRIPOD statement defines this as a type 4 modelling strategy, which is the most reliable way to validate a prognostic scoring system [9]. Therefore, the aim of this study is to validate the prognostic scoring system for LRR in BC developed by Cheng et al. by using a large, external and independent cancer database of patients with BC treated between 2000 and 2007.

2. Material and methods

2.1. Study design

This study consists of the validation of a previously developed LRR scoring system by Cheng et al. by using retrospectively collected data from an independent cancer database [7,8].

2.2. Scoring system by Cheng et al

The scoring system is presented in Table 1.

In this scoring system patients receive a score from 0 to 6, thereby dividing all patients into 3 subgroups: a low-risk group (LRR score 0–1), an intermediate-risk group (LRR score 2–3) and a high-risk group (LRR score ≥4). The different risk factors account for different scores: age ≤40, prominent LVI, ER negativity and 1–3 positive axillary LN all have a prognostic score of 1. The presence of 4–9 positive axillary LN has a prognostic score of 2 and the presence of 10 or more positive axillary LN has a prognostic score of 3. The LRR score is obtained by summing up the values of each risk factor that is present, leading to a score of at least 0 to a maximal score of 6 for each patient.

Table 1
LRR scoring system by Cheng et al.

Risk factor	Presence	Prognostic score
Age	>40 years	0
	≤40 years	1
Lymphovascular Invasion	Not present	0
	Present	1
Estrogen Receptor Status	Positive	0
	Negative	1
Positive Axillary Lymph Nodes	None	0
	1–3	1
	4–9	2
	≥10	3
LRR score		**Total score**
Low Risk		0–1
Intermediate Risk		2–3
High Risk		≥4

2.3. Patient selection and data collection

Patients who underwent ME between 2000 and 2007 for primary invasive BC of which at least ME and/or PMRT had to be performed at the University Hospitals Leuven were included. Exclusion criteria included (i) male sex; (ii) distant metastasis at diagnosis, (iii) bilateral invasive BC at diagnosis and (iv) neo-adjuvant chemotherapy (CT), (v) neo-adjuvant hormonal therapy (HT) or (vi) neo-adjuvant radiotherapy (RT).

The Ethical committee of the University Hospitals Leuven accepted this study.

2.4. Locoregional recurrence

Time until LRR was determined as the time from the first day of treatment until the day of chest wall or regional nodal recurrence.

2.5. Statistical analysis

This analysis was performed in analogy with Cheng et al. [7]. However, given the unequal times of follow-up, analysing LRR as a binary variable was not indicated. LRR was therefore analysed as a time-to-event variable. Cox proportional hazards models were used to analyse the association between potential risk factors and locoregional control (LRC) (LRR as a time-to-event variable). The multivariable model included the same variables as in Cheng et al. The Kaplan-Meier method was used to estimate 5-y LRC. The log-rank test was used to compare local control between groups. Finally, in analogy with the validation of Cheng et al. the influence of PMRT on the 5-year LRC rate was analysed by subgroup analyses with tumour size, multicentricity and the LRR score as defining factors. Analyses have been performed using SAS software (version 9.4 of the SAS System for Windows).

3. Results

3.1. Patient selection

We retrospectively identified 1989 BC cases, treated with ME of which either PMRT and/or ME were performed at the University Hospitals Leuven from 2000 until 2007. 32 male patients were excluded from analysis, followed by exclusion of 14 patients with distant metastasis at diagnosis; 106 patients with concurrent bilateral invasive BC and 211 and 40 patients whom received neo-adjuvant CT or neo-adjuvant HT respectively.

1586 patients remained eligible for analysis (Fig. 1).

3.2. Patient characteristics

An overview of patient characteristics is presented in Table 2.

According to the LRR scoring system 62.38% of patients were at low risk of recurrence (LRR score 0–1); 30.37% of patients were at intermediate risk of recurrence (LRR score 2–3) and 7.25% patients were at high risk of recurrence (LRR score 4 or more). In each group the majority of patients received adjuvant RT; in particular 58.43% of patients in the low-risk group, 88.96% of patients in the intermediate-risk group and 90.00% of patients in the high-risk group.

Median follow-up time was 11.4 years (range 0.0–18.7 years).

3.3. Locoregional recurrence

At the time of data collection only 46 (2.90%) patients had relapsed with a LRR.

Table 3 shows the univariable and multivariable analysis of prognostic factors for LRR analysed by Cox proportional hazards regression modelling. Significant risk factors for LRR on univariable analysis include nuclear grade 3 (HR 2.3, 95% CI 1.2–4.3), LVI (HR 4.0, 95% CI

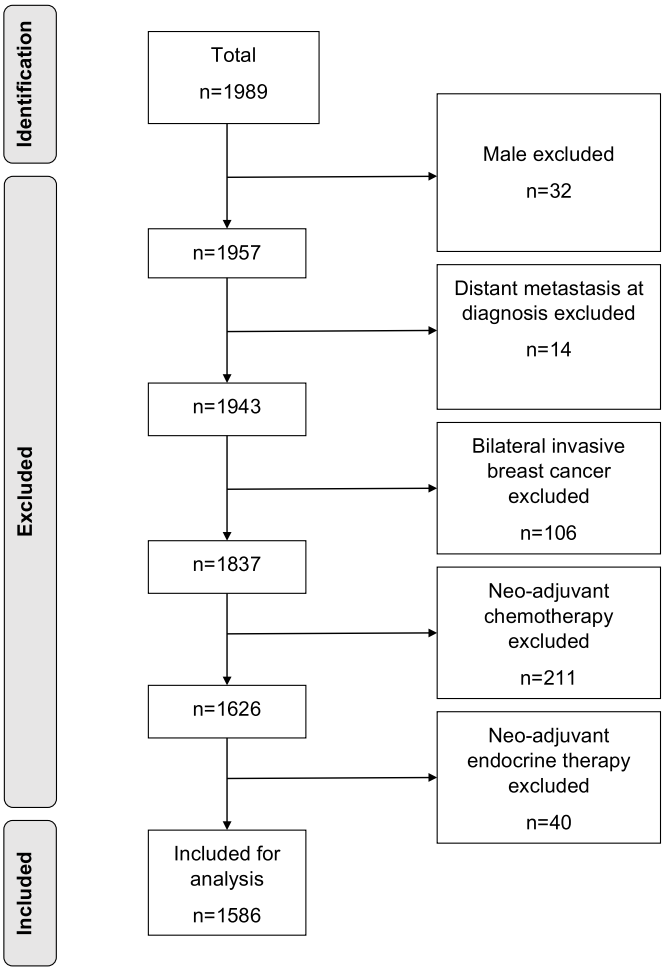

Fig. 1. Flow diagram of the patient selection process.

2.0–8.1), a LRR score of 2–3 (HR 2.4, 95% CI 1.2–5.1) and a LRR score of 4 or more (HR 3.4, 95% CI 1.1–10.3). The multivariable model includes the predictors from the multivariable model reported by Cheng et al. and shows that the LRR score is the most significant independent prognostic risk factor for predicting LRR. A LRR score of 2–3 has a HR of 4.1 (95% CI 1.8–9.6) and a LRR score of 4 or more has a HR of 6.4 (95% CI 1.9–22.1). Furthermore, multivariable analysis shows adjuvant RT is a significant independent factor for reducing LRR with a HR of 0.3 (95% CI 0.1–0.7).

3.4. LRC and the influence of PMRT

Table 4 demonstrates the influence of PMRT on LRC for different LRR scores and according to the nodal status. 1103 patients were classified according to the LRR scoring system developed by Cheng et al. of which 688 (62.38%) patients were at low risk of recurrence (LRR score 0–1), 335 (30.37%) patients were at intermediate risk of recurrence (LRR score 2–3) and 80 (7.25%) patients were at high risk of recurrence (LRR score ≥4). Of these the 5-year LRC rates with and without PMRT were 99.20% versus 99.21% ($p = 0.43$) in the low-risk group; 98.24% versus 85.74% ($p < 0.0001$) in the intermediate-risk group and 96.87% versus 85.71% ($p = 0.10$) in the high-risk group respectively. Furthermore Table 4 also shows the effect of PMRT on LRC for node negative and node positive patients separately. For the node negative patients in the low-risk group, no difference was found in the 5-year LRC rates with and without PMRT ($p = 0.3628$). However, even with a small number of 29 patients in the node negative intermediate risk group a remarkably statistically significant LRC rate difference was found of 100.00% versus

Table 2
Clinical characteristics of patients in this validation cohort.

Characteristics	Patient no.
Age	
≤35	n/N (%) 51/1586 (3.22%)
36–40	n/N (%) 86/1586 (5.42%)
41–50	n/N (%) 379/1586 (23.90%)
51–60	n/N (%) 419/1586 (26.42%)
>60	n/N (%) 651/1586 (41.05%)
Menstruation status	
Premenopausal	n/N (%) 566/1549 (36.54%)
Postmenopausal	n/N (%) 983/1549 (63.46%)
Missing data	*n 37*
Histology	
Favorable[a]	n/N (%) 48/1584 (3.03%)
Infiltrating ductal	n/N (%) 1136/1584 (71.72%)
Other invasive	n/N (%) 326/1584 (20.58%)
Mixed type	n/N (%) 74/1584 (4.67%)
Missing data	*n 2*
Axillary LN surgery	
Sentinel LN biopsy only	n/N (%) 61/1586 (3.85%)
Axillary LN dissection	n/N (%) 1518/1586 (95.71%)
No axillary LN surgery	n/N (%) 7/1586 (0.44%)
Pathological tumour size (cm)	
≤2.0	n/N (%) 481/1559 (30.85%)
>2.0	n/N (%) 1078/1559 (69.15%)
Missing data	*n 27*
LN positive	
0	n/N (%) 781/1578 (49.49%)
1–3	n/N (%) 519/1578 (32.89%)
4–9	n/N (%) 183/1578 (11.60%)
≥10	n/N (%) 95/1578 (6.02%)
Missing data	*n 8*
Pathology stage	
I	n/N (%) 349/1573 (22.19%)
II	n/N (%) 819/1573 (52.07%)
III	n/N (%) 405/1573 (25.75%)
Missing data	*n 13*
Estrogen receptor	
Negative	n/N (%) 317/1576 (20.11%)
Positive	n/N (%) 1259/1576 (79.89%)
Missing data	*n 10*
Progesterone receptor	
Negative	n/N (%) 503/1571 (32.02%)
Positive	n/N (%) 1068/1571 (67.98%)
Missing data	*n 15*
LVI	
Absent	n/N (%) 787/1108 (71.03%)
Present	n/N (%) 321/1108 (28.97%)
Missing data	*n 478*
Nuclear grade	
Grade 1	n/N (%) 134/1565 (8.56%)
Grade 2	n/N (%) 698/1565 (44.60%)
Grade 3	n/N (%) 733/1565 (46.84%)
Missing data	*n 21*
HER2/Neu	
Negative	n/N (%) 1268/1525 (83.15%)
Positive	n/N (%) 257/1525 (16.85%)
Missing data	*n 61*
Multiple foci or centers	
Absent	n/N (%) 1279/1579 (81.00%)
Present	n/N (%) 300/1579 (19.00%)
Missing data	*n 7*
ECE of axillary LN	
LN (−)	n/N (%) 781/1515 (51.55%)
LN (+) ECE (−)	n/N (%) 330/1515 (21.78%)
LN (+) ECE (+)	n/N (%) 404/1515 (26.67%)
Missing data	*n 71*
Adjuvant radiation therapy	
No	n/N (%) 519/1586 (32.72%)
Yes	n/N (%) 1067/1586 (67.28%)
Adjuvant hormonal therapy	
No	n/N (%) 357/1586 (22.51%)
Yes	n/N (%) 1229/1586 (77.49%)
Adjuvant chemotherapy	
No	n/N (%) 842/1586 (53.09%)
Yes	n/N (%) 744/1586 (46.91%)

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Table 2 (*continued*)

Characteristics	Patient no.
LRR score	
0–1	n/N (%) 688/1103 (62.38%)
2–3	n/N (%) 335/1103 (30.37%)
≥4	n/N (%) 80/1103 (7.25%)
Missing data	*n 483*

Abbreviations: ECE = extracapsular extension; LN = lymph node; LRR = locoregional recurrence; LVI = lymphovascular invasion.

[a] Favorable includes medullary, tubular and mucinous carcinomas.

76.92% (p = 0.045). There were no high-risk patients in the node negative group. For the node positive patients an additional difference was made between 1 - 3 node positive patients and 4 or more node positive patients. In the 1 to 3 node positive group 206 patients were found to be at low risk of recurrence, all having a 100.00% 5-year LRC rate with or without PMRT (p = 0.63). In the intermediate-risk group 5-year LRC rates were superior in the PMRT group than in the group without PMRT (97.55% versus 87.50% respectively, p = 0.01). In the high-risk group all 4 patients underwent PMRT so no comparison of 5-year LRC with or without PMRT could be made. For the patients with 4 or more positive axillary LN the 5-year LRC rates with and without PMRT were 97.55% versus 87.50% (p = 0.01) in the-intermediate risk group and 96.87% versus 85.71% (p = 0.10) in the high-risk group. No patients with 4 or more positive axillary LN were found to be at low risk.

3.5. Other prognostic factors

Table 5 shows the influence of PMRT on the 5-year LRC rate when tumour size and multicentricity are added to the LRR score as additional factors. For patients at low risk of recurrence (LRR score 0–1) there was no significant influence of primary tumour size nor multicentricity or PMRT on the 5-year LRC rate. For patients at intermediate risk (LRR score 2–3) with a tumour size > 2 cm or multicentricity on the other hand, the use of PMRT showed significantly improved 5-year LRC rates versus no PMRT (98.04% versus 84.25% respectively, p < 0.0001). Intermediate-risk patients without primary tumour size > 2 cm nor multicentricity had a 5-year LRC rate of 100.00% with PMRT versus 90.00% without PMRT (p = 0.07). When patients at intermediate risk have 0 to 3 positive axillary LN and a primary tumour size > 2 cm or multicentricity PMRT also leads to a superior 5-year LRC versus no PMRT in this group (97.40% versus 80.00% respectively, p < 0.0001). When these patients do not have primary tumour size > 2 cm nor multicentricity, PMRT does not lead to statistically significant better 5-year LRC rates than no PMRT (100.00% versus 88.89% respectively, p = 0.43). For patients at high risk of recurrence (score ≥4) with a primary tumour size > 2 cm or multicentricity our validation could not demonstrate a statistically significant benefit from PMRT at 5-year LRC (98.31% PMRT versus 85.71%, p = 0.05).

4. Discussion

Despite years of investigation selection of patients to undergo PMRT remains controversial. Initially, international guidelines stated that PMRT was recommended for high-risk patients only, including involved resection margins, at least four involved axillary LN and T3-T4 tumours independent of the nodal status [4]. Nevertheless, several more recent studies suggest we should also consider the routine use of PMRT in intermediate-risk patients with 1–3 positive axillary LN with the exception of axillary micrometastasis and isolated tumour cells [5,6,10]. Until now several studies have investigated this matter with conflicting results. On the one hand, the Early Breast Cancer Trialists' Collaborative Group for instance demonstrated a 10% 10-year risk reduction of any recurrence (locoregional and distant), as well as an 8% 20-year risk reduction of BC-related mortality with PMRT in node-positive patients

Table 3
Factors associated with 5-y LRR by univariable and multivariable analyses.

		Univariable analysis		Multivariable analysis	
Variables	**Patient no. n/N (%)**	**Hazard ratio of LRR (95% CI)**	**P value**	**Hazard ratio of LRR (95% CI)**	**P value**
Age at diagnosis					
>40	1449/1586 (91.36%)	1			
≤40	137/1586 (8.64%)	1.74 (0.78; 3.89)	0.18		
Tumour size (cm)					
≤2.0	481/1559 (30.85%)	1		1	
>2.0	1078/1559 (69.15%)	1.04 (0.55; 1.95)	0.91	0.84 (0.37; 1.85)	0.64
LN positive					
0	781/1578 (49.49%)	1			
1–3	519/1578 (32.89%)	1.04 (0.53; 2.05)	0.90		
≥4	278/1578 (17.62%)	1.41 (0.65; 3.09)	0.38		
Estrogen receptor					
Positive	1259/1576 (79.89%)	1			
Negative	317/1576 (20.11%)	1.57 (0.81; 3.04)	0.18		
HER2					
Negative	1268/1525 (83.15%)	1			
Positive	257/1525 (16.85%)	0.98 (0.44; 2.21)	0.97		
Nuclear grade					
I-II	832/1565 (53.16%)	1			
III	733/1565 (46.84%)	2.32 (1.24; 4.35)	0.01		
LVI					
Absent	787/1108 (71.03%)	1			
Present	321/1108 (28.97%)	4.02 (2.00; 8.08)	<0.0001		
Multicentricity					
Absent	1279/1579 (81.00%)	1		1	
Present	300/1579 (19.00%)	1.59 (0.82; 3.09)	0.17	1.81 (0.79; 4.12)	0.16
ECE					
Absent	1111/1515 (73.33%)	1			
Present	404/1515 (26.67%)	1.05 (0.51; 2.15)	0.90		
LRR score					
Score 0-1	688/1103 (62.38%)	1		1	
Score 2-3	335/1103 (30.37%)	2.43 (1.15; 5.10)	0.02	4.14 (1.79; 9.61)	<0.01
Score ≥4	80/1103 (7.25%)	3.36 (1.09; 10.30)	0.03	6.43 (1.87; 22.08)	<0.01
Adjuvant radiation therapy					
No	519/1586 (32.72%)	1		1	
Yes	1067/1586 (67.28%)	0.59 (0.33; 1.05)	0.07	0.32 (0.14; 0.74)	0.01
Adjuvant hormonal therapy					
No	357/1586 (22.51%)	1			
Yes			0.06		

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Table 3 (*continued*)

Variables	Patient no. n/N (%)	Univariable analysis Hazard ratio of LRR (95% CI)	P value	Multivariable analysis Hazard ratio of LRR (95% CI)	P value
	1229/1586 (77.49%)	0.56 (0.30; 1.03)			
Adjuvant chemotherapy					
No	842/1586 (53.09%)	1			
Yes	744/1586 (46.91%)	1.04 (0.58; 1.85)	0.90		

Table 4
LRC versus LRR score and nodal status.

Risk group	Radiation therapy	Patient no. n/N (%)	5-y LRC (%)	P value
All patients				
LRR score 0-1	Yes	402/772 (52.07%)	99.20%	0.43
	No	286/331 (86.40%)	99.21%	
LRR score 2-3	Yes	298/772 (38.60%)	98.24%	<0.0001
	No	37/331 (11.18%)	85.74%	
LRR score ≥4	Yes	72/772 (9.33%)	96.87%	
	No	8/331 (2.42%)	85.71%	0.10
Node (−) patients				
LRR score 0-1	Yes	223/239 (93.31%)	98.55%	0.36
	No	259/272 (95.22%)	99.15%	
LRR score 2-3	Yes	16/239 (6.69%)	100.00%	
	No	13/272 (4.78%)	76.92%	0.045
Node 1–3 (+) patients				
LRR score 0-1	Yes	179/354 (50.56%)	100.00%	0.63
	No	27/44 (61.36%)	100.00%	
LRR score 2-3	Yes	171/354 (48.31%)	97.55%	0.01
	No	17/44 (38.64%)	87.50%	
LRR score ≥4	Yes	4/354 (1.13%)	–	
	No	0/44 (0.00%)	–	–
Node ≥4 (+) patients				
LRR score 2-3	Yes	111/179 (62.01%)	97.55%	0.01
	No	7/15 (46.67%)	87.50%	
LRR score ≥4	Yes	68/179 (37.99%)	96.87%	
	No	8/15 (53.33%)	85.71%	0.10

Abbreviations: LRC = locoregional control; LRR = locoregional recurrence.

Table 5
Incorporating other risk factors into the LRR score.

Risk group	T > 2 cm or multiple	Radiation therapy	Patient no. n/N (%)	5-y LRC (%)	P value
LRR score 0-1	Yes	Yes	346/401 (86.28%)	99.37%	0.79
		No	168/284 (59.15%)	98.60%	
		Yes	55/401 (13.72%)	98.11%	
	No	No	116/284 (40.85%)	100.00%	0.58
LRR score 2-3	Yes	Yes	268/297 (90.24%)	98.04%	<0.0001
		No	27/37 (72.97%)	84.25%	
		Yes	29/297 (9.76%)	100.00%	
	No	No	10/37 (27.03%)	90.00%	0.07
LRR score 2–3 and LN (+) < 4	Yes	Yes	161/186 (86.56%)	97.40%	<0.0001
		No	21/30 (70.00%)	80.00%	
		Yes	25/186 (13.44%)	100.00%	
	No	No	9/30 (30.00%)	88.89%	0.43
LRR score ≥4	Yes	Yes	65/72 (90.28%)	98.31%	0.05
		No	8/8 (100.00%)	85.71%	
		Yes	7/72 (9.72%)	–	
	No	No	0/8 (0.00%)	–	–

[5]. Additionally they demonstrated that the benefits of PMRT are independent from the number of involved axillary LN. On the other hand some other recent studies question the advantages of PMRT. The breast international group (BIG 02.98 trial) for example confirmed LRC improved with PMRT in 1–3 node positive patients, but did not confirm superior BC specific nor overall survival with PMRT [11]. Another study showed similar results, with no significant overall survival with PMRT in patients with T1-T2 N1 disease [12]. As a result of these controversial findings some studies even discourage using nodal cut-off as an indicator for adjuvant therapy, because they could not demonstrate a prognostic cut-off in the number of involved LN to differ between a low and a high-risk group [13].

In this respect many research has been conducted in an attempt to identify prognostic factors that indicate those patients that benefit the most from PMRT [14–21]. Besides nodal stage, risk factors identified were young age, tumour size, ECE, ER negative status, triple negative breast cancer, histologic grade, lymph node ratio (ratio of the number of metastatic lymph nodes to the number of removed lymph nodes), a preoperative high neutrophil-to-lymphocyte ratio and a low neutrophil-to-monocyte ratio. The SUPREMO trial (BIG 2.04) is a current on-going trial that determines the overall survival of women at intermediate risk for LRR of BC treated with adjuvant ipsilateral chest wall RT after ME [22]. The results of this study are awaited. To date, guidelines and nomograms help us in the clinical decision-making of PMRT. The scoring system developed by Cheng et al. validated in this study, incorporates four risk factors: young age, LVI, ER negativity, and the number of involved axillary LN [7].

The aim of our study was to validate this scoring system developed by Cheng et al. From our data we can conclude patients in the low-risk group (LRR score 0–1) have good local control with or without PMRT. In the intermediate-risk group (LRR score 2–3) all patients benefit significantly from PMRT with an improved 5-year LRC rate. For patients at high risk of recurrence (LRR score ≥4) our data show a trend towards improved 5-year LRC rates with PMRT, although this tendency is not found to be statistically significant perhaps because numbers in this subgroup were too small to draw conclusions from.

Therefore, we would recommend to spare patients at low risk of recurrence (LRR score 0–1) from PMRT, in this manner avoiding unnecessary side-effects of breast irradiation without compromising 5-year LRC. On the other hand, we would recommend adding PMRT to the treatment of patients at intermediate and high risk of recurrence (LRR score 2 or more) because our data show significantly better 5 year LRC rates with PMRT in the intermediate-risk group versus no PMRT, as well as a tendency towards significant better 5 year LRC in the high-risk group with PMRT versus no PMRT.

There are of course several limitations to our study. Mostly the retrospective design leading to several missing data, as well as the sometimes small numbers in specific subgroups and a low event rate with a total of 46 patients with a LRR perhaps leading to statistically insignificant results in some subgroups. Furthermore, the increasing role of neoadjuvant systemic treatment in BC care was not represented in our

study due to the exclusion of patients treated with neoadjuvant chemotherapy and hormonal therapy from analysis. Consequently, the efficiency of the LRR scoring model in this subgroup of patients remains to be determined.

We expect that in the future the selection of patients to undergo PMRT will be increasingly based on biological and molecular profiling of the tumour cells. Several studies already investigated this matter, with potential aid of genetic profiling (e.g., Oncotype-DX) and the tumour response to preoperative chemotherapy in decision making for PMRT [23–26].

5. Conclusion

To conclude, our validation of the LRR scoring system by Cheng et al. suggests it can be used to point out patients that would benefit from PMRT. We recommend further validation of this scoring system by other independent institutions before application in clinical practice.

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Declaration of competing interest

None.

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