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Postmastectomy radiotheraphy

The Cambridge post-mastectomy radiotherapy (C-PMRT) index: A practical tool for patient selection

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ABSTRACT

Background and purpose: Post mastectomy radiotherapy (PMRT) reduces loco-regional recurrence (LRR) and has been associated with survival benefit. It is recommended for patients with T3/T4 tumours and/or ⩾4 positive lymph nodes (LN). The role of PMRT in 1–3 positive LN and LN negative patients is contentious. The C-PMRT index has been designed for selecting PMRT patients, using independent prognostic factors for LRR. This study reports a 10 year experience using this index.
Materials and methods: The C-PMRT index was constructed using the following prognostic factors (a) number of positive LN/lymphovascular invasion, (b) tumour size (c) margin status and (d) tumour grade. Patients were categorised as high (**H**) risk, intermediate (**I**) risk and low (**L**) risk. PMRT was recommended for **H** and **I** risk patients. The LRR, distant metastasis and overall survival (OS) rates were measured from the day of mastectomy.
Results: From 1999 to 2009, 898 invasive breast cancers in 883 patients were treated by mastectomy (**H**: 323, **I**: 231 and **L**: 344). At a median follow up of 5.2 years, 4.7% (42/898) developed LRR. The 5-year actuarial LRR rates were 6%, 2% and 2% for the **H**, I and **L** risk groups, respectively. 1.6% (14/898) developed isolated LRR (**H** risk $n = 4$, I risk group $n = 0$ and **L** risk $n = 10$). The 5-year actuarial overall survival rates were 67%, 77% and 90% for **H**, I and **L** risk groups, respectively.
Conclusion: Based on published literature, one would have expected a higher LRR rate in the **I** risk group without adjuvant RT. We hypothesise that the **I** risk group LRR rates have been reduced to that of the **L** risk group by the addition of RT. Apart from LN status and tumour size, other prognostic factors should also be considered in selecting patients for PMRT. This pragmatic tool requires further validation.

Post mastectomy radiotherapy (PMRT) reduces loco-regional recurrence (LRR) and improves overall survival [1–3]. There is international consensus to recommend PMRT for patients with tumour size ⩾5 cm (T3), tumour invasion of the skin, pectoral muscle or chest wall (T4) and patients with ⩾4 positive lymph nodes (LN) [4–6]. However, the role of PMRT for patients with 1–3 positive LN and LN negative patients is contentious. Trials endorsing the use of PMRT for 1-3 positive LN are often criticised for the use of less intensive chemotherapy and limited axillary dissection and the role of radiotherapy in this subgroup of patients'

remains unclear [7,8]. An international survey amongst members of the American Society for Therapeutic Radiology and Oncology (ASTRO) and the European Society for Therapeutic Radiology and Oncology (ESTRO) highlighted a 40:60 split opinion amongst respondents on the role of PMRT for patients with 1–3 positive LN [9]. Apart from LN status, other prognostic factors for LRR include tumour grade, lymphovascular invasion (LVI), oestrogen receptor (ER) status, tumour size and young age, with the risk of LRR increasing proportionally to the number of adverse prognostic factors [10–14]. It is unclear on how these prognostic factors should be used for selecting patients for PMRT.

The need for clinical trials of PMRT for this sub-group of patients has been recognised as an international priority. The North American Breast Intergroup trial, set up specifically to address this issue, closed prematurely in 2003 due to poor accrual [15]. The

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European SUPREMO trial has completed recruitment to investigate the effects of PMRT on LRR, overall survival (OS) and quality of life for this group of patients. However, it will take some years before any conclusive results become available [16]. In 1999, a practical index was designed at the Cambridge Breast Unit (CBU) for selecting patients for PMRT. The Cambridge post-mastectomy radiotherapy (C-PMRT) index is based on patient's LN status and other prognostic factors for LRR. This study reports a 10 year experience of using this index.

Methods and materials

Cambridge post mastectomy radiotherapy index (C-PMRT index)

The C-PMRT index was constructed with scores (1–3) allocated in each of four categories including the number of positive LN/LVI, tumour size, margin status and tumour grade (Table 1). T3/T4 tumour and/or positive deep margin and/or $\geqslant 4$ positive LN resulted in a score of 3 and patients were categorised as high (**H**) risk. 1–3 positive LN or a tumour size of 3–5 cm resulted in a score of 2. A score of 1 was allocated for any of the following factors: LVI, tumour size 2–3 cm or grade 3 tumour. Other patients with an aggregate score $\geqslant 3$ were categorised as intermediate (**I**) risk and <3 as low (**L**) risk. PMRT was recommended for the **H** and **I** risk patients.

Study population

All women treated by simple mastectomy for invasive breast cancer from 1999 to 2009 at the Cambridge Breast Unit (CBU) were included in this study. Patients were identified from the joint clinical information service (JCIS) database and their paper and electronic hospital records were reviewed to obtain the relevant information. Patients treated with mastectomy for local recurrence after breast conserving surgery and non-radical surgery were excluded. All patients had either sentinel lymph node biopsy (SLNB) or axillary clearance (if LN positive). Patients with microscopic axillary disease were regarded as lymph node positive and given a score of "2" on the C-PMRT index. Patients received adjuvant chemotherapy according to local protocols and radiotherapy was deferred until the completion of chemotherapy. Anthracycline-based chemotherapy was predominantly used with additional taxanes in selected cases. For patients receiving neo-adjuvant chemotherapy, a decision for PMRT was made prior to starting their chemotherapy, based on clinical, radiological and histopathological features. These patients had SLNB prior to starting neo-adjuvant chemotherapy. All ER positive patients also received systemic endocrine therapy. Routine staging investigations were carried out for patients with American Joint Committee on Cancer stage 3 disease unless clinically indicated. LRR and systemic relapse were treated as per the local policy.

Radiotherapy treatment

Radiotherapy was delivered to the chest wall using tangents with 6MV photons to a dose of 40 Gy in 15 fractions over 3 weeks. 0.5 cm tissue equivalent bolus for 7 of 15 fractions was applied to increase the skin dose in most cases. If the skin was involved (T4 lesions), a full 1 cm bolus was applied to all 15 fractions. The radiotherapy field borders extended medially to the midline, laterally to the mid axillary line, inferiorly to 1–2 cm below the level of the inframammary fold and superiorly below the level of the supra-sternal notch. A supraclavicular (SCF) radiation field was only added if there were $\geqslant 4$ positive axillary LN. Axillary fields were not routinely used unless there was evidence of macroscopic residual disease following axillary clearance. The internal mammary LN chain was only irradiated if a positive internal mammary LN was encountered during surgery or radiological imaging. The radiation dose to the SCF and/or internal mammary LN chain was 40 Gy in 15 fractions over 3 weeks.

Treatment endpoints and statistical analysis

All patients were followed up annually at the Cambridge Breast Unit for a minimum of five years. The LRR, distant metastasis and OS data was collected from patient's medical records. The median length of follow up was measured from the date of mastectomy to the date of last follow up or date of death. Isolated LRR was defined as recurrent disease on the ipsilateral chest wall and/or regional nodal fields without evidence of distant metastases for at least 3 months. The probabilities of LRR and OS were calculated by the Kaplan–Meier method. The comparison between the **L** and **I** risk group was performed using the log rank test with a two sided t-test. All statistical analysis was done using STATA version 10.1 (STATA statistical software, release10; Stata Corporation, College station, TX).

Results

From 1999 to 2009, a total of 898 invasive breast cancers in 883 patients were treated by mastectomy at the CBU (**H**: 323, **I**: 231 and **L**: 344). 42/231 (18%) **I** risk group patients were LN negative, but had an aggregate score $\geqslant 3$ from other adverse prognostic factors and were recommended PMRT. 35/344 (10%) LN positive patients had an aggregate score <3 and were categorised into the **L** risk group. The patients median age was 60 years (range 23–96 years). For patients with positive LN (486/898) on SLNB, completion axillary clearance was recommended. The median number of LN removed during axillary clearance was 16 (range 1–48). 130/898 (14.5%) patients received neo-adjuvant chemotherapy and 220/898 (24.5%) received adjuvant chemotherapy. Anthracycline ± taxanes based chemotherapy regimens were most commonly used. Other patient characteristics are summarised in Table 2.

At a median follow up of 5.2 years, 4.7% (42/898) developed LRR. 5 year actuarial LRR rates were 6%, 2% and 2% for the **H**, I and **L** risk groups, respectively (Fig. 1). Only 1.6% (14/898) developed isolated LRR (**H** risk $n = 4$, I risk $n = 0$ and **L** risk $n = 10$). The most common sites of LRR were the chest wall ($n = 22$) and axilla ($n = 11$) (Table 3). 5 year metastatic free rates were 71%, 83% and 95% for the **H**, I and **L** risk groups, respectively. 5 year actuarial

Table 1
Cambridge post-mastectomy radiotherapy (C-PMRT) index.

Score	3	2	1
Number of positive lymph nodes or LVI	$\geqslant 4$	1–3	LVI
Invasive tumour size	>50 mm (T3) or T4	30–50 mm	20–29 mm
Excision margins	Deep margin <1 mm or pectoral muscle invasion	–	–
Tumour grade	–	–	Grade 3

LVI: lymphovascular invasion.
T4: tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules).

Table 2
Summary of patient's characteristics.

Characteristic	Number of patients (%)
Tumour size	
⩽2 cm	373 (41.5)
2–5 cm	408 (45.5)
⩾5 cm	117 (13)
Tumour grade	
Grade 1	76 (8.5)
Grade 2	416 (46.3)
Grade 3	380 (42.3)
Unknown	26 (2.9)
ER status	
Positive	771 (85.9)
Negative	118 (13.1)
Unknown	9 (1.0)
Her2 status	
Positive	104 (11.6)
Negative	421 (46.9)
Unknown/not done	373 (41.5)
Lympho-vascular invasion (LVI)	
Absent	557 (62.1)
Present	267 (29.7)
Unknown	74 (8.2)
Lymph nodes status	
0	412 (45.9)
1–3	301 (33.5)
4–9	118 (13.1)
⩾10	67 (7.5)
Deep margins clear	
No	23 (2.6)
Yes	871 (97)
Unknown	4 (0.4)
Systemic chemotherapy	
No	534 (59.5)
Neo-adjuvant	130 (14.5)
Adjuvant	220 (24.5)
Unknown	14 (1.5)

Table 3
Sites of loco-regional recurrence (LRR).

Site	LRR (%)	Risk group	Isolated LRR (%)	Risk group
Chest wall	22 (52.4%)	**H**: 10, **I**: 3 and **L**: 9	9 (64.3%)	**H**: 1 and **L**: 8
Axilla LN	11 (26.2%)	**H**: 9 and **L**: 2	4 (28.6%)	**H**: 2 and **L**: 2
SCF LN	5 (11.9%)	**H**: 2 and **I**: 3	1 (7.1%)	**H**: 1
IMC LN	1 (2.4%)	**I**: 1	0	–
Chest wall + regional nodes	3 (7.1%)	**H**: 3	0	–
Total patients	42		14	

LN: lymph nodes.
IMC: internal mammary chain.
H: high risk group.
I: intermediate risk group.
L: low risk group.
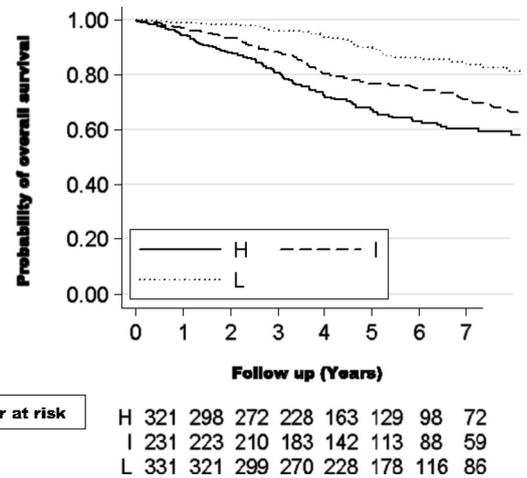
Fig. 2. Five-year overall survival rates within the low (**L**), intermediate (**I**) and high (**H**) risk group.

Fig. 1. The loco-regional recurrence rates within the low (**L**), intermediate (**I**) and high (**H**) risk group.

OS rates were 67%, 77% and 90% for the **H**, I and **L** risk groups, respectively (Fig. 2).

Compliance to C-PMRT index

305/323 (94%) **H** risk category cases and 185/231 (80%) **I** risk category cases received PMRT. The reasons for non-compliance to the index were: old age (25 cases), medical co-morbidities (9

cases), metastatic disease/death pre-radiotherapy (7 cases), patient refusal (5 cases), wound healing (2 cases) and unknown (16 cases). 27/344 (8%) **L** risk category cases had PMRT as recommended by the multi-disciplinary team (MDT). The reasons for recommending PMRT were multi-focal disease (11 cases), young age (6 cases), ER negative tumour (3 cases), limited axillary dissection (1 case), patient request (1 case) and unknown (5 cases).

Discussion

PMRT lowers the risk of LRR and for some patients, improves overall survival [17]. The international consensus recommends PMRT for patients with T3/T4 tumours or ⩾4 positive LN. The Danish Breast Cancer Cooperative Group (DBCCG) trials 82b and 82c and the British Columbia trial concluded that PMRT improves overall survival irrespective of the number of positive LN [1–3]. However, these trials were criticised for using less intensive chemotherapy and limited axillary dissection. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview also indicated similar benefits of PMRT for patients with 1–3 and ⩾4 positive LN [17]. However, data on LN involvement was not available for more than half the patients and most of the patients included in the meta-analysis were from the DBCCG trials. Overgaard et al.

[18] presented a subgroup analysis of the DBCCG trials, only including LN positive patients who met the criteria of having 8 or more LN removed and showed similar survival benefit of PMRT in patients with 1–3 and ⩾4 positive LN. As a result of this, some international guidelines now suggest that PMRT should be considered for women with 1–3 positive LN [19,20].

Loco-regional and/or systemic cancer recurrence are both devastating for patients and the overall treatment strategy should include both optimal local and systemic therapy. On-line tools like *Adjuvant online* and *Predict* take into account several prognostic factors to aid selection of patients for systemic therapy [21,22]. Apart from LN status, a number of other prognostic factors for LRR have been reported, with the risk of LRR increasing proportionally to the number of adverse prognostic factors [10,12,13]. Jagsi et al. [10] reported tumour size >2 cm, LVI, margins <2 mm and premenopausal status as independent prognostic factors for LRR in LN negative patients treated with mastectomy. The 10 year LRR was 10% for those with one risk factor, 18% with two risk factors and 40% with three risk factors without PMRT. Similarly, a study from Massachusetts reported tumour size ⩾2 cm, positive margins, young age, no systemic therapy and LVI as poor prognostic factors for LRR in LN negative patients, with a 20% risk of LRR without PMRT amongst patients with three or more prognostic factors [11].

The CBU developed the C-PMRT index in 1999, based on the principle that along with LN status, other prognostic factors for LRR should also be considered for selecting PMRT patients. The published literature at that time supported that the risk of LRR without adjuvant radiotherapy could be ⩾20% for the **H** and **I** risk patients and hence these patients were considered for PMRT. The 5 year LRR in this study is excellent for all three risk groups (**H**: 6%, **I**: 2%, **L**: 2%) with no significant difference between the **I** and **L** risk group patients ($p = 0.95$ on the log rank test). The incidence of LRR is falling, which can be attributed to the improvement in imaging, histopathology assessment and surgery, more effective systemic therapy and better RT techniques [23]. We hypothesise that the **I** risk group LRR rates could have been reduced to that of the **L** risk group in this study by the addition of PMRT.

Unlike the DBCCG trials and the British Columbia trial, RT was limited to the chest wall alone in this series, except for patients with ⩾4 positive LN and/or internal mammary LN. Isolated nodal recurrences were uncommon in this series and the most common site of isolated LRR was the chest wall (see Table 3). These results are in keeping with the other reports which suggest that for patients with adequate axillary assessment, the most common site of LRR is the chest wall [10,11,24,25].

Role of PMRT with systemic therapy

The use of contemporary systemic therapies also reduces the risk of LRR and one can argue that the risk of LRR for the **I** risk group without RT will now also be lower (∼10%) [26]. Many clinicians however will still consider PMRT for a LRR risk of 10%. In addition, if one believes that the ratio between prevention of LRR and breast cancer death is four to one [17], the addition of PMRT for the **I** risk group may equate to an improvement in OS by 2–3%. It is also plausible that the ratio between prevention of LRR and breast cancer death may not be constant across all patient groups. Patients with ⩾4 positive LN are more likely to harbour micro-metastatic disease than those with 1–3 positive LN or LN negative patients with other adverse prognostic features. The improvement in loco-regional control with PMRT in the **I** risk group is more likely to translate into survival benefit as the competing risk of dying from pre-existing micro-metastatic disease is lower. This hypothesis has been supported in the EBCTCG overview and other retrospective studies [17,27,28]. In the EBCTCG overview, PMRT reduced the 5 year LRR by 11.6% (15.5% versus 4%)

and 15 years breast cancer specific mortality by 4.4% (47.7% versus 43.3%) amongst women with 1–3 positive LN. In contrast, for women with ⩾4 positive LN, 5 year LRR was reduced by 14.8% (26.3% versus 11.6%) but the 15 year breast specific mortality was only reduced by 2.3% (70.3% versus 68%). Kyndi et al. [27] divided 1000 patients from the DBCCG trials 82b and 82c into three sub-groups of good, intermediate and poor prognosis based on their local recurrence risk probability. For the "poor" prognosis group, PMRT reduced the local recurrence probability by 36% but this large reduction in local recurrence failed to translate into absolute reduction in breast cancer mortality. In contrast, PMRT reduced the local recurrence probability by 21% and 11% in the "intermediate" and "good" prognosis group respectively, and this translated into an 11% reduction in breast cancer mortality in both groups. Similar results were shown in the combined analysis of the EORTC 10801, 10854 and 10902 trials, with PMRT improving loco-regional control for both 1–3 and ⩾4 positive LN patients, with the survival benefit amongst patients with 1–3 positive LN alone [28]. Contemporary systemic therapy can more successfully eradicate distant micro-metastatic disease and is more likely to compliment PMRT, than being competitive.

Molecular predictors of loco-regional recurrence (LRR)

Apart from clinical variables discussed above, molecular markers including oestrogen receptor, Her-2 and Ki-67 status have also been associated with risk of LRR post mastectomy [29–31]. Based on these molecular markers, patients have been sub-classified as: luminal A/B, Her-2 enriched and basal phenotype with the risk of LRR highest amongst Her-2 enriched and basal phenotype tumours [29]. Similarly, Voduc et al. [32] completed a semi quantitative analysis of oestrogen receptor, progesterone receptor, Ki-67, Her-2, epidermal growth factor receptor and cytokeratin 5/6 on 2985 patients and classified patients into the following categories: luminal A, luminal B, luminal-Her-2, Her-2 enriched, basal type and triple negative phenotype-non basal. At a median follow up of 12 years after mastectomy, patients with luminal B, luminal Her-2, Her-2 enriched and basal phenotype were found to be at the higher risk of LRR. Mamounas et al. [33] showed a strong association between the 21-gene OncotypeDX recurrence score and risk of LRR ($p < 0.001$) amongst node negative, oestrogen receptor positive breast cancer patients treated with tamoxifen. However, most of the studies using molecular profiling for LRR were conducted in the pre-trastuzumab era and it is possible that the use of adjuvant trastuzumab will negate Her-2 overexpression as a risk factor for LRR [34].

In the current study, both oestrogen receptor and Her-2 phenotype were available for 523 patients and most patients with Her-2 overexpression received adjuvant trastuzumab. As an exploratory analysis, these patients were subcategorised as: Er+ve/Her2−ve,

Table 4
LRR after sub-classification of patients based on molecular profiling.

	Loco-regional recurrence rates	
	PMRT: yes (number of patients)	PMRT: no (number of patients)
Er+ve/Her2−ve (n = 369)	3.1% (225)	5.5% (144)
Er+ve/Her2+ve (n = 64)	6.2% (48)	6.2% (16)
Er−ve/Her2+ve (n = 40)	6.9% (29)	0% (11)
Er−ve/Her2−ve (n = 50)	9.1% (33)	0% (17)

Er: oestrogen receptor.
Her-2, human epidermal growth receptor-2.

Er+ve/Her2+ve, Er−ve/Her2−ve and Er−ve/Her2+ve and their LRR were analysed at five years (Table 4). For "High" and "Intermediate" risk patients who received PMRT, the LRR rates were higher amongst ER−ve and Her-2 overexpressing tumours. On the contrary, for patients with favourable clinical variables ("Low" risk group), this did not hold true. It is possible that these results can be explained by chance as there were small numbers of patients in the Low risk group. However, it is also possible that these results are real and molecular profiling of tumours provide additional information on LRR risk when used in conjunction with other clinical variables including tumour size, lymph node status and LVI. This hypothesis is supported by the large study of 2985 patients, where along with tumour molecular phenotype; large tumour size, positive lymph nodes and high grade tumour were reported as independent predictors of LRR [32]. The European SUPREMO trial sub-study TRANS-SUPREMO is collecting tissue block for patients who have developed recurrence and will provide more information on the role of molecular profiling in the future [16].

Late side effects with PMRT

Clinicians may have concerns that the late cardiac/pulmonary toxicity and risk of secondary cancer from RT may counterbalance the potential benefit of PMRT in the I risk group. However, with improvement in RT techniques and use of CT planning, irradiation dose to the healthy normal tissue is decreasing [35]. The risk of cardiac- and pulmonary-related mortality and secondary cancer continues to decrease and may only be slightly higher as compared to the non-RT patients in the era of modern RT [36,37]. The interaction between cardiotoxic agents (anthracycline and trastuzumab) and RT remains to be elucidated. Another important adverse effect of PMRT is the increased risk of capsular contracture amongst patients with implant-based reconstruction [38]. Hence, the risks and benefits of PMRT should be individually discussed with patients. In this series, only four I risk patients declined PMRT secondary to implant based reconstruction.

Limitations

This study reports on the patients outcome stratified according to the C-PMRT index over a 10 year period and like any other retrospective study is prone to stage migration. Ideally, the variables for a prognostic index should be based on multivariate analysis from a RCT. However, with paucity of trial data, a more pragmatic approach was taken and the C-PMRT index was generated using published literature on prognostic factors for LRR. As there is insufficient evidence to rank individual risk factors in order of their impact on LRR, an arbitrary weighting was given to the variables. The tumour grade and LVI were identified as risk factors from retrospective series and given a low weighting (score = 1). 1–3 positive LN was given a higher weighting (score = 2) based on the results of the RCTs [1,2]. Increment in tumour size has been associated with higher risk of LRR [24]. So tumour size 2–3 cm was given low weighting (score = 1) and tumour size 3–5 cm was given a higher weighting (score = 2). Other possible prognostic factors for LRR including young age and ER status were not included in the index, though it influenced the MDT recommendations for some patients. We accept that a pragmatic tool like C-PMRT index will benefit from external validation and require adaptation as new information on predictive and prognostic markers of LRR becomes available [32].

The C-PMRT index was designed for patients treated with adjuvant systemic therapy. However, there is little consensus on the role of PMRT after primary chemotherapy. Patients who received primary chemotherapy are also included in this report as the same index was used for patient selection. The decisions on PMRT were made prior to patients starting chemotherapy using all available information. A repeat analysis after excluding patients with primary chemotherapy show similar results (appendix: LRR Fig. 3 and OS Fig. 4).

Conclusions

Apart from LN status and tumour size, other adverse prognostic factors should also be considered in selecting patients for PMRT. The SUPREMO trial will provide level I evidence on the role of PMRT for intermediate risk patients in the future. The molecular profiling of tumour is likely to complement clinical variables when selecting patients for PMRT and merits further investigation. Meanwhile, based on the available evidence today, it is reasonable to consider a practical tool like the C-PMRT index for patient's selection outside the framework of a clinical trial. This pragmatic tool will benefit from further validation.

Conflict of interest

None.

Disclaimer

The views expressed in this publication are those of the authors and not necessarily those of the Medical Research Council, National Health Services, National Institute for Health Research or the Department of Health.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2013.09.024.

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