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Factors Predicting Locoregional Recurrence after Wide Local Excision – Experience from a Tertiary Centre

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Abstract

Introduction: Locoregional Recurrence (LR) can still develop after breast conserving surgery despite adequate surgical margins and whole breast radiation, even with a boost to the tumour bed. In this study, we evaluated predictors of LR and examined its effect on survival.

Methods: Retrospective review was performed of 713 women diagnosed with breast cancer from 2004 to 2011.

Results: Locoregional recurrence developed in 74 women (10.4%) and occurred adjacent to the previous tumour bed in half the instances. Surgical margins (P<0.001), nodal involvement (P=0.002), radiation (P=0.003) and 5 years of hormonal therapy (P<0.001) were independent predictors of LR. While LR had no effect on overall survival in women with DCIS (P=0.756), it was associated with poorer distant recurrence-free and overall survival in women with invasive cancer (P<0.001, HR 114.200, 95% CI 40.630–320.900 and P<0.001, HR 14.210, 95% CI 5.651–35.720 respectively). Radiation and hormonal therapy improved survival, showing an additive effect. Radiation, without hormonal therapy, did not improve recurrence-free survival, both locoregional (P=0.190) and distant (P=0.189), nor overall survival (P=0.236) in node-positive disease. However, radiation conferred survival benefit even when given alone in node-negative disease.

Conclusion: The rate of locoregional recurrence after breast conserving surgery was 10.4%. Adequate surgical margins and nodal disease were independently associated with LR and both radiation and hormonal therapy improved survival. Survival benefit was greatest in women who completed both radiation and 5 years of hormonal therapy.

Keywords: Recurrence; Wide local excision; Radiation; Hormonal therapy

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Introduction

Breast conservation therapy offers women with breast cancer a cosmetically more acceptable alternative to mastectomy. Post-operative whole breast radiation given after Wide Local Excision (WLE) eradicates occult residual foci in the remnant breast and produces long-term survival outcomes that are equivalent to mastectomy [1,2]. But despite adequate surgical margins and whole breast radiation, including a boost to the tumour bed, Locoregional Recurrence (LR) rates after WLE are still slightly higher than after mastectomy [2,3]. Overall survival is not compromised since LR can develop in the absence of systemic disease. However, LR is strongly associated with systemic failure and in the absence of reliable indicators to predict the likelihood of this, there is a move towards recommending further systemic treatment even for isolated LR, especially in hormone unresponsive disease [4,5]. Over-treatment is inevitable with this approach and reducing the incidence of LR therefore not only improves survival, but also limits the economic and psychological burden of treatment.

Despite the significance of surgical margin status, the definition of what constitutes an adequate surgical margin was not standardized until the latest consensus released by the Society of Surgical Oncology-American Society for Radiation Oncology. At our unit, close margins where the tumour was less than 1 mm away from the resection edge, were also considered inadequate and repeat surgery was recommended. The latest consensus considers the margin clear so long as no tumour is demonstrated on the inked margins, without any requirement of a minimum distance from the

Table 1: Univariate correlation analyses of Locoregional Recurrence (LR) with standard clinicopathological parameters and treatments.

	Women with LR (n=74)	Women without LR (n=639)	P value
Median age (years)	53.5 (28–90)	53 (24–90)	0.538
Tumour size (mm)	20.0 (1–50)	17.0 (1–60)	0.068
Ethnicity			
Chinese	53 (71.6)	528 (82.6)	0.005
Malay	5 (6.7)	55 (8.6)	
Indian	11 (14.9)	33 (5.2)	
Others	5 (6.7)	23 (3.6)	
Disease stage			
DCIS	18 (24.3)	155 (24.3)	0.126
I	22 (29.7)	249 (39.0)	
II	24 (32.4)	192 (30.0)	
III	10 (13.5)	43 (6.7)	
Margin status			
Clear	49 (66.3)	541 (84.7)	<0.001
Close and involved	25 (33.8)	98 (15.3)	
Tumour histology			
DCIS	18 (24.3)	155 (24.3)	0.99
Invasive carcinoma	56 (75.7)	484 (75.7)	
ER status			
Positive	43 (58.1)	477 (74.6)	0.007
Negative	24 (32.4)	129 (20.2)	
PR status			
Positive	31 (41.9)	358 (56.0)	0.053
Negative	35 (47.3)	245 (38.3)	
HER2 status*			
Positive	7 (12.5)	58 (12.0)	0.224
Negative	18 (32.1)	262 (54.1)	
Nodal status*			
Positive	25 (44.6)	123 (25.4)	0.002
Negative	31 (55.4)	361 (74.6)	
Radiation therapy			
Yes	51 (68.9)	586 (91.7)	<0.001
No	23 (31.1)	53 (8.3)	
Hormonal therapy+			
Yes	11 (14.9)	334 (52.3)	<0.001
No	39 (52.7)	164 (25.7)	
Chemotherapy*			
Yes	26 (46.4)	254 (52.5)	0.37
No	13 (23.2)	92 (19.0)	
Targeted therapy*			
Yes	2 (3.6)	31 (6.4)	0.17
No	8 (14.3)	34 (7.0)	

*Invasive cancers only. DCIS: Ductal Carcinoma *in Situ*; ER: Oestrogen Receptor; PR: Progesterone Receptor; HER2: Human Epidermal Growth Factor Receptor 2; +Refers to women who completed 5 years of hormonal therapy.

resection edge [6]. Close margins are therefore now considered clear and repeat surgery may have little additional benefit given that a boost to the tumour bed is also routine [7]. An incremental reduction in LR has not been observed with wider surgical margins and would suggest that apart from possible microscopic foci of residual tumour around the surgical bed that may remain undetected, occult tumour foci are also present in the rest of the remnant breast, underscoring the importance of whole breast radiation [6]. However, LR can still

occur in spite of adequate surgical margins and an optimal radiation regimen. Various other factors, including young age at diagnosis, high tumour grade, have also been identified as risk factors [8]. The association with young age may in fact be related to tumour biology rather than to the treatments. Tumours with more aggressive features are more frequently found in younger women, and LR rates are known to be higher in triple negative and HER2-overexpressing subtypes, and in presence of proliferative gene over-expression [8-12]. In this study, we have examined the rate of LR following WLE in our local women and aimed to identify clinicopathological predictors of LR. The impact of LR on clinical outcome, specifically the endpoints of distant recurrence free and overall survival, was also evaluated.

Materials and Methods

This retrospective review included 713 women who were diagnosed with breast cancer from 1st January 2004 to 31st December 2011 at our unit. Institutional ethics approval for the study was obtained (DSRB 2010/00032). All women were histologically confirmed to have either invasive cancer or Ductal Carcinoma-*In-Situ* (DCIS) and all were treated with WLE with curative intent. All women were followed up for more than 5 years, with the median follow-up period being 100.10 months (ranging from 60.97 to 143.5 months). Women who had subsequently undergone mastectomy for inadequate margins were excluded, since LR recurrence after a mastectomy is less frequent than with WLE. Those who presented with metastatic disease, those in whom WLE was done for palliation and male patients were also excluded. Study endpoints included Locoregional Recurrence (LR), defined as histological proven invasive or *in situ* (DCIS) recurrence in the ipsilateral breast or axilla, disease recurrence and overall survival.

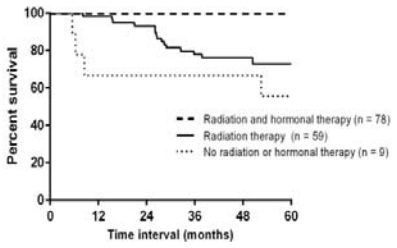
All surgeons at our unit performed WLE in a similar manner, resecting the tumour en bloc from the subcutaneous layer just deep to the skin down to the pectoralis muscle. The anterior and posterior margins were considered 'non-breast' margins. Gross radial margins of at least 1 cm were targeted and the adequacy of resection was determined intra-operatively by gross palpation or with specimen radiograph in instances where hookwire localisation had been necessary for a non-palpable tumour. The resection specimen was oriented with 3 sutures; with one suture marking the anterior margin, another medial and the third the lateral margin. The specimen was then fixed in 10% neutral buffered formalin for further analysis. All six margins were inked separately and the specimen sectioned serially in a medial to lateral direction to obtain consecutive 3 mm thick slices, which were then further processed to obtain haematoxyin and eosin stained glass slides for microscopic examination. Standard pathological parameters were reported in accordance to the latest cancer protocols from the College of American Pathologists. Distance in millimeters of each of the inked margins to the invasive and/or *in situ* carcinoma was reported individually, and the shaved medial and lateral ends were further sectioned perpendicularly for more accurate measurement of tumour distance to the respective margins. The margin was considered involved when tumour was present on the inked margin, close when the tumour was less than 1 mm away from the inked margin and clear when the tumour was 1 mm or further from the inked margin. Full Axillary Lymph Node Dissection (ALND) was routinely performed in all cases of invasive cancers prior to 2006; was not generally performed for DCIS. From 2006 onwards, Sentinel Lymph Node Biopsy (SLNB) became routine and ALND was performed only when metastases was identified in the sentinel node; ALND was performed (without prior SLNB) when there were clinically palpable nodes or pre-operative histological confirmation of nodal metastases.

All cases were discussed at the weekly multidisciplinary breast tumour board meetings. Patients with involved and close radial (excluding the 'non-breast') margins were considered to have inadequate surgical margins and were recommended further surgery. Whole breast irradiation was recommended in all cases. A dose of 50 Gy in 25 fractions was the most common regimen used; with some node-negative patients recommended 42.5 Gy in 16 fractions. A routine additional boost to the tumour bed of 10 Gy was given for invasive carcinomas, and in some instances, a higher boost of 16 Gy was given if the margins were inadequate. No routine

Table 2: Logistic regression model stratified by locoregional recurrence in women treated with wide local excision (n=670).

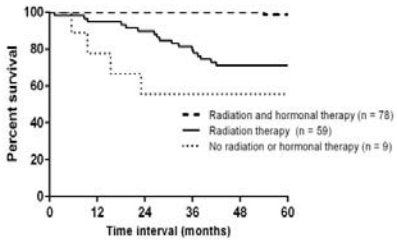
Parameter	Odds ratio	SE	P value	95% CI
Indian Ethnicity	3.581	1.662	0.006	1.442–8.892
Margin status	3.768	1.261	<0.001	1.956–7.260
Tumour histology*	1.283	0.529	0.546	0.572–2.878
Tumour size	0.999	0.014	0.93	0.972–1.027
Nodal status	2.708	0.887	0.002	1.425–5.146
ER status	1.246	0.422	0.515	0.642–2.419
Radiation therapy	0.32	0.122	0.003	0.152–0.675
Hormonal therapy	0.15	0.058	<0.001	0.070–0.322

*whether DCIS or invasive carcinoma



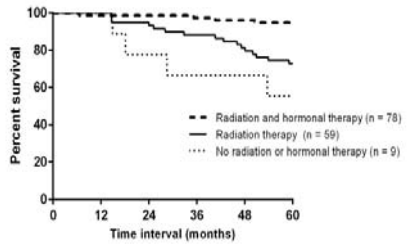
Comparison	P value	HR	95% CI
Radiation and hormonal therapy versus No radiation or hormonal therapy	<0.001	<0.001	<0.001 to <0.001
Radiation and hormonal therapy versus Radiation alone	<0.001	0.08	0.029 to 0.218
Radiation alone versus No radiation or hormonal therapy	0.19	0.39	0.095 to 1.595

Figure 1a: Kaplan-Meier curves showing 5-year locoregional recurrence-free survival of women with node-positive invasive cancer stratified by treatments received (n=148). *3 women who received hormonal therapy only were excluded.



Comparison	P value	HR	95% CI
Radiation and hormonal therapy versus No radiation or hormonal therapy	<0.001	<0.001	<0.001 to 0.002
Radiation and hormonal therapy versus Radiation alone	<0.001	0.098	0.038 to 0.253
Radiation alone versus No radiation or hormonal therapy	0.189	0.39	0.095 to 1.590

Figure 1b: Kaplan-Meier curves showing 5-year distant recurrence-free survival of women with node-positive invasive cancer stratified by treatments received (n=148). *3 women who received hormonal therapy only were excluded.



Comparison	P value	HR	95% CI
Radiation and hormonal therapy versus No radiation or hormonal therapy	<0.001	0.005	<0.001 to 0.057
Radiation and hormonal therapy versus Radiation alone	<0.001	0.193	0.079 to 0.472
Radiation alone versus No radiation or hormonal therapy	0.236	0.436	0.111 to 1.721

Figure 1c: Kaplan-Meier curves showing 5-year overall survival of women with node-positive invasive cancer stratified by treatments received (n=148). *3 women who received hormonal therapy only were excluded.

boost to the tumour bed was given to those with DCIS, unless the margins were inadequate. Recommendations for systemic therapy were in accordance with existing NCCN Guidelines. Patients with node-positive disease were recommended chemotherapy, as well as those with high-risk node-negative disease. Prior to 2006, the Cyclophosphamide/Doxorubicin/5-Fluorouracil (CAF) regimen was most common, and the doxorubicin/cyclophosphamide followed by taxol (AC-T) regimen became the most often used from 2006 onwards. Some patients with node-negative disease received a non-anthracycline-based regimen. Trastuzumab was recommended in those with HER2-overexpressing tumours after HER2 testing became routine after 2006. Those with ER-positive disease were recommended hormonal therapy; prior to 2006, tamoxifen was the agent most often used, and the aromatase inhibitor anastrozole was increasingly recommended to post-menopausal women after 2006. In this study, we made a distinction between women who had received hormonal therapy and those who had completed the recommended 5-year treatment, given that there were several instances where the hormonal agent was prematurely discontinued.

Locoregional recurrence was correlated with standard clinicopathological parameters and treatments received using Chi-square or the Fisher's exact test, where appropriate; the chi-square test for trend was used to analyse tumour grade and disease stage. Comparisons between age and tumour size were performed with the Mann-Whitney test. Univariate analyses were performed with GraphPad Prism version 6 (GraphPad software Inc., San Diego, CA, USA). Logistic regression to identify independent predictors of LR was carried out using the Stata package release 11.0 (Stata Corporation, 4905 Lakeway Drive, College Station, Texas 77845, USA). Correlation with distant recurrence free and overall survival was analysed with Kaplan-Meier survival curves using Graphpad Prism version 6 (GraphPad software Inc., San Diego, CA, USA). A 2-tailed P value test was used and a P value of less than 0.05 was considered statistically significant.

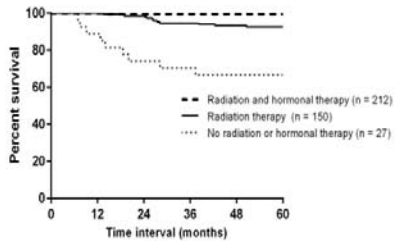
Results

A total of 713 women underwent WLE for non-metastatic breast cancer over the 7-year period from 2004 to 2011. Details are presented in Table 1. Median age was 52 years (ranging from 24 to 90 years). Ethnicity make-up was relatively consistent with the general population demographics. Seventy-five percent (540 of 713) of women had invasive cancers; of which invasive ductal carcinoma not otherwise specified was the most common histology (460 of 540, 85.2%), and 173 women (24.3%) had Ductal Carcinoma *In Situ* (DCIS). More than two thirds of tumours (520 of 713, 72.9%) were Oestrogen Receptor (ER)-positive and 65 tumours were HER2-positive. Median invasive tumour size was 18.0 mm (ranging from 1 mm to 60 mm) and median DCIS tumour size was 11.0 mm (ranging from 1 mm to 50 mm). Surgical margins were considered adequate in 590 women. Not all 123 women with inadequate margins underwent repeat surgery; 41 declined further surgery but proceeded with radiation while another 10 women defaulted both further surgery and radiation.

Ipsilateral breast tumour recurrence developed in 74 women (10.4%); 18 of whom were initially diagnosed with DCIS (5 with *in-situ* recurrence; 13 with invasive recurrence) and 56 with invasive cancer (6 with *in-situ* recurrence; 50 with invasive recurrence). Tumour recurrence was documented to be adjacent to the previous tumour bed (surgical cavity) in 41 women (55.4%), was documented as being in the same quadrant as the previous tumour in 13 women and in a different quadrant in 20 women. Among those women with tumour recurrence adjacent to the previous tumour bed, surgical margins of at least 1 mm were obtained in 28 women, margins were close (less than 1 mm) in 3 women and were involved in the remaining 10 women. Of the 28 women who recurred despite clear margins, 20 (71.4%) had completed whole breast radiation therapy (with 7 of the 13 with invasive cancers receiving an additional 10 Gy boost to the tumour bed); 8 defaulted on radiation. Margins remained inadequate in 13 women who declined further surgery, 9 of whom proceed with and completed radiation therapy (4 received an additional boost to the tumour bed of 10 Gy and one a boost of 16 Gy). Thirteen of the 19 women with ER-positive tumours received hormonal therapy and 6 had completed the entire 5-year treatment.

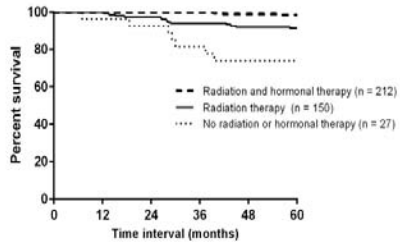
Another 10 women with invasive cancer developed nodal recurrence without any ipsilateral breast tumour recurrence. Full axillary lymph nodal dissection had been performed in 9 of these women (with a median of 25 nodes being harvested, ranging from 10 to 39) and 4 women were found with nodal involvement; some of these surgeries took place before SLNB became the standard for clinically node-negative cases. Sentinel lymph node biopsy had been performed without axillary clearance in one woman where the SLN had returned negative for metastases. Eight of these 10 women had been recommended adjuvant chemotherapy; 5 completed the prescribed regimen while the other 3 declined chemotherapy. Two women who declined chemotherapy also declined hormonal therapy. All 4 women with node-positive disease completed chemotherapy and radiation, which was documented to have included levels I, II and III nodal basins in 3 women. Three of the women had ER-negative disease and did not receive hormonal therapy, while the fourth woman with ER-positive disease received tamoxifen but relapsed 15.43 months after diagnosis.

Inadequate surgical margins (P<0.001, OR 0.355, 95% CI 0.201–0.602) and unfavourable tumour factors such as nodal involvement (P<0.01, OR 2.367, 95% CI 1.345–4.166) and absent tumour ER expression (P=0.007, OR 0.486, 95% CI 0.284–0.828) were significantly associated with LR (Table 1). No significant association with age at diagnosis, tumour size or tumour histology (whether *in-situ* or invasive) was observed. Both surgical margin status (P<0.001, OR 3.768, 95% CI 1.956–7.260) and nodal disease (P=0.002, OR 2.708, 95% CI 1.425–5.146) remained significant on multivariate analysis (Table 2), and while tumour ER status was no



Comparison	P value	HR	95% CI
Radiation and hormonal therapy versus No radiation or hormonal therapy	<0.001	<0.001	<0.001 to <0.001
Radiation and hormonal therapy versus Radiation alone	<0.001	0.121	0.038 to 0.384
Radiation alone versus No radiation or hormonal therapy	<0.001	0.053	0.014 to 0.200

Figure 2a: Kaplan-Meier curves showing 5-year locoregional recurrence-free survival of women with node-negative invasive cancer stratified by the different treatments received (n=392). *3 women who received hormonal therapy only were excluded.

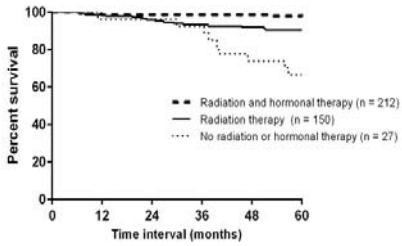


Comparison	P value	HR	95% CI
Radiation and hormonal therapy versus No radiation or hormonal therapy	<0.001	0.001	<0.001 to 0.009
Radiation and hormonal therapy versus Radiation alone	<0.001	0.183	0.068 to 0.500
Radiation alone versus No radiation or hormonal therapy	0.008	0.18	0.051 to 0.634

Figure 2b: Kaplan-Meier curves showing 5-year distant recurrence-free survival of women with node-negative invasive cancer stratified by the different treatments received (n=392). *3 women who received hormonal therapy only were excluded.

longer significant (P=0.515, OR 1.246, 95% CI 0.642–2.419), 5 years of hormonal therapy significantly reduced the risk of LR (P<0.001, OR 0.150, 95% CI 0.070–0.322). Radiation was another independent predictor of LR (P=0.003, OR 0.320, 95% CI 0.152–0.675) (Table 2). In addition, an association with ethnicity was observed, with LR risk being 4-fold higher among Indian women (P=0.006, OR 3.581, 95% CI 1.442–8.892) (Table 2). The occurrence of LR resulted in shorter 5-year distant recurrence-free survival in women with invasive cancer (P<0.001, HR 114.200, 95% CI 40.630–320.900) and was associated with poorer 5-year overall survival (P<0.001, HR 14.210, 95% CI 5.651–35.720). On the other hand, distant disease recurrence was rarely seen in women with DCIS and the occurrence of LR did not adversely affect overall survival in women with DCIS (P=0.756, HR 0.753, 95% CI 0.126–4.496).

The occurrence of LR was two-fold higher in women with node-positive disease. In our study, 25 of 148 women (16.9%) with node-positive disease developed LR, with Distant Recurrence (DR) being also present in 48% (12 of 25). The majority of these 25 women had received systemic treatment and nodal radiation. Twenty women received chemotherapy and 11 of 15 women with ER-positive disease received hormonal therapy (3 had declined treatment and disease recurred in 1 prior to starting hormonal treatment) although only 3 women completed 5 years of hormonal therapy; hormonal therapy was prematurely discontinued in 4 women who developed early relapse and 4 other women made a personal decision to discontinue treatment. Only 1 woman had received trastuzumab; another 5 women



Comparison	P value	HR	95% CI
Radiation and hormonal therapy versus No radiation or hormonal therapy	<0.001	0.002	<0.001 to 0.013
Radiation and hormonal therapy versus Radiation alone	0.003	0.254	0.102 to 0.636
Radiation alone versus No radiation or hormonal therapy	0.001	0.136	0.042 to 0.434

Figure 2c: Kaplan-Meier curves showing 5-year overall survival of women with node-negative invasive cancer stratified by the different treatments received (n=392). *3 women who received hormonal therapy only were excluded.

with HER2-overexpressing tumours had been diagnosed prior to 2006 before trastuzumab was standard of care. Seventeen women received nodal radiation, covering levels I, II and III. In comparison, only 31 of the 392 women (7.9%) with node-negative disease developed LR within the first 5 years, although similarly, close to half (13 of 31 women, 41.9%) also developed systemic disease.

Five-year locoregional disease-free, distant disease-free and overall survival, were significantly improved with a combination of radiation and 5 years of hormonal therapy, regardless of nodal status (P<0.001) (Figures 1 and 2). Women with node-positive disease who completed 5 years of hormonal therapy in addition to radiation treatment had better 5-year LR-free, DR-free and overall survival compared to those who completed only radiation (P<0.001) (Figure 1). In these women, radiation alone did not confer any survival advantage. Numbers were too small for a meaningful evaluation of the effect of hormonal therapy alone. A combination of radiation and 5 years of hormonal therapy was also superior to radiation alone in women with node-negative disease, but in contrast to those with node-positive disease, radiation alone still conferred better 5-year LR-free, DR-free and overall survival (P<0.001, P=0.008, P=0.001 respectively) (Figure 2).

Discussion

The incidence of Locoregional Recurrence (LR) observed in this study is similar to that reported in several other large studies [13-15]. Some studies have reported LR rates of less than 5% [16,17]. Locoregional recurrence rates have decreased over time following stricter adherence to adequate surgical margin clearance, the routine use of a radiation boost to the tumour bed and more effective systemic treatments [17,18]. While the importance of clear surgical margins has always been acknowledged, it was debatable as to what constituted a clear margin. The latest Society of Surgical Oncology–American Society for Radiation Oncology Consensus Guideline recommends that the margin be considered adequate when no tumour is demonstrated on the inked margin. The same review also noted that LR was more frequent when margins were close (less than 1 mm) compared to when they were at least 1 mm, but found this not to be significant [6]. Wider margins did not further decrease LR risk and there was no 'minimum safe' margin [6,19]. At our unit, a close margin, where the tumour is less than 1 mm away from the inked margin was considered inadequate during the study period and in a previous study, we reported finding residual tumour at repeat operation in 17% of those with close margins [20]. A 10 Gy boost

to the tumour bed was routine during the study period. It was not routine then to give a higher boost of 16 Gy even when the final surgical margins were involved or close. This has changed in recent years and a 16 Gy boost is now often given when the margins are deemed inadequate. An additional boost to the tumour bed reduced local recurrence, but did not improve overall survival [21,22].

Our observation that more than half the recurrences developed adjacent to the previous tumour bed in spite of clear margins and radiation suggests the contribution of other factors. Studies have reported higher LR rates in HER2-overexpressing and triple negative tumours [18]. While we did observe more HER2-overexpressing tumours among those who recurred, this did not achieve statistical significance; perhaps because of the small sample size as HER2 status was unknown prior to 2006. Tumour ER expression was no longer significant on multivariate analysis but the reduction in LR risk in women who completed 5 years of hormonal therapy does imply a significant contribution from tumour ER status. Nodal involvement was identified as an independent predictor of LR, with the incidence of LR being 2-fold higher in women with node-positive disease. This has been similarly reported and LR risk was further noted to be proportional to the nodal disease burden [23-25]. The risk of LR remains low even in locally advanced disease should there be complete pathological response in the nodes following neoadjuvant chemotherapy [26-28]. It would appear that pathological response in the nodes has a greater impact on recurrence and overall survival, than the response in the tumour itself [28,29].

Locoregional recurrence was found to adversely affect distant recurrence-free and overall survival in women with invasive cancer, both in our study and in others [4,16]. Locoregional recurrence was present in half of those who relapsed systemically and preceded the systemic disease in 8 women. Several large studies have reported distant metastasis to be more frequent in women with positive surgical margins, suggesting that the LR, like the primary tumour, could potentially be responsible for disease dissemination [30,31]. This underlies the rationale for systemic therapy following LR, even in the absence of systemic disease [5]. We did not find a significant association with chemotherapy in our study, but showed that both radiation and hormonal therapy reduced LR risk following WLE. A combination of radiation and 5 years of hormonal therapy conferred the greatest survival advantage, both in node-positive and node-negative disease. Radiation alone, without hormonal therapy, failed to improve recurrence-free and overall survival in women with node-positive disease although a benefit was still seen in node-negative disease. This highlights the importance of systemic treatment in node-positive disease where the risk of systemic failure is significantly higher.

Radiation is recommended to all women with invasive cancer following WLE based on findings from the landmark NSABP B-06 study and the EBCTCG meta-analyses [1,16]. Absolute overall survival gain was small and did not reach statistical significance, but this benefit could have been offset by the higher cardiac mortality associated with older radiation techniques [32,33]. On the other hand, it has been suggested that radiation may not be as important in DCIS when surgical margins are adequate. Some studies have suggested that the higher LR rates when radiation is omitted after WLE did not have a significant impact on the overall survival in selected women [34-36]. We too did not find LR to adversely impact overall survival in women with DCIS, possibly because majority of LR were *in-situ* disease and the risk of systemic disease was low, but our study does not justify the omission of radiation. The Van Nuys Prognostic Index and the Oncotype DX DCIS score have been used to stratify recurrence risk after WLE and to guide the decision for post-operative radiation, but neither is used on a routine basis [35,37-39]. Surgical margins in several of the studies in support of omitting radiation were wider than what is currently being advocated and it is unclear whether the current guidelines would apply to instances where radiation is omitted [40]. Uncertainty also remains over the long-term safety of omitting radiation as LR rates reportedly increase over time, and with half the tumours recurring as invasive cancers, it may be safe to omit radiation only in women with limited life expectancy [41].

The benefit of hormonal therapy in ER-positive disease is also well established [42]. The CALGB 9343 study has even suggested that tamoxifen alone, without radiation, accords adequate long-term survival after WLE in elderly women with small T1 node-negative tumours [43]. In this study, we showed that 5 years of hormonal therapy increased the benefit derived from radiation and in fact, radiation without hormonal therapy conferred no significant benefit in node-positive disease. Chemotherapy is of definite survival benefit in node-positive disease, but we did not find it or trastuzumab to reduce LR risk [42]. Chemotherapy was also not found to reduce LR in the Alabama Breast Cancer Project, though it should be noted that the chemotherapy regimens used then are no longer first-line and trastuzumab was not available then [25]. Multimodality treatments no doubt improve survival in women with breast cancer and each complement the other such that the omission of one modality affects the overall outcome. Chemotherapy and trastuzumab may have a more significant role in preventing systemic relapse but radiation and hormonal therapy are important in reducing locoregional recurrence.

Conclusion

Locoregional recurrence after WLE was found to be 10.4% in our study and most often occurred adjacent to the previous tumour bed despite adequate surgical margins and whole breast radiation. Surgical margins status, nodal disease, radiation and hormonal therapy were independently associated with LR. Locoregional recurrence adversely affected overall survival in women with invasive cancer, but in those with DCIS. Radiation and hormonal therapy, especially when given in combination improved recurrence-free and overall survival. Radiation alone was of benefit in women with node-negative disease, but did not improve survival in those with node-positive disease.

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