Original Article

Can the size of chest wall recurrence after mastectomy in breast cancer patients predict the presence of systemic metastasis?

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Background: One of the manifestations of recurrence after mastectomy is the presentation of chest wall lesion. However, it is unclear if the size of the chest wall recurrence (CWR) is related to the presence of simultaneous systemic metastasis in these patients. We aimed to determine if the size of the CWR could affect the outcome in these patients.

Methods: Stage I–III breast cancer patients who underwent mastectomy and developed invasive ipsilateral CWR were included. Patients with bilateral mastectomy were excluded. Demographic, radiologic and pathological data were analysed between patients with CWR and simultaneous systemic metastasis versus those with isolated CWR.

Results: Of the 1,619 patients treated with mastectomy, 214 (13.2%) patients developed recurrences. 57/214 (26.6%) patients had invasive ipsilateral CWR. 48 patients were analysed after exclusion of patients with missing data. Mean age at diagnosis of first cancer and at recurrence were 55.2 years (32–84 years) and 58.5 years (34–85 years) respectively. 26/48 (54.2%) had CWR with simultaneous systemic metastasis. Mean CWR size was 30.7 mm (6–121 mm) and 21.4 mm (5.3–90 mm) for the patients with simultaneous systemic metastasis and those without respectively (P=0.441). Grade (P=0.0008) and nodal status (P=0.0009) at primary diagnosis, grade (P=0.0011) and progesterone receptor (PR) status (P=0.0487) at recurrence were statistically significant for systemic metastasis in patients with CWR.

Conclusions: Biologic factors such as grade of primary and recurrent cancer, PR status of recurrent cancer and nodal status at primary diagnosis, instead of CWR size, were associated with simultaneous systemic metastasis in patients with CWR.

Keywords: Breast cancer; mastectomy; recurrence; size; metastasis

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Introduction

Breast cancer is the commonest cancer among women worldwide. Despite improvement in the treatment for breast cancer, a 10-year recurrence rate of 20.5% (1) was reported. The recurrence can be loco-regional or systemic.

Several risk factors for recurrence such as molecular subtypes, grade, nodal burden, primary tumour size etc. have been identified (2,3). In particular, primary tumour size was one of the parameters used in the anatomic TNM (tumour size, node, metastases) staging (4). In mastectomy patients, it was also used to guide the use of radiotherapy in patients with >5 cm cancer (5).

In patients with mastectomy, one of the manifestations of recurrence is the presentation of chest wall lesion. However, it is unclear if the size of the chest wall recurrence (CWR) at diagnosis is related to the presence of systemic metastasis in these patients. We aimed to determine if the size of the CWR at diagnosis could affect the outcome in these patients. This is the first reported study, to the best of our knowledge, which specifically examines the correlation of the size of CWR to the presence of simultaneous systemic metastasis. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-673/rc).

Methods

Newly diagnosed stage I–III breast cancer patients who were treated with mastectomy from 1st September 2005 to 31st Oct 2017 and developed invasive ipsilateral CWR were included. In this study, a mastectomy was undertaken due to primary tumour characteristics, such as large tumour to breast size, tumour multifocality and/or patient's preference. Each patient was discussed at the multidisciplinary tumour board meeting for their individualised treatment. Human epidermal growth factor receptor 2 (HER2) targeted treatment was given if needed. Following treatment, the patient was followed up with a clinical examination at 3–4 monthly intervals in the 1st 2 years, then at 6 monthly intervals in the 3rd–5th year and then annually from the 5th year onwards. A contralateral mammogram was performed annually. Upon diagnosis of a recurrence, staging CT and bone scan were performed.

A recurrence was established, in this study, when there was proven pathological evidence of a relapse with the histological morphology similar to the primary cancer and/or based on the clinical and radiological presentation. Patients with bilateral mastectomy were excluded.

Demographic, radiologic and pathological data of the primary and recurrent cancer were collected from a prospectively maintained database. In patients with neoadjuvant chemotherapy, the tumour size was obtained based on imaging done prior to commencement of therapy, if there was response to treatment. Specifically, the recorded CWR size at the time of diagnosis was retrieved from excision histology reports. If this was not available, the measurement of the CWR were retrieved from imaging or clinical records. If there were multiple foci of cancer, the measurement of the largest focus was used.

The data collected were then analysed between patients with CWR and simultaneous systemic metastasis on staging scans versus those with CWR with or without ipsilateral nodal metastasis but without systemic metastasis.

Highlight box

Key findings

- Size of chest wall recurrence (CWR) post mastectomy is not predictive of the presence of systemic metastasis.

What is known and what is new?

- Several risk factors for breast cancer recurrence, including primary tumour size, have been identified.
- It is unclear if the size of CWR at diagnosis is related to the presence of systemic metastasis.
- This is the first study, to the best of our knowledge, examining specifically the relationship of the size of CWR in predicting simultaneous systemic metastasis.

What is the implication, and what should change now?

- Biologic tumour factors, instead of CWR size, were predictive of systemic metastasis.
- Regardless of the size of CWR, these patients should be staged with systemic imaging and treated accordingly.

Statistical analysis

A Fisher's exact test was used to compare the categorical variables between patients with CWR and simultaneous systemic metastasis versus those without systemic metastasis. $P<0.05$ was defined as statistically significant. Graphpad statistical software (version 2022) was used for the analysis.

Ethical statement

The study was approved by SingHealth Centralised Institutional Review Board (CIRB Ref: 2020/2147). The

informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Results

A total of 1,619 stage I–III breast cancer patients were treated with mastectomy. Of these patients, 214 (13.2%) patients developed recurrences at a mean 39.9 months from primary cancer diagnosis. Of the 214 patients with recurrence, 57 (26.6%) patients had invasive ipsilateral CWR. 9 (15.8%) had missing CWR size and were excluded, leaving 48 patients for analysis.

Of these 48 patients, 26 (54.2%) had CWR and simultaneous systemic metastasis. 19 (39.6%) had isolated CWR and 3 (6.3%) had CWR and nodal metastasis but without systemic metastasis at diagnosis of recurrence.

Mean age at diagnosis of first cancer was 55.2 years (32–84 years). Majority of the patients (85.4%) had primary cancer histology of invasive ductal carcinoma (*Table 1*). Mean primary tumor was 35.5 mm (2.5–95 mm).

The mean age at recurrence was 58.5 years (34–85 years). The CWR were detected on clinical examination in 40 (83.3%) patients while the remaining patients had their CWR detected via imaging. Mean CWR size was 26.5 mm (5.3–121 mm) (*Table 2*). The mean CWR size was 30.7 mm (6–121 mm) and 21.4 mm (5.3–90 mm) for the patients with simultaneous systemic metastasis and those without respectively.

The recurrences occurred at a mean of 33.1 months (range, 2–116 months) and 45.6 months (range, 7–107 months) from primary cancer treatment for the group with and without systemic metastasis respectively. Patients with CWR and systemic metastasis had a poorer prognosis than the patients without systemic metastasis. The average overall survival after diagnosis of recurrence was 21.2 and 41.0 months in patients with and without systemic metastasis respectively.

All patients generally displayed similar histological features between primary and recurrent cancer, though there were some subtle differences. While estrogen receptor (ER) and HER2 status remained unchanged in the primary and recurrent cancer, progesterone receptor (PR) status, in contrast, displayed a change from positivity in the primary cancer to a negative status in the recurrent cancer in 6 (12.5%) patients. In addition, another notable difference was the upgrading from grade I in primary cancer to grade II in patients with recurrent cancer.

Grade (P=0.0008) and nodal status (P=0.0009) at primary diagnosis, grade (P=0.0011) and PR status (P=0.0487) at recurrence were statistically significant for systemic metastasis in patients with CWR. CWR size was however not statistically associated with simultaneous systemic metastasis.

Discussion

Following mastectomy in breast cancer patients, 26.6% had invasive ipsilateral CWR. Of these patients with known CWR size, 54.2% had simultaneous systemic metastasis. Biologic tumour factors, such as grade and nodal status at primary diagnosis, grade and PR status at recurrence, were predictive of simultaneous systemic metastasis. CWR size, on the other hand, was not indicative of the presence of systemic metastasis. This is the first study, to the best of our knowledge, examining specifically the relationship of the size of CWR in predicting simultaneous systemic metastasis.

The findings in our study were consistent with literature which showed that biologic factors such as grade etc. and nodal status, were risk factors of recurrence and prognosis (6,7). As a result, the revised American Joint Committee on Cancer Breast Cancer Staging System (AJCC) breast cancer staging had included biologic characteristics, such as tumour grade, HER2, ER, PR status and multigene panel (such as Oncotype DX) status (8) to improve its prognostication value and refine treatment for patients.

The size of the primary tumour has also been implicated as a risk factor for recurrence (2,9) While the biologic factors (i.e., grade) are representative of tumour aggressiveness, tumour size was a reflection of the duration of growth of the tumour (10). Not only is tumour size used as a prognostic factor in TNM staging, it is also often being used to guide treatment. For example, radiotherapy is indicated in mastectomy patients with primary tumour size >5 cm (5) and a cut-off invasive cancer size >10 mm was used as a general guide for chemotherapy in patients with unfavourable histologic subtypes (11) though biologic factors remained the most crucial consideration for commencing chemotherapy. Finally, the size of the primary cancer would determine between a mastectomy or breast conserving surgery. On the contrary, CWR size was not associated with the presence of systemic metastasis. As a result, regardless of the size of CWR, systemic staging by imaging at the time of recurrence is warranted (12). Size of CWR however would affect its resectability and size >4 cm

Table 1 Characteristics of primary cancer in patients with chest wall recurrences

Characteristics	Patients with chest wall recurrences and systemic metastasis (N=26), n (%)	Patients with chest wall recurrences without systemic metastasis (N=22), n (%)	P value*
Age (years)			0.7704
<50	10 (38.5)	10 (45.5)	
≥50	16 (61.5)	12 (54.5)	
Histology			0.154
Invasive ductal carcinoma	22 (84.6)	19 (86.4)	
Invasive lobular carcinoma	4 (15.4)	1 (4.5)	
Others	0 (0.0)	2 (9.1)	
Tumour size# (mm)			0.098
≤20	6 (23.1)	9 (42.9)	
>20–50	11 (42.3)	10 (47.6)	
>50	9 (34.6)	2 (9.5)	
Unknown	0	1	
Grade			0.0008
I	3 (11.5)	13 (59.1)	
II	2 (7.7)	0 (0.0)	
III	21 (80.8)	9 (40.9)	
ER			0.2212
Positive	15 (57.7)	17 (77.3)	
Negative	11 (42.3)	5 (22.7)	
PR			0.1320
Positive	14 (53.8)	17 (77.3)	
Negative	12 (46.2)	5 (22.7)	
HER2 receptor			0.3071
Positive	7 (26.9)	3 (13.6)	
Negative	19 (73.1)	19 (86.4)	
Nodal status			0.0009
Positive	22 (84.6)	8 (36.4)	
Negative	4 (15.4)	14 (63.6)	
Chemotherapy			0.3929
Yes	13 (50.0)	8 (36.4)	
No	13 (50.0)	14 (63.6)	
Radiotherapy			0.1179
Yes	11 (42.3)	4 (18.2)	
No	15 (57.7)	18 (81.8)	
Endocrine therapy			0.0825
Yes	12 (46.2)	16 (72.7)	
No	14 (53.8)	6 (27.3)	

*, Fisher's exact test; #, in cases of multiple foci of cancer, the largest size was used for analysis. ER, estrogen receptor; PR, progesterone receptor.

Table 2 Characteristics of recurrences

Characteristics	Patients with chest wall recurrences and systemic metastasis (N=26), n (%)	Patients with chest wall recurrences without systemic metastasis (N=22), n (%)	P value*
Age (years)			0.7456
<50	8 (30.8)	5 (22.7)	
≥50	18 (69.2)	17 (77.3)	
Histology			0.804
Invasive ductal carcinoma	22 (84.6)	20 (91.0)	
Invasive lobular carcinoma	3 (11.5)	1 (4.5)	
Others	1 (3.8)	1 (4.5)	
Tumour size# (mm)			0.441
≤20	13 (50.0)	15 (68.2)	
>20–50	10 (38.5)	5 (22.7)	
>50	3 (11.5)	2 (9.1)	
Grade			0.0011
I	2 (7.7)	3 (13.6)	
II	3 (11.5)	12 (54.5)	
III	21 (80.8)	7 (31.8)	
ER			0.2212
Positive	15 (57.7)	17 (77.3)	
Negative	11 (42.3)	5 (22.7)	
PR			0.0487
Positive	10 (38.5)	15 (68.2)	
Negative	16 (61.5)	7 (31.8)	
HER2 receptor			0.3071
Positive	7 (26.9)	3 (13.6)	
Negative	19 (73.1)	19 (86.4)	
Nodal status			0.4783
Positive	6 (23.1)	3 (13.6)	
Negative	20 (76.9)	19 (86.4)	
Overall survival (months)	21.2	41.0	–
Time from primary cancer (months), mean (range)	33.1 (2–116)	45.6 (7–107)	

*, Fisher's exact test; #, in cases of multiple foci of cancer, the largest size was used for analysis. ER, estrogen receptor; PR, progesterone receptor.

could increase the risk of a second local recurrence, as reported in one study (13).

In our study, there was change of some histologic characteristics between the primary and recurrent cancer. Similarly, previous studies have shown receptor discordances in up to 30% of patients with recurrent disease (14,15). Of all the receptors, PR was reported to display the most inconsistency (16). Possible explanations for

receptor discordance include clonal genome evolution and biological heterogeneity of the tumour, biological drift due to clonal selection under the pressure of therapy (hormonal, targeted) and test factors. As a result, a repeat biopsy, wherever possible in cases of recurrence, was needed not only for the confirmation of malignancy but also to guide the therapeutic approach.

Strengths of the study include a well-kept database where the data for recurrences can be retrieved. This study also has a large number of patients who underwent mastectomy.

Limitations of the study include that being a retrospective study, there may be variations in the treatment regimen of the primary cancer. However, the treatment for each patient was discussed at the multidisciplinary meeting, ensuring consistency in treatment. Another limitation is that this is a single centre study. However, our recurrence rates were comparable with that reported in literature. Finally, the study size was small however, this is the first such reported study which specifically examines the correlation of the size of CWR to systemic metastasis. Larger studies could be performed in future to validate our findings.

Conclusions

In mastectomy patients with recurrence, 26.6% had invasive ipsilateral CWR. Of these patients with known CWR size, 54.2% had simultaneous systemic metastasis with poor prognosis. Biologic tumour factors, instead of CWR size, was predictive of systemic metastasis. Regardless of the size of CWR, these patients should be staged with systemic imaging and treated accordingly.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-673/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-22-673/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-673/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by SingHealth Centralised Institutional Review Board (CIRB Ref: 2020/2147). The informed consent was waived.

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