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De-novo metastatic breast cancers with or without primary tumor resection – A 10-year study

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ABSTRACT

Background: Treatment of de novo metastatic breast cancer is usually palliative with systemic treatment; surgical excision of the primary tumour is reserved in patients with significant symptoms from the primary tumour. Survival benefit of surgical removal of the primary tumour remains controversial.
Methods: All patients treated with de novo metastatic breast cancer (MBC) between 2007 and 2016 were retrieved from a prospectively-maintained database. Demographic and tumour characteristics were compared. Overall survival (OS) was analysed using Kaplan–Meier Method and log rank tests. Multivariate analysis was performed to evaluate the prognosticators of OS in de novo MBC.
Results: Median age of diagnosis was 53 years old (Range 24–91 years old). 91 patients received resection of the primary tumour, including 86 mastectomies and 5 breast conserving surgeries (surgical group). 81 patients were never treated surgically (non-surgical group). Baseline demographic data were comparable apart from being younger age in the surgical group. 5-year OS in surgical group was significantly better than non-surgical group (43.9% vs. 33.9%, $p = 0.026$). Multivariate analysis found that advanced age (Hazard ratio: 1.034, $p = 0.005$, 95% CI 1.010–1.058) and presence of visceral metastasis (Hazard ratio: 1.672, $p = 0.038$, 95% CI 1.028–2.719) were significant adverse prognosticators through multivariate analysis; while positive oestrogen receptor (ER) status was the only positive prognosticator in the analysis (Hazard ratio: 0.42, $p = 0.001$, 95% CI 0.256–0.688).
Conclusion: Surgical excision of primary breast tumour may confer survival benefit in de novo MBC.

Introduction

Metastatic breast cancer at presentation is diagnosed in less than 10% of all patients [1]. This group of patients is usually treated with palliative intent, in the form of systemic treatment such as chemotherapy or hormonal therapy and locoregional radiotherapy [2[. With the introduction of new systemic treatments and targeted therapies such as trastuzumab or pertuzumab, there is a significant improvement of survival among metastatic breast cancer patients over the past decade [3]. That having said, the role of breast cancer surgery in the context of de novo metastatic breast cancer remains controversial. Some researchers postulated that the physiological stress resulted from surgery under general anesthesia would promote metastatic proliferation; moreover, the primary tumour was thought to inhibit angiogenesis in metastatic lesion [4]. However, these theories against surgical resection of primary tumor in metastatic breast cancer setting were based on animal studies, without translational clinical endpoints to determine to what degree they affect survival [4]. The common practice nowadays is still to reserve surgical resection of the primary tumor to patients with refractory tumor bleeding, ulceration, or pain.

Evidence of survival benefits with surgery in de novo breast cancers in the literature has been conflicting. In 2015, Badwe et al. conducted the first randomised controlled study, suggesting that locoregional treatment is not associated with an improved survival in de novo metastatic breast cancer patients [5]. Similar results were presented in the American Society of Clinical Oncologists (ASCO) Annual Meeting in 2016 by a U.S. registry-based study, showing the lack of benefit [6]. However, some studies were able to demonstrate an improved survival with surgical treatment of the primary tumor. Khan et al reported in 2002 using the data from the National Cancer Data Bank of the American College of Surgeons showed a survival benefit of local therapy in the stage IV setting [7]. Subsequently, a few retrospective studies also reported similar findings, suggesting that the removal of the primary tumor was associated with improved survival, and it appears that mastectomy was associated with significant improvement in overall survival [8–10]. Although many researchers may argue that the

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results from these retrospective studies were subjected to selection bias and confounders due to the fact that surgically-treated patients were generally younger with better performance status; a meta-analysis of 15 studies in 2012 showed survival benefit in the surgery group [11]. In addition, a recent prospective randomised study conducted in Turkey has also concluded similar findings, results were presented in ASCO [12].

Therefore, it is still controversial whether surgical excision of the primary tumour would translate into survival benefit. In addition, data on the survival of metastatic breast cancers in Asian population is lacking. Here we present our results from a retrospective study based on the 10-year data from a prospectively-maintained database, aiming to review the survival of patients with de novo stage IV breast cancer managed surgically or non-surgically in our centre.

Patients and methods

Institutional board review approval was obtained All patients with de novo stage IV invasive ductal carcinoma (IDC) treated between January 2007 and December 2016 were retrieved from a prospectively-maintained database. We include all biopsy proven de novo metastatic IDC, with or without resection of the primary breast tumour. Surgical excision of primary breast tumour with mastectomy and breast conserving surgery (BCS) were included. Patients with distant metastasis developed after initial treatment and patients with tumour histology other than IDC were excluded from the analysis.

All patients received standard breast cancer management according to a standardised departmental protocol, based on the National Comprehensive Cancer Network (NCCN) guidelines. All patients were managed with multi-disciplinary approach since 2007, by breast surgeons, medical and clinical oncologists with appropriate systemic treatment or radiotherapy based on tumor staging and immunohistochemistry profile. Surgical excision of primary tumor was performed only after careful patient selection in the multidisciplinary meeting, based on patients' pre-morbidity and performance status and patient's wish. Indications for surgical excision of primary tumor include symptomatic control for tumor bleeding, pain, ulceration and patient's wish as assessed by specialist breast surgeon. Fitness for surgery were assessed by anesthesiologist pre-operatively, American Society of Anaesthesiologists (ASA) scores were documented.

Survival analysis was performed by Kaplan–Meier Method with log rank test, categorical and continuous data were analysed with Chi-square test, Fisher's exact test or student *T*-test where appropriate. Adverse survival prognosticators were analysed with multivariate analysis. Statistical significance level of 0.05 was adopted. Oligometastasis was defined as number of metastatic site of $<=3$.

Results

1769 IDC patients were treated in Queen Mary Hospital and its affiliated hospital Tung Wah Hospital – a tertiary academic based public breast cancer centre in Hong Kong, from January 2007 to December 2016, of which 172 (9.7%) were de novo stage IV IDC.

Median age of diagnosis was 53 years old (Range 24–91 years old). 91 patients received resection of the primary tumour, including 86 mastectomies and 5 breast conserving surgeries (surgical group); 81 patients were never treated surgically on the primary tumor (Non-surgical group). All patients receiving surgery had clear surgical margins (defined as no tumor at inked margin). Comparing the baseline demographic characteristics between the two groups; apart from age (which was significantly younger in the surgical group), other baseline patient or tumor characteristics (including T/N stages, number of distant metastasis, ASA score, tumor molecular biology and systemic treatment received) were comparable between surgical and non-surgical group. (Table 1)

Using Kaplan–Meier method, the 2-year overall survival (OS) of stage IV breast cancer was estimated to be 79.4%. The 5-year OS of stage IV breast cancer was estimated to be 38.9%. The median survival time was estimated to be 48 months.

Table 1
Baseline patient demographics.

Factors	Non-surgical group (n = 81)	Surgical group (n = 91)	p-value*	
Diagnosis Age	>= 50	63 (77.8%)	41 (45.1%)	<0.001
	< 50	18 (22.2%)	50 (54.9%)	
T stage	Non-locally advanced (T1 - 3)	27 (33.3%)	43 (47.3%)	0.064
	Locally advanced (T4)	54 (66.7%)	48 (52.7%)	
N stage	N0	56 (69.1%)	69 (75.8%)	0.326
	N+	25 (30.9%)	22 (24.2%)	
Contralateral axillary metastasis	Yes	6 (7.4%)	6 (6.6%)	1
	No	75 (92.6%)	85 (93.4%)	
Oligometastasis				
	Yes (<=3)	77 (95.1%)	89 (97.8%)	0.328
	No (>3)	4 (4.9%)	2 (2.2%)	
Estrogen receptor	Positive	57 (70.4%)	68 (74.7%)	0.723
	Negative	20 (24.7%)	21 (23.1%)	
	Unknown	4 (4.9%)	2 (2.2%)	
HER 2 receptor	Positive	33 (40.7%)	44 (48.4%)	0.397
	Negative	44 (54.4%)	45 (49.4%)	
	Unknown	4 (4.9%)	2 (2.2%)	
Premorbid (ASA score)	1 & 2	44 (54.3%)	43 (47.3%)	0.355
	3 or above	37 (45.7%)	48 (52.7%)	
Hormonal therapy	Yes	56 (69.1%)	69 (75.8%)	0.268
	No	25 (30.9%)	21 (23.1%)	
	Unknown	0 (0%)	1 (1.1%)	
Chemotherapy / Targeted therapy	Yes	37 (45.7%)	54 (59.3%)	0.073
	No	44 (54.3%)	37 (40.7%)	

N.B.
p-values in **bold** denotes statistically significant value.
ASA = American Society of Anesthesiologists, TNBC = Triple negative breast cancer.
* Chi-sqaure test or Fisher exact test where appropriate.

Concerning the survival outcome between surgical and non-surgical group, the 2-year OS rate in the surgical group was estimated to be 84.5%, while that of non-surgical group was estimated to be 73.7%. The 5-year OS rate of stage IV breast cancer with surgery done was estimated to be 43.9%, while that of non-surgical group was estimated to be 33.9%. The median survival time for surgical group was estimated to be 55 months, while that for non-surgical group was estimated to be 40 months. Significant difference of OS was demonstrated by log-rank test ($p = 0.026$). (Fig. 1)

Survival outcome of patients with or without oligometastasis was evaluated. In patients with single site of distant metastasis, the median survival duration was 69 months, when there were 2 metastatic sites, median survival was 47 months, in patients with 3 sites of distant metastasis, median survival was 38 months, in patients with 4 sites of distant metastasis, median survival was 48 months, and in patients with 5 sites of distant metastasis, the median survival was 61 months. Statistical significant difference in survival cannot be demonstrated between patients with different number of sites of distant metastasis (Log rank test, $p = 0.072$). (Fig. 2)

Survival prognosticators were evaluated by multivariate analysis. Factors such as age, estrogen receptor (ER) status, human epidermal growth factor 2 (HER2) status, metastatic sites, oligometastasis and T-stage of the primary tumour were included in the analysis. Advanced age (Hazard ratio: 1.034, $p = 0.005$, 95% CI 1.010–1.058) and presence of visceral metastasis (Hazard ratio: 1.672, $p = 0.038$, 95% CI 1.028–2.719) were the onlyjb statistically significant adverse

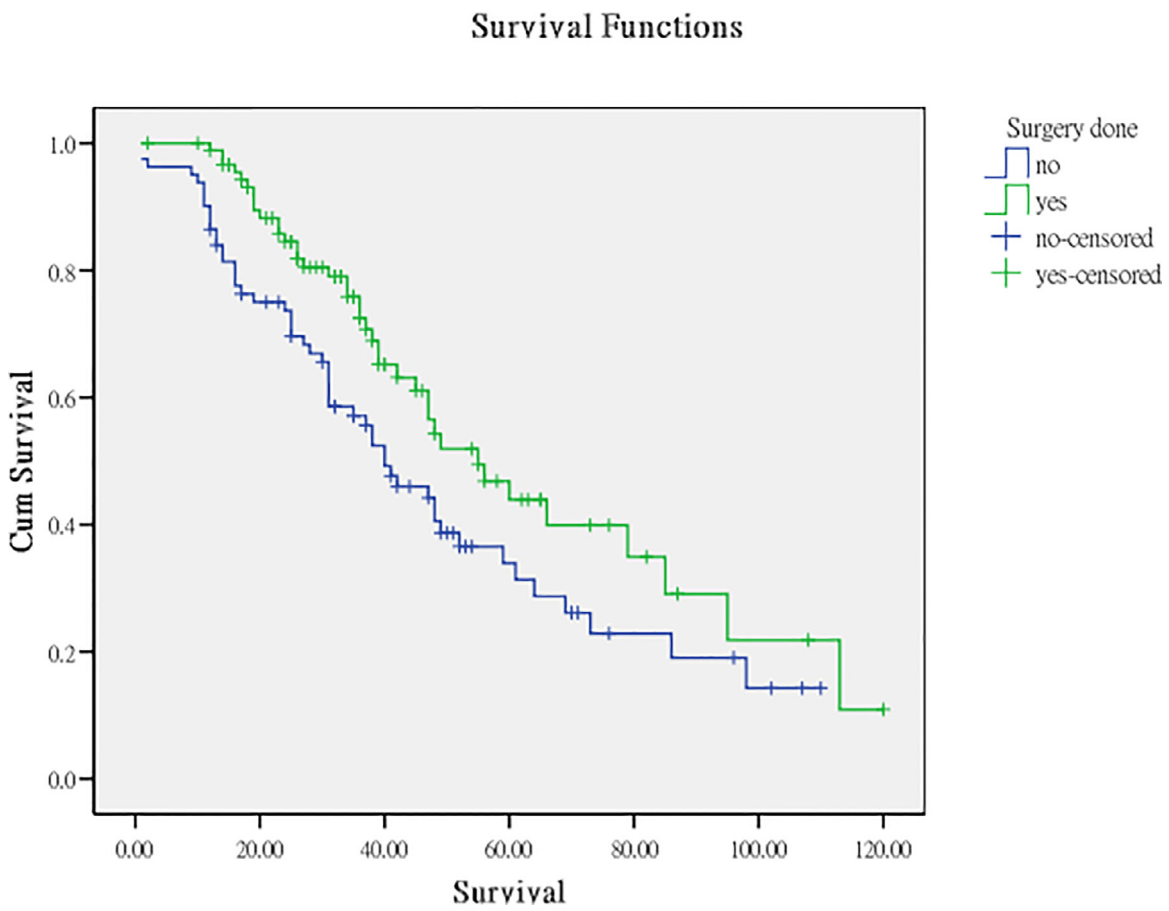

Fig. 1. Kaplan–Meier curve of overall survival between patients with or without surgery.

prognosticators on 2-year OS; while positive ER status was the only positive prognosticator in the analysis (Hazard ratio: 0.42, $p = 0.001$, 95% CI 0.256–0.688). (Table 2)

Discussion

Management of de novo metastatic breast cancer remains a challenging task for breast surgeons worldwide. The current standard of care is to offer palliative management with systemic treatments such as chemotherapy, targeted therapy or hormonal therapy, and in selected cases, radiotherapy to the primary tumour or distant metastatic sites such as the bone.

Evidence on surgical resection of primary tumour in de novo metastatic breast cancer has been controversial in the literature. While some researchers pioneer surgical resection of primary tumour, believing that better disease control can be achieved by removing the main tumor bulk [7–11]; some others consider surgery under general anaesthesia as a physiological stress to the body, which can result in decreased immunity and worsen the metastasis [4].

According to the current study, up to 10% of breast cancer patients treated in our centre presented with stage IV disease at presentation. This is partly due to the fact that population-wide breast cancer screening is not available in Hong Kong, and hence a percentage of patients present late. [13]. In our centre, we manage all breast cancer patients with multi-disciplinary approach. All de novo metastatic breast cancer patients are managed jointly by breast surgeons, medical and clinical oncologists. Systemic treatment will be given according to the tumour immunohistochemical status while surgical resection of the primary tumour was only performed in carefully selected patients. Indications for surgical resection include: refractory tumour bleeding, difficult wound care, significant tumor pain, and patient wish. All surgical operations in the current cohort were performed by breast surgeon specialists and negative margins were achieved in all surgically-treated patients.

Pre-operative patient preparation includes the referral of all potential surgical candidates to anaesthetists for pre-operative assessment. Only patients who were medically fit for an operation underwent surgical resection of the primary tumor, and hence the younger average age in the surgical group in this study. In fact, as in many other retrospective studies in the literature comparing surgery and no surgery for de novo metastatic breast cancers; favourable prognostic factors in the surgery group may result in selection bias. Younger age, better performance status, smaller size of primary tumor, limited metastatic dissemination, and good response to prior systemic therapy may have influenced the decision to perform surgery and possibly limiting the scientific value and reliability of many retrospective studies [14–18]. However, in the current study, baseline demographic characteristics including performance status, tumour stages and subtypes and extent of distant metastasis etc; between surgical and non-surgical group were comparable statistically, thus improving the reliability of our findings.

While 5-year OS remains poor in de novo breast cancer patients, in the range of 30–40%; our study has demonstrated that patients treated with surgical resection of primary breast tumor have significantly better 2-year and 5-year OS. In further analysis of our prospective database, we found that advanced age and presence of visceral (lung and liver) metastasis were the only significant adverse prognosticators for survival in the surgically treated group. We believe surgical resection of the primary breast tumour should be prudently considered in selected "good-risk" patients, especially in young and otherwise medically fit patients.

We recognize the inherent limitations of our study of being retrospective in nature which opens it to possible selection bias and inability

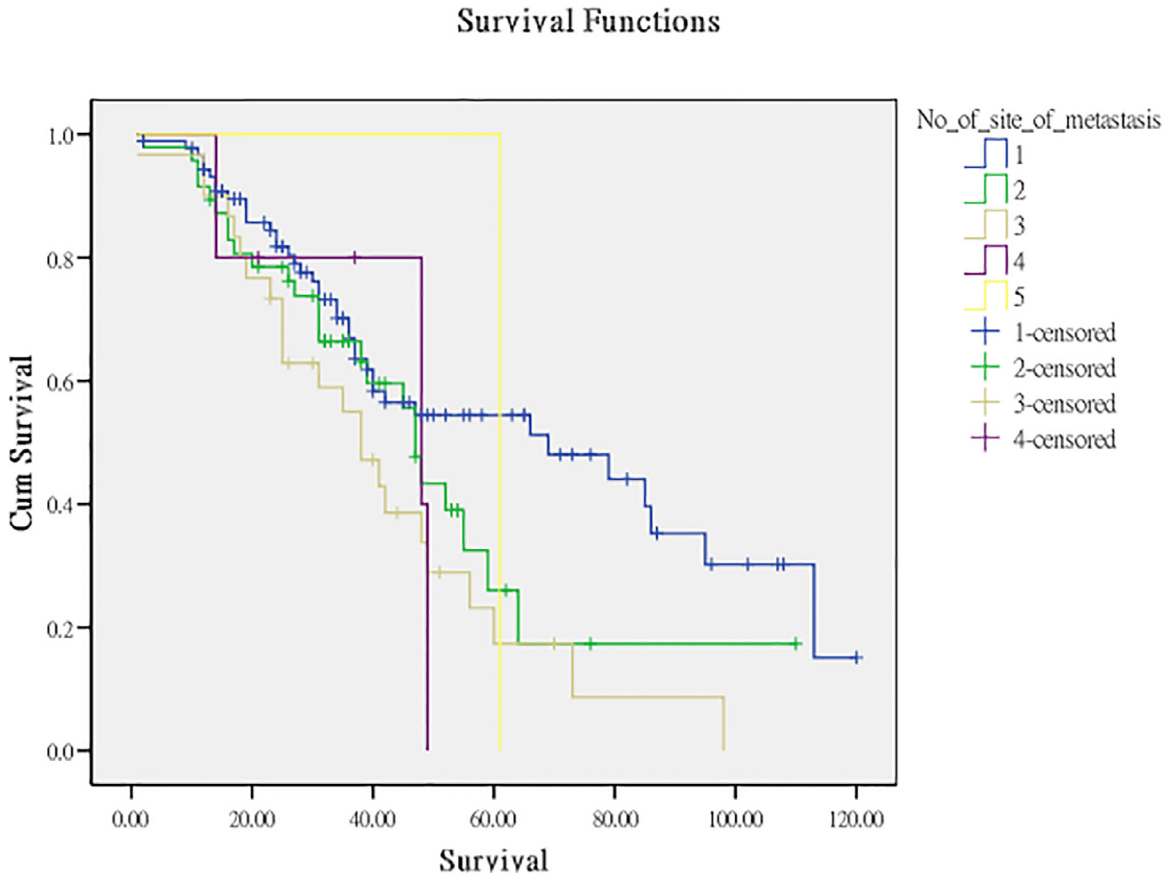

Fig. 2. Kaplan–meier curve of patients with different number of distant metastatic site.

Table 2
Multivariate analysis of prognosticators of overall survival in surgically-treated group.

Variables	Hazard ratio	*p-value*	95%CI for hazard ratio
Age > = 50 at diagnosis	1.034	0.005	(1.010, 1.058)
ER positivity	0.420	0.001	(0.256, 0.688)
HER2 positivity	0.626	0.052	(0.391, 1.004)
Visceral (Lung or liver) metastasis	1.672	0.038	(1.028, 2.719)
Brain metastasis	2.808	0.058	(0.964, 8.183)
Oligometastasis	3.27	0.677	(1.272, 8.400)
Locally advanced primary (T3 or above)	1.126	0.753	(0.537, 2.361)

N.B.
ER = Estrogen receptor.
HER2 = Human epidermal growth factor receptor 2.
p-values in **bold** denotes statistically significant value.

of draw direct causative relationships. In addition, our study population is mainly Chinese which limits the generalisability. However, our analysis was based on a sizable cohort of 172 patients with data collected through a large prospectively-maintained database. All patients received standardised treatment according to a strict multidisciplinary protocol. Comparable baseline demographic background between surgical and non-surgical group had also reduced the effects of possible bias / confounders from our analysis. We believe results of our study represent another large retrospective cohort to the literature in the context of management of de novo metastatic breast cancers.

Conclusion

While 5-year OS in de novo metastatic breast cancer remains poor, surgical resection of the primary tumour may confer survival benefit in carefully selected patients.

Conflict of interest statement

All authors report no potential conflict of interests

Clinical practice points

- 5-year overall survival in de novo metastatic breast cancer (MBC) remains poor at the range of 30–40%
- Surgical excision of primary breast tumor may result in survival benefit in carefully selected patients
- Advanced age and presence of visceral metastasis are adverse prognosticators of overall survival in surgically treated MBC patients.

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