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Original article

Does primary tumor resection improve outcomes for patients with incurable advanced breast cancer?

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ABSTRACT

Background: Metastatic breast cancer (MBC) is considered incurable, and surgery has only limited benefit in the treatment of this disease. However, recent reports have indicated that primary tumor resection may improve patient outcomes. We retrospectively analyzed the surgical benefits and prognostic factors for patients with MBC who were treated at our center.

Methods: Ninety-two women, who had tumors of greater than 5 cm and distant metastasis at diagnosis, were included in this study. The effect of surgical treatment on survival was evaluated. Patient demographics and tumor characteristics were also investigated.

Results: Thirty-six patients had surgery for resection of primary tumors. There were no substantive differences between individuals, or between tumor characteristics, for patients who underwent surgery versus patients who did not. The median survival time for surgically treated patients was 25.0 months versus 24.8 months for patients who did not undergo surgical resection ($P = 0.352$). Only three patients relapsed within three months of surgery. For the remaining majority of patients, primary tumor resection gave some relief from the often severe symptoms that come from harboring a large tumor for an extended time. In univariate and subsequent multivariate analyses of predictive indicators, a diagnosis of triple-negative breast cancer and/or metastasis to more than three sites was significantly associated with a severe prognosis.

Conclusion: Primary tumor resection failed to prolong overall survival times in patients with incurable advanced breast cancer that was greater than 5 cm. However, surgery did improve the quality of life in patients who were expected to have a relatively long prognosis.

Introduction

MBC is considered incurable, and is therefore an unfavorable prognostic for survival. This remains true despite the fact that the survival rate of patients with MBC has slowly and steadily improved due to the development of diagnostic tools for earlier detection of metastatic lesions, and systemic therapies that include new biologics.[1,2] Because of the low cure rate, therapy for patients with MBC often seeks to prolong survival or to palliate symptoms, while preserving quality of life. Systemic chemotherapy is one of the most effective treatments for MBC, and has become increasingly central to the therapeutic strategy for this disease. Although this is traditionally done according to Hortobagyi's algorithm,[3] successful chemotherapy depends on the expression status of the estrogen receptor (ER), the progesterone receptor (PgR), and the human epidermal growth factor receptor 2 (HER2), or on the existence of life-threatening visceral metastases.

Surgical removal of primary tumors has not been established as a standard treatment for MBC because it is generally accepted that local therapy provides no survival advantage once metastases have occurred. Additionally, tumor excision may further stimulate metastasis.[4] Therefore, primary tumor resection in patients with MBC is usually only applied as a palliative treatment for symptomatic wound complications such as bleeding, ulcer formation, unpleasant smell, and purulent discharge. In recent years, however, some retrospective studies have reported advantages of debulking surgery in terms of improving patient outcome.[5–10]

The aim of this study was to determine through retrospective analyses if surgical removal of primary tumors affected the outcome of patients with incurable advance breast cancer. We also attempted to identify other predictive indicators for prognosis based on patient demographics and tumor characteristics.

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Patients and methods

Patients

We retrospectively reviewed individual medical records from the Hokkaido Cancer Center. In this study, incurable advanced breast cancer is defined as the presence of a tumor larger than 5 cm, and shows either invasion to chest wall or skin or is an inflammatory carcinoma and at least one metastatic site, including distant lymph nodes, bone, or visceral organs (lung, pleura, mediastinum, liver, and brain) at diagnosis. Between January 2000 and June 2010, 92 women were diagnosed with incurable advanced breast cancer at Hokkaido Cancer Center.

Evaluation of pathological factors

ER and PgR expression status was considered positive when ≧10% of cancer cell nuclei exhibited positive immunohistochemistry (IHC) staining, regardless of intensity. HER2-positive breast cancer was defined as a condition where tumors were immunohistochemically scored with a value of 3+, or 2+ with positive for fluorescein in situ hybridization.

Statistical analysis

Baseline characteristics were compared between women who received therapeutic breast surgery versus those who did not, using the chi-square test for independence. Overall survival time was plotted using a method based on the Kaplan–Meier estimator, and a log-rank test was applied for comparison. Prognostic factors predictive of survival were assessed through a univariate analysis using the Cox proportional hazards model, and hazard ratios (HR) are presented with their 95% confidence intervals (95% CI). Multivariate modeling was performed using the Cox proportional hazards model with forward selection. $P < 0.05$ was considered statistically significant.

Results

Surgical decision-making and complications

A total of 92 patients were included in this study. Median follow-up time for survivors was 27.4 months. Of 92 patients, 36 (39.1%) had surgery focused on a primary tumor. All of 36 patients had a total mastectomy, with or without axillary dissection, and three patients needed a skin graft. The mean time from diagnosis to surgery in the patients who received surgery was 6.5 months. Seven patients (19.4%) had emergency operations for uncontrollable bleeding from the tumor. The primary reason for elective surgery was to improve cancer-related local symptoms, such as pain or purulent discharge (22 patients, 61.1%). Seven patients undertook surgery based on their own desire to have the tumor removed. The average operation time was 118 ± 40 min, and blood loss was 289 ± 276 ml. Surgical complications were observed in six patients (16.7%), including: surgical site infection in four individuals, postoperative bleeding in one patient, and skin flap necrosis in one patient. No severe surgical morbidities or mortalities were observed.

Patient demographics and tumor characteristics

The patient demographics and tumor characteristics for surgically or non-surgically treated patients are listed in Table 1. There was no significant difference between patients who had primary tumor surgery and those who did not.

Patient outcomes

Overall survival was plotted using Kaplan–Meier curves based on the patient cohort according to surgery as shown in Fig. 1. Besides one patient who died from other disease 11 months after surgery, all patients died from primary breast cancer. Primary tumor resection did not significantly improve overall survival time in patients with incurable advanced breast cancer (surgery versus no surgery, median survival time (MST): 25.0 versus 24.8 months, $P = 0.352$). On the other hand, primary tumor resection allowed most patients some relief from symptoms relating to the skin-invasion tumor, such as odious smell, purulent discharge, and bleeding. Only 3 of 36 patients relapsed with local disease by three

Table 1
Comparison of characteristics of surgically versus non-surgically treated patients with incurable advanced breast cancer at diagnosis ($N = 92$).

Variable	Surgical removal of primary tumor		*P*-value
	Yes ($N = 36$)	No ($N = 56$)	
	No. of patient (%)	No. of patient (%)	
Age at diagnosis (years)			
<60	25 (69)	38 (68)	0.954
≥60	11 (31)	18 (32)	
Size (cm)			
<10	19 (53)	31 (55)	0.846
≥10	17 (47)	25 (45)	
Period of diagnosis			
2000–2005	18 (50)	19 (34)	0.125
2006–present	18 (50)	37 (66)	
Radiation therapy to the breast			
Yes	8 (22)	7 (13)	0.427
No	28 (78)	49 (88)	
Estrogen receptor (ER)			
Positive	19 (53)	38 (68)	0.074
Negative	17 (47)	17 (30)	
Unknown	0 (0)	1 (2)	
Progesterone receptor (PgR)			
Positive	9 (25)	22 (39)	0.101
Negative	27 (75)	33 (59)	
Unknown	0 (0)	1 (2)	
HER2 overexpression			
Yes	8 (22)	12 (21)	0.573
No	25 (69)	43 (77)	
Unknown	3 (8)	1 (2)	
Subtype			
ER+/HER2−	18 (50)	33 (59)	0.482
ER+/HER2+	1 (3)	5 (9)	
ER−/HER2+	7 (19)	7 (13)	
ER−/HER2− (Triple negative)	7 (19)	10 (18)	
Unknown	3 (8)	1 (2)	
Site(s) of metastasis at presentation			
Bone	17 (47)	44 (79)	
Lung	15 (42)	15 (27)	
Liver	13 (36)	11 (20)	
Brain	4 (11)	3 (5)	
Others	5 (14)	21 (38)	
Number of metastatic site			
1	21 (58)	29 (52)	0.568
2	12 (33)	17 (30)	
≥3	3 (8)	10 (18)	
Lines of chemotherapy			
0	7 (19)	14 (25)	0.595
1	10 (28)	19 (34)	
2	12 (33)	11 (20)	
≥3	7 (19)	12 (21)	