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## Metastasectomy and Surgical Resection of the Primary Tumor in Patients With Stage IV Breast Cancer:

### Time for a Second Look?

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### Abstract

Patients with metastatic or stage IV breast cancer have limited therapeutic options, and the mainstay of treatment remains systemic chemotherapy. Traditionally, the role of surgery has been confined to strict palliation. Improvements in the efficacy of chemotherapeutic regimens, coupled with the use of hormonal and targeted therapy, have resulted in an expansion of surgical resection beyond simple palliation. Several single-institution studies have reported improved survival and even long-term cures after surgical resection for oligometastatic stage IV breast cancer. Similarly, provocative new data suggest that removal of the primary tumor in some patients may confer a survival advantage. The aim of this review is to summarize studies in the medical literature pertaining to the use of surgical resection in patients with stage IV breast cancer. We believe there is enough evidence to challenge conventional thinking about the role of surgery in stage IV breast cancer and to consider a new multimodality treatment paradigm to optimize patient outcomes. It is time to conduct a carefully designed randomized trial to see whether surgery in stage IV breast cancer does indeed warrant a second look.

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The prognosis for patients with stage IV breast cancer is poor, and most patients will ultimately succumb to the disease. Improvements in systemic chemotherapy, as well as hormonal and targeted therapies, have helped improve 5-year survival from about 10% in the 1970s to about 40% in the late 1990s.<sup>1</sup> Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database demonstrate a 5-year survival of 26% for patients with stage IV breast cancer.<sup>2</sup> In many patients the focus is shifting away from palliation to the search for a durable cure. In this new era of improved systemic therapy, the traditional nihilistic view of

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surgery in the management of these patients is being challenged. Many tumors eventually recur after systemic treatment and a decrease in response occurs with each subsequent line of systemic treatment. In many patients surgical resection may be another weapon in the physician's armamentarium to bend the survival curve.

The poster child for this shift in thinking is the progress made with hepatic resection of metastases from colorectal cancer. There has been an explosion of studies documenting long-term durable cures for patients undergoing R0 hepatic resection for colorectal liver metastases, with 5-year survival rates of 25% reported for 1 nationwide study.<sup>3</sup> The impetus for this change in treatment approach has come from improvements in traditional 5-fluorouracil (5-FU)-based chemotherapy regimens to the FOLFOX and FOLFIRI regimens in vogue today, as well as targeted therapy with anti-EGFR (epidermal growth factor receptor) monoclonal antibodies.<sup>4</sup> Improved systemic chemotherapy has emboldened surgeons to try the same approach with breast cancer, which biologically has a slower doubling time than colon cancer and may even be more amenable to such an approach. Several single-institution studies in which solitary metastases were treated with surgical resection followed by systemic therapy have reported long-term survival.<sup>5</sup> A multimodality approach to select patients with limited metastatic disease may also control tumor burden while limiting toxicity and thus improving overall quality of life for these patients.

The aim of this study was to review the current medical literature on the role of surgery for treatment of stage IV breast cancer both for the sites of metastatic disease and for the primary tumor itself. We believe that there is now enough evidence to suggest that some patients with stage IV breast cancer will benefit from removal of metastases and/or the primary tumor as part of a multimodality treatment strategy and that the time has come to give surgery a second look.

## METHODS

A MEDLINE search of the English-language medical literature was performed to identify all relevant articles on the use of surgical therapy for stage IV breast cancer. The search was limited to articles published between January 1, 1990, and September 1, 2009, in order to evaluate patients in the current era of systemic therapy and surgery. The main keywords searched were "breast neoplasms," "surgery," "neoplasm metastases," "hepatic neoplasms (secondary)," "pulmonary neoplasms (secondary)," "metastasectomy," "prognosis," and "survival rate." Articles were screened on the basis of their importance, quality, number of patients, and relevance to the aims of the review. The preponderance of articles focused on resection of hepatic and pulmonary metastases, which are reviewed in detail. There were few studies on the resection of metastases in other sites, and these were mostly limited to case reviews or small case series so are only reviewed briefly. The rest of the articles reported on studies about the impact of surgical resection of the primary tumor on survival in patients with stage IV breast cancer.

### Hepatic Metastases

Of patients newly diagnosed with metastatic breast cancer, 15% present with liver metastases; in about one-third of these patients, liver metastases are the only site of distant disease.<sup>6,7</sup> Ultimately, liver metastases will develop in as many as 50%, with a median survival of 3–15 months.<sup>8,9</sup>

Several reports in the medical literature have examined hepatic resection for patients with metastatic breast cancer (Table 1).<sup>10–25</sup> These series have been relatively small, and they have varied by their inclusion criteria and the use of preoperative or postoperative systemic therapy. The reported 5-year survival rate varies from 18% to 61%. Current surgical techniques allow

for hepatic resection to be performed with a 0.0–0.6% incidence of postoperative mortality and a morbidity of 0.8–5.4%.<sup>26</sup> Isolated liver recurrences may represent a favorable biology in which aggressive therapy with hepatic resection would lead to improvement in survival, similar to that for patients with isolated hepatic colorectal metastases.<sup>27</sup>

The largest series on the subject is by Adam et al., who reported on the outcomes for 85 patients with hepatic breast cancer metastases who were operated on between 1984 and 2004 at the Paul Brousse Hospital in France.<sup>21</sup> Most patients had metachronous (89%), multiple (62%), and unilobar (61%) disease. A total of 16 of the 85 patients (19%) had extrahepatic disease (e.g., bone, lung, or brain); 11 of these 16 had curative resection or complete response to systemic therapy before hepatectomy, and 5 had bone metastases that were controlled by systemic therapy or local radiotherapy. Most patients (71/85 [84%]) received systemic therapy for a median of 8 cycles before surgical resection. By 1979 World Health Organization response criteria, 55 patients (78%) had an objective response, 10 (14%) had stable disease, and 6 (8%) progressed despite therapy. A subgroup of 71 patients (84%) also received systemic therapy after hepatic resection. Various types of hepatic resection were performed; 54 patients (64%) underwent a major hepatectomy, defined as the resection of  $\geq 3$  segments. The median number of metastases resected was 2, with 15 of the 85 patients (18%) receiving an R1 resection and 14 patients (16%) receiving an R2 resection. With a median follow-up of 38 months, median survival after hepatic resection was 32 months and survival at 5 years was 37%. The median recurrence-free interval for the 85 patients was 15 months, and the 5-year recurrence-free survival was 12%. By univariate analysis, 4 factors were associated with poor survival: (1) lack of response to prehepatectomy chemotherapy ( $P = 0.004$ ), (2) presence of extrahepatic metastases at hepatectomy ( $P = 0.004$ ), (3) R2 resection ( $P = 0.00001$ ), and (4) absence of repeat hepatectomy because of extrahepatic recurrence or recurrent unresectable hepatic disease ( $P = 0.01$ ). By multivariate analysis, all factors except the presence of extrahepatic disease remained significant. Additional hepatic disease developed in 59 patients (69%), with recurrence limited to the liver in 28 (47%) of these patients. Median time to recurrence was 10 months.

Another series reported on 54 patients, most of whom (81%) underwent R0 resection for hepatic metastases.<sup>16</sup> Overall 3-year and 5-year survival was 50 and 34%, respectively, with 3-year and 5-year disease-free survival of 42 and 22%, respectively. Median survival was 34.3 months. Regarding disease-free survival, only positive hormone-receptor status and objective response to chemotherapy had a significant impact ( $P = 0.01$  and  $P = 0.04$ , respectively).

The importance of achieving an R0 resection with negative margins is reflected by the fact that positive margins were adverse predictors of survival in several studies.<sup>10,21,25</sup> Other adverse predictors of survival were hormone status, lack of response to chemotherapy, vascular invasion, number of metastases, and a disease-free interval of  $< 1$  year after resection of the primary breast cancer.<sup>12,16,21,24,25</sup> On the basis of these studies, the ideal candidate for resection of liver metastases in breast cancer would be the patient with estrogen receptor-positive cancer, a disease-free interval of  $> 1$  year with a good response to preoperative chemotherapy, and an isolated metastasis who undergoes an R0 resection—a highly select population.

### Pulmonary Metastases

There are many advocates of surgical resection in patients with lung metastases from breast cancer. A complete surgical excision of all pulmonary metastases is often technically feasible with low morbidity and mortality. A review of the largest retrospective studies in the medical literature is summarized in Table 2.<sup>28–37</sup> Overall, 15–25% of women with breast cancer metastases will have an isolated metastatic focus in the lung or pleural space.<sup>38–39</sup> The 5-year survival ranges from 27% to 54%, with a single outlier of 80%, and median survival is 35–97

months. Unfortunately, data are scarce on direct comparison of primary medical therapy compared with surgical resection for treatment of pulmonary metastases in breast cancer. One small retrospective study evaluated primary surgical therapy in 33 patients compared with systemic therapy in 30 patients.<sup>40</sup> Of the 33 patients treated with surgical resection, 20 had surgery alone, 9 also had systemic therapy, and 4 also had radiotherapy. Of the 30 patients treated with systemic therapy, 8 had both systemic therapy and radiotherapy. Mean survival after resection was longer than that after systemic therapy (58 months vs. 34 months, respectively). The 5-year overall survival was also higher after surgery than after systemic therapy (36% vs. 11%, respectively).

Because of controversy about the benefit of pulmonary resection for cancer metastases, the International Registry of Lung Metastases was established in 1997 to demonstrate long-term survival after resection for numerous types of tumors. A focused analysis of lung metastasectomy for breast cancer patients was performed in 2002.<sup>32</sup> A total of 467 women (mean age, 53 years) underwent surgical resection of pulmonary breast cancer metastases. A complete (R0) resection was performed in most patients (84%), whereas 3% had an R1 resection and 13% had an R2 resection. Surgical approaches included thoracotomy (75%; unilateral in 72%), sternotomy (20%), and thoracoscopic resection (4%), with most of the resections being wedge or segmental (73%); other procedures included lobectomy (24%) and pneumonectomy (1%) or were unknown (2%). Most (66%) patients had solitary metastases. Additional chemotherapy was given in only 33% of patients: 8% preoperatively, 19% postoperatively, and 6% both before and after resection. Median survival was 37 months, with 5-year, 10-year, and 15-year survival of 38%, 22%, and 20%, respectively, for patients who underwent complete resection. Patients who had incomplete resection had a 5-year survival of 18%. Prognostic factors associated with increased survival were a disease-free interval of  $\geq 36$  months, R0 resection, and solitary metastases; factors that had no impact on survival included type of resection and additional chemotherapy.

Many of the studies listed in Table 2 also report on clinical and pathologic factors in these patients that were associated with adverse survival after resection. The most consistent finding was the longer the disease-free interval between the primary tumor and the appearance of the metastases, the better the likelihood of survival.<sup>28,29,31-34,36,37</sup> A prolonged disease-free interval may reflect a more indolent biology of the primary tumor and should be an important consideration in the decision to resect metastatic disease. Other factors associated with improved survival were positive estrogen receptor status, HER-2 (human epidermal growth factor receptor 2)/neu status, and the number of metastases.<sup>28,29,32,35,37</sup>

Although no definitive conclusions can be drawn from these small-scale retrospective studies, they do suggest that a subset of patients may benefit from an approach combining surgical resection of metastases with systemic chemotherapy. They also suggest that survival rates may be higher with a combination approach than with traditional chemotherapy alone and that further evaluation is warranted.

### Other Metastatic Sites

Breast cancer patients do manifest isolated metastases to sites other than the liver and lungs. These groups are much less studied than those with hepatic or pulmonary metastases. A few studies have evaluated the benefit of surgical resection in association with whole-brain irradiation in patients with isolated brain metastases.<sup>41-43</sup> There is some suggestion of improved survival, but brain metastases still carry a poor prognosis. Reports about the benefits of resection of isolated bone metastases also suggest some benefit, but long-term survival of patients with bone metastases has also been achieved without surgical resection.<sup>44</sup> The exception to this approach is isolated sternal or chest wall metastasis, which probably reflects isolated internal mammary lymph node recurrence. Chest wall resection of these metastases

has demonstrated long-term survival.<sup>45,46</sup> Most physicians reserve surgical resection for symptomatic, refractory, isolated bone metastases unresponsive to other treatment modalities.

Other studies report on surgical resection of adrenal, ovarian, and gastrointestinal metastases from breast cancer, but the small number of patients precludes drawing reasonable conclusions.<sup>47–49</sup> Nonetheless, it is noteworthy that these reports have indicated prolonged survival in some patients.

### **Surgery for the Intact Primary Tumor in Stage IV Breast Cancer**

Several retrospective studies from single institutions and population databases have demonstrated improved survival in women with stage IV disease who undergo surgery for an intact primary tumor.<sup>50–56</sup> A summary of these studies is provided in Table 3.

In a population-based study using the National Cancer Database, 16,023 patients with metastatic breast cancer diagnosed between 1990 and 1993 were analyzed for treatment modalities and survival outcomes.<sup>50</sup> Of that total, 9,162 women (57%) underwent therapeutic breast procedures consisting of a partial mastectomy (38%) or a total mastectomy (62%). Women with single-organ metastases were significantly more likely to have surgery of the primary tumor than were those with multiorgan disease ( $P < 0.001$ ). Multivariate analysis using a Cox proportional hazards model showed the following covariates to be independently associated with patient outcomes: (1) surgical resection of the primary tumor, (2) systemic therapy, (3) the number of metastatic sites, and (4) the type of metastatic disease. Overall survival was improved in women who underwent surgical resection, with 3-year survival rates of 17% for no surgery, 28% for partial mastectomy, and 32% for mastectomy.

These results were confirmed in a second population-based study by Gnerlich et al. using the SEER database.<sup>54</sup> Of a total of 9734 identified patients with metastatic breast cancer and an intact primary tumor, 47% underwent resection of the primary breast cancer. Median survival was longer for women who had surgery of the primary than for women who did not. The improved median survival with surgery vs. without surgery was true both for women who were alive during the study period (36 vs. 21 months, respectively;  $P < 0.001$ ) and for women who died during the same study period (18 vs. 7 months, respectively;  $P < 0.001$ ). When confounding variables were controlled for by multivariate analysis, patients who underwent surgery were found to have been less likely to die during the study period compared with women who did not undergo surgery (adjusted hazard ratio, 0.63 [95% confidence interval, 0.60–0.66]).

Outside the United States, a review of the Geneva Cancer Registry identified 300 patients treated between 1977 and 1996 for intact primary tumor and metastatic disease.<sup>52</sup> Of the 127 (42%) who underwent therapeutic breast surgery, 87 (69%) had mastectomy and 40 (31%) had partial mastectomy. Additionally, 73 patients (57%) underwent lymph node dissection. Again, patients were more likely to undergo surgery if they had only 1 meta-static site (61% vs. 41%;  $P < 0.0001$ ) and nonvisceral metastases (58% vs. 43%;  $P = 0.007$ ). Women who underwent breast surgery had a 50% reduction in breast cancer mortality compared with women who did not have surgery. Other factors associated with improved survival included the use of systemic therapy, whereas brain metastasis was associated with worse survival.

Another retrospective study, from the University of Texas MD Anderson Cancer Center, evaluated patients who presented with stage IV breast cancer and an intact primary tumor who were treated between 1997 and 2002.<sup>51</sup> Of 224 patients, 82 (37%) had either a partial mastectomy (48%) or a total mastectomy (52%). Surgery was associated not only with a trend toward improved overall survival ( $P = 0.12$ ) but also with improvement in metastatic progression-free survival ( $P = 0.0007$ ). Patients who underwent breast surgery were younger,



had a lower tumor burden, and were more likely to have liver metastases and HER-2 amplification. Multivariate analysis showed overall survival to be influenced by the number of metastases (1 vs. >1) and the lack of HER-2 amplification.

Several other single-institution studies are also reviewed. A study from Washington University Medical Center evaluated 409 patients who presented with stage IV disease and an intact primary tumor.<sup>53</sup> A total of 187 (46%) underwent surgical resection of the primary. Most of these 187 patients (103 [55%]) underwent mastectomies, and most (53%) underwent surgery for palliation, compared with 29% who underwent resection to “establish diagnosis” and 14% who underwent resection for “definitive treatment.” The latter two groups had metastatic disease diagnosed 1 month after surgery. When various confounding variables (e.g., age, comorbidity, tumor grade, histology, and sites of metastasis) were controlled for, patients who underwent surgery of the primary tumor had a longer median survival ( $P < 0.0001$ ). A second study, from the University of Texas Health Science Center, comprised 395 patients, most of whom had definitive surgery of the primary tumor (242 patients [61%]); 191 (78%) underwent mastectomy and 53 (22%) underwent lumpectomy.<sup>55</sup> Patients most likely to not undergo surgery were those with estrogen receptor-negative tumors, visceral metastases, or multiple sites of metastases. Overall survival was improved in patients who underwent definitive surgery of the primary. Multivariate analysis confirmed that primary surgery was associated with improvement in overall survival, as was estrogen-receptor positivity, progesterone-receptor positivity, and the number of metastases.

Although the data from these single-institution and population-based studies suggest a survival advantage to resection of the intact primary tumor in patients with metastatic disease, there is inherent bias in the studies. All the studies were retrospective in nature, and patients selected for surgery were not randomly assigned to surgery or an alternate treatment but were instead selected by the treating physician. As observed in the reports that emanated from these studies, the patients selected for surgery generally had a lower burden of systemic disease.

In an attempt to control for selection bias, researchers performed a study using a matched-pair analysis of 622 patients who presented with an intact primary and meta-static disease.<sup>57</sup> Of these stage IV patients, 388 (62%) had no primary site surgery whereas 234 (38%) had surgery. Overall survival was better for patients who underwent surgery ( $P < 0.0001$ ). Further analysis using case-matched controls for type of metastases (i.e., bone, visceral, or distant lymph nodes) demonstrated that the impact of surgery diminished or was abrogated. Furthermore, the timing of chemotherapy played a major role in outcome. Those patients who had preoperative chemotherapy followed by surgery did significantly better than patients who had surgery first or who had chemotherapy alone, suggesting a selection bias toward patients who had a better response to chemotherapy.

If one accepts the fact that surgical extirpation of the primary tumor improves the overall survival of patients with metastatic breast cancer, then the next question is whether the extent of surgical excision plays an important role. Unfortunately, most of the studies do not address this issue.<sup>51,53–55,57</sup> Two studies evaluated the impact of margin status.<sup>50,52</sup> Both studies demonstrated an improvement in survival if negative margins were obtained after surgical resection of the breast tumor by mastectomy or lumpectomy. The ramifications of positive margins were different in both studies. Patients with positive margins in the National Cancer Data Base study had worse survival compared with those with negative margins but had better survival compared with those without surgery, whereas the patients with positive margins in the Geneva Cancer Registry study had equivalent survival to that of patients without surgery.<sup>50,52</sup> The issue of surgical treatment of the axilla remains largely unanswered. Only 1 study addressed this issue and found that the addition of axillary dissection did not have an impact

on overall survival.<sup>56</sup> The extent of primary surgery in patients with stage IV breast cancer remains unanswered and needs to be addressed in any upcoming studies.

The biological rationale for an improvement in survival seen with resection of the primary tumor in metastatic breast cancer is based on several lines of reasoning. The primary tumor may act as a “seed source” for development of new metastases, and its removal would theoretically diminish the chances of disease progression.<sup>50</sup> Decreasing the tumor burden by removal of the primary could also increase the efficacy of chemotherapy by reducing the chances of a resistant clone appearing.<sup>54</sup> Finally, a certain degree of immune modulation may be achieved by eliminating the immunosuppression associated with the presence of the primary tumor.<sup>55,58</sup> Without a well-designed controlled randomization trial, we will not be able to answer these questions.

## CONCLUSIONS

As outlined in this review, a substantial body of evidence exists to suggest that there may be benefit to the surgical resection of limited metastatic disease in patients with stage IV breast cancer. In addition to improvement in survival, an improvement in quality of life because of discontinuation of chemotherapy and decreased tumor burden are also potential benefits. However, much of the data are limited to single-institution series with variable adjuvant or neoadjuvant approaches and are subject to selection bias by treating physicians.

Similarly, the question of resection of the primary tumor in patients with metastatic breast cancer has ignited a debate that can only be conclusively settled by a carefully designed randomized trial, as has been proposed by others as well.<sup>59</sup> Even with attempts to control for confounding factors by multivariate analysis as well as by matched pair analysis, the question remains as to whether an improvement in survival in these patients may well be the result of selection criteria rather than any inherent benefit. The results of such a trial not only would hold significance for breast cancer, but also might provide for insight into understanding cancer biology and the development of new treatment paradigms for other cancer types.

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**TABLE 1**

Survival outcomes after hepatic metastasectomy secondary to breast cancer

Authors	No. of patients	Median disease-free survival (months)	Median survival (months)	5-year survival (%)
Raab et al. <sup>10</sup>	34	NR	27	18
Seifert et al. <sup>11</sup>	15	NR	57	18
Selzner et al. <sup>12</sup>	17	NR	24	22
Yoshimoto et al. <sup>13</sup>	25	NR	34	NR
Pocard et al. <sup>14</sup>	65	NR	47	46 <sup>a</sup>
Carlini et al. <sup>15</sup>	17	NR	53	46
Elias et al. <sup>16</sup>	54	34	NR	34
Vlastos et al. <sup>17</sup>	31	22	63	61
Sakamoto et al. <sup>18</sup>	34	NR	36	21
d'Annibale et al. <sup>19</sup>	18	NR	32	30
Ercolani et al. <sup>20</sup>	21	NR	42	25
Adam et al. <sup>21</sup>	85	20	38	37
Caralt et al. <sup>23</sup>	12	NR	36	33
Lubrano et al. <sup>24</sup>	16	NR	42	33
Thelen et al. <sup>25</sup>	39	NR	NR	42

NR not reported

<sup>a</sup>Value reported was 4-year survival versus 5-year survival

TABLE 2

Survival outcomes after pulmonary metastasectomy secondary to breast cancer

Authors	No. of patients	Median disease-free survival (months)	Median survival (months)	5-year survival (%)
Lanza et al. <sup>28</sup>	37	NR	47	50
Friedel et al. <sup>29</sup>	103	NR		27
	68 <sup>a</sup>		36	31
McDonald et al. <sup>30</sup>	60	18	42	38
Murabito et al. <sup>31</sup>	28	NR	79 <sup>b</sup>	80
Friedel et al. <sup>32</sup>	467	NR	35	35
	392 <sup>a</sup>		37	38
Ludwig et al. <sup>33</sup>	21	27.6	96.9	53
Planchard et al. <sup>34</sup>	125	36	50	45
Welter et al. <sup>35</sup>	47	43	32	36
Yoshimoto et al. <sup>36</sup>	90	NR		54
Chen et al. <sup>37</sup>	41	NR	NR	51

NR not reported

<sup>a</sup>Complete resection<sup>b</sup>Value is mean versus median

TABLE 3

Resection of primary tumor in women presenting with stage IV breast cancer

Authors	Patients (No.)		Patients with surgery, No. (%)		3-year survival (%)			
	Total	Without surgery	With surgery, No. (%)	Partial mastectomy	Total mastectomy	Overall	Without surgery	With surgery
Khan et al. <sup>50</sup>	16,023	6,861	9,162 (57)	3,513 (38)	5,649 (62)	25	17	28 (PM) 32 (TM)
Babiera et al. <sup>51</sup>	224	142	82 (37)	39 (48)	43 (52)	83 <sup>a</sup>	80 <sup>a</sup>	95 <sup>a</sup>
Rapti et al. <sup>52</sup>	300	173	127 (42)	40 (32)	87 (69)	31	NR <sup>b</sup>	NR <sup>b</sup>
Fields et al. <sup>53</sup>	409	222	187 (46)	61 (33)	103 (55)	NR	26 <sup>a</sup>	46 <sup>a</sup>
Gnerlich et al. <sup>54</sup>	9,734	5,156	4,578 (47)	1,844 (40)	2,485 (54)	NR	25 <sup>a</sup>	45 <sup>a</sup>
Blanchard et al. <sup>55</sup>	395	153	242 (61)	191 (78)	53 (22)	NR	20 <sup>a</sup>	40 <sup>a</sup>
Ruiterkamp et al. <sup>56</sup>	728	440	288 (40)	85 (30)	189 (66)	NR	25 <sup>a</sup>	45

NR not reported, PM partial mastectomy, TM total mastectomy

<sup>a</sup>Estimated from the data reported in the reference<sup>b</sup>The 5-year survival was 13% for patients who did not undergo surgery, 27% for patients who underwent surgery with negative margins, and 16% for patients who underwent surgery with positive margins