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Long-Term Results and Predictors of Survival After Conservative Breast Surgery for Breast Cancer During Pregnancy

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Breast cancer is one of the most frequently encountered malignancies in women. Although the prognosis is good for most breast cancer patients, little is known about the outcomes of breast carcinoma during pregnancy. The long-term results and predictors of survival of conservative breast surgery for breast cancer during pregnancy are especially unclear.

Material/Methods: Patients with primary diagnosis of breast cancer during pregnancy who received conservative breast surgery were recruited in this study from October 2009 to January 2015. Clinical data were collected and compared to individuals without associated pregnancies. The primary outcome disease-free survival (DFS) and the secondary outcome, overall survival (OS), were compared between the 2 groups (pregnant *vs.* nonpregnant women). Cox proportional hazards regression analysis was used to assess the potential predictors of survival for breast cancer patients during pregnancy.

Results: Sixty-three pregnant patients underwent conservative breast carcinoma. The median gestational age was 26 weeks and the median age was 34 years. The nonpregnant group consists of 82 individuals with median age of 37 years. All the patients received chemotherapy after surgery. The follow-up period was 3 years. The 3-year DFS was 79.3% in the pregnant group and 81.7% in the nonpregnant group. The 3-year OS was 87.3% (pregnant) and 89% (nonpregnant), respectively. Multivariable analysis revealed that tumor stage and chemotherapy were independent predictors for survival.

Conclusions: Our study showed that conservative breast surgery is a reliable therapy for breast cancer patients during pregnancy, with similar DFS and OS compared to nonpregnant patients.

MeSH Keywords: Breast Neoplasms • Mastectomy, Segmental • Pregnancy • Prognosis

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Background

Breast cancer is among the most common malignancies in women, with an incidence of 71.7 per 100 000 population in developed countries and 29.3 per 100 000 population in developing countries [1]. Although the occurrence of cancer in pregnant women is not a common phenomenon, it is estimated that up to 3% of breast cancers are diagnosed in pregnant women, making it the second most common malignancy diagnosed during pregnancy [2,3]. The incidence is expected to increase because more women are now deferring childbearing until they are older. There has been controversy about the influence of pregnancy on prognosis, and management of breast cancer with associated pregnancy can be challenging because of the possibility of adverse effects on both the fetus and mother. A report from Amant et al. insisted that immediate treatment during pregnancy will decrease the need for preterm delivery and subsequent potential prematurity [4]. In general, the aim of treatment for breast cancer during pregnancy is the same as that for nonpregnant patients.

Breast-conserving surgery (BCS) is a reliable therapeutic option with similar overall survival as mastectomy [5,6]. In addition, BCS provides significant benefit for patients due to much better cosmetic effect. Although some research claimed that BCS increased local reoccurrence incidence on the long term [7], it is obvious that the benefit outweighed the cost in selected patients [8,9]. Previous studies have reported surgery was the definitive therapeutic approach for breast cancer, followed by multidisciplinary treatment [10]. However, few studies have focused on the long-term results or predictive factors of survival for gestational breast cancer patients who underwent conservative breast surgery.

The present study compared the long-term results between pregnant and nonpregnant patients who underwent BCS, and also explored the potential predictors of survival after conservative breast surgery for breast cancer during pregnancy.

Material and Methods

Participants

Patients with diagnosis of breast cancer in our institution were recruited in this study from October 2009 to January 2015. Diagnosis was confirmed using the combination of mammography, ultrasonography, magnetic resonance imaging (MRI), and core biopsy. Cancer was staged according to the American Joint Committee on Cancer (AJCC) staging system. Hormone receptor status and HER2 status were investigated preoperatively. All eligible patients underwent breast-conserving surgery followed by radiotherapy immediately after delivery. For the nonpregnant group, patients with similar backgrounds were recruited. The exclusion criteria were lack of complete clinical data, follow-up less than 6 months, locally widespread or recurrent breast cancer, and previous breast irradiation. All medical records, including age, cancer staging, ER/PR status, HER2 status, trimester at diagnosis, and follow-up data, were collected and reviewed. This study was approved by the Institutional Review Board of our institution. Owing to the nature of retrospective research, the written informed consent requirement was waived for this study.

Treatment

All patients were informed about various therapeutic approaches and the pros and cons of these strategies. Breast-conserving surgery was adapted, with comprehensive consideration of tumor staging, tumor biology, gestational status, and the patient's wishes, and was performed by a multidisciplinary team of breast surgeons, anesthetists, pediatricians, and obstetricians. Owing to the potential fetal damage in the period of organogenesis, patients diagnosed at the first trimester were not given chemotherapy until 8 weeks of gestational age. Radiation therapy was initiated immediately after delivery. Tamoxifen was avoided because of potential risk of inducing birth defects. Termination of pregnancy was not recommended since it would not improve maternal outcome. To prevent adverse effects of drugs on newborns, breastfeeding in the first weeks after delivery was not recommended.

Clinical outcomes and follow-up

The primary outcome was disease-free survival (DFS), which was considered as the period from the date of treatment of breast carcinoma to the date of confirmed diagnosis with a secondary malignancy or any loco-regional or distant recurrence of disease, whichever occurred first. The secondary outcome was overall survival (OS), which was the period from the date of diagnosis to death by any cause. Follow-up ceased at the date of first confirmed date of recurrence or death. Individuals without any events at the end of follow-up were censored. Clinical visits were performed at every 6 months for 3 years during follow-up. Ultrasonography or mammography was used for patients suspected to have recurrence or new primary breast cancer.

Statistical analysis

Patient data, including baseline demographic and clinical characteristics, were analyzed using descriptive statistics and frequency tabulation and are presented as mean ± standard deviations. Survival analysis, including DFS and OS, was estimated using Kaplan-Meier curves. To investigate potential predictors for long-term outcomes, we selected 6 candidate predictors,

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including age (20–30 y; 30–40 years), AJCC staging, chemotherapy, ER/PR status, HER2 status, and trimester at diagnosis based, in previous retrospective studies and *a priori* hypotheses. Univariate associations between candidate predictors and survival were examined with 95% confidence interval (CI) by using the Cox proportional hazards model. Multivariate Cox regression analysis with backward elimination was performed to select significant prognostic factors. All reported P values were 2-sided, and a value less than.05 was set as the level of significance. All statistical results were calculated using SAS (v 9.3; SAS Institute, Inc, NC, USA)

Results

Characteristics of study participants

A total of 815 cases diagnosed with breast cancer in our institution from October 2009 to January 2015 were reviewed. We recruited 63 individuals with primary diagnosis of breast cancer during pregnancy who received conservative breast surgery and 82 nonpregnant patients with similar background as the nonpregnant group. The patient cohort profile is shown in Figure 1. The median age was 34 years (range 20–44) in pregnant patients and 37 years (range 22–55) in nonpregnant patients.

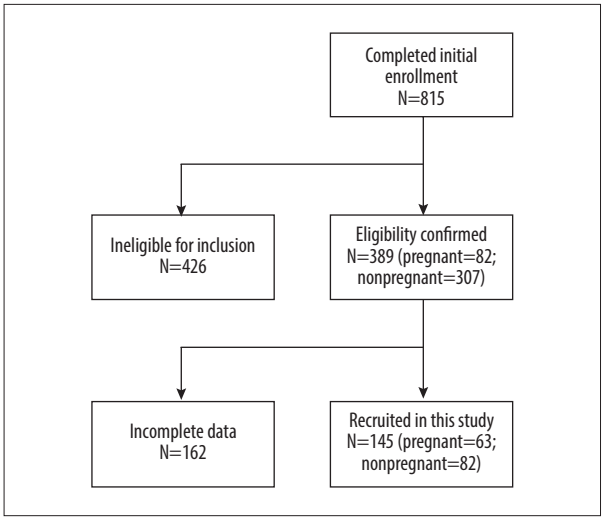

Figure 1. Profile of the patient cohort.

The median gestational age was 26 weeks (range 6–34 weeks). The gestational ages at diagnosis were: 6 individuals with trimester I, 29 individuals with trimester II, and 28 individuals with trimester III. A total of 41 (65.1%) pregnant patients were diagnosed with tumors stage II or III, and 46 (56.1%) were stage II or III in the nonpregnant group. Most of the patients were diagnosed with pathological stage I or II. There was no

Table 1. Demographic and clinical characteristics.

Variable	Pregnant group (n=63)	Nonpregnant group (n=82)	P value
Age (Mean ±SD, yrs)	34.5±15.2	37.6±17.5	0.82
Tumor stage			0.26
1	22	36	
2	26	28	
3	15	18	
Pathological stage			0.17
I	20	33	
IIA	18	22	
IIB	17	15	
III	8	12	
ER/PR positivity			0.08
Yes	29	50	
No	34	32	
HER2 positivity			
Yes	27	22	0.03
No	36	60	
Chemotherapy			
Yes	39	52	
No	24	30	0.37

SD – standard deviations; ER – estrogen receptor; PR – progesterone receptor; HER2 – human epidermal growth factor receptor 2.

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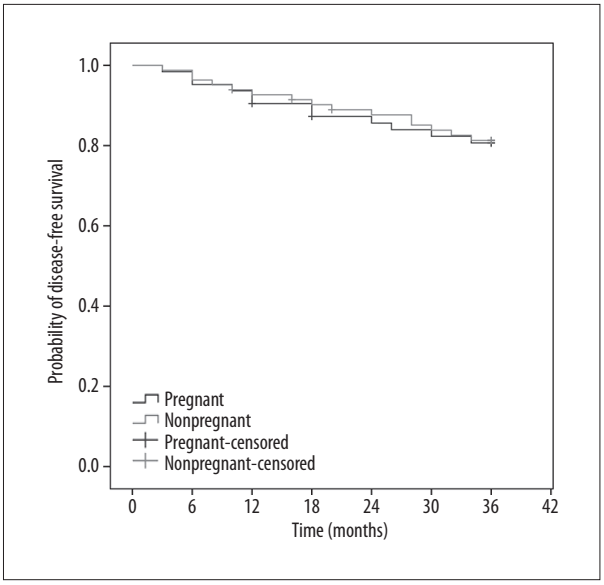

Figure 2. Kaplan-Meier survival estimates of disease-free survival for breast cancer patients with or without pregnancy.

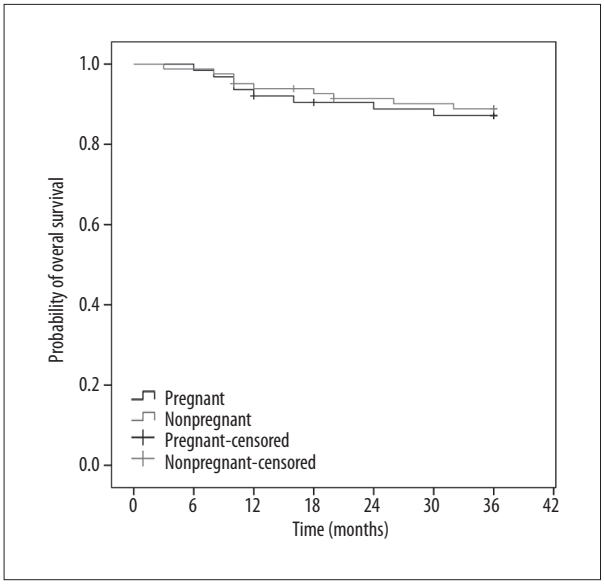

Figure 3. Kaplan-Meier survival estimates of overall survival for breast cancer patients with or without pregnancy.

significant difference in pathological stage at diagnosis between pregnant and nonpregnant women (P>0.05). As expected with premenopausal breast carcinoma, most of the women in the pregnant group had estrogen-negative (ER–) or progesterone receptor-negative (PR-) tumors. Regarding human epidermal growth factor receptor 2 (HER2) status, 42.8% of patients diagnosed during pregnancy were positive, compared with only 26.8% of cancers in nonpregnant women. All patients underwent breast-conserving surgery, and a total of 91 patients received chemotherapy. The chemotherapy regimen included Cytoxan, 5-fluorurical, and Adriamycin. The mean gestational age at first chemotherapy was 16.4±9.2 weeks. The baseline demographic and clinical characteristics of patients are shown in Table 1.

Clinical outcomes

A total of 145 patients were recruited in this study. Of these, 137 individuals were evaluated at 3-year follow-up, while 5 patients (2 pregnant patients and 3 nonpregnant patients) were lost to follow-up during this period. Recurrence of breast cancer or secondary malignancy was the first event in 27 patients (12 pregnant patients and 15 nonpregnant patients). Of these, 24 patients (14 had local recurrence and 10 had distant recurrence of disease) had local or distant recurrence and 3 had a secondary malignancy (2 had lung metastases and 1 had liver metastases). In addition, recurrence or metastases were detected in 16 patients within the first 2 years after surgery. The 3-year DFS rate was 79.3% in the pregnant group and 81.7% in the nonpregnant group (Figure 2). No significant difference in DFS was detected between the 2 groups. Six patients diagnosed with pregnancy and 9 patients without pregnancy were reported to have dies during follow-up. The observed 3-year OS was 87.3% in pregnant women and 89% in nonpregnant women (Figure 3). Among all 15 deaths, 11 were related to primary or metastatic cancer and 4 were due to other causes. There was no significant difference in OS between pregnant and nonpregnant groups (P>0.05). A total of 60 patients gave birth to 62 liveborn babies and 3 patients had a discontinuation of pregnancy. Two liveborn infants were had adverse effects related to preterm delivery before 32 weeks of gestation, and 1 of them died within 1 month after delivery. No malformations or newborn complications were observed for the rest of the infants. At 4 weeks after delivery, the median birthweight of infants was 2897 g in the pregnant group and 3842 g in the nonpregnant group. There were no abnormal hemoglobin concentrations, leucocyte counts, or thrombocyte counts at time of delivery or at 1 month after birth.

Identification of predictive factors

Six candidate risk factors – age, AJCC staging, chemotherapy, ER/PR status, HER2 status, and trimester at diagnosis – were selected for further investigation based on previous retrospective research and *a priori* hypotheses. All relevant medical data were obtained from the electronic database of our institution. Tumor stage was assessed according to the AJCC guidelines, and stage VI was excluded in this study because of different treatment regimens. Univariate analysis revealed that 4 of these factors were statistically significant in recurrence-free survival, including AJCC stage, chemotherapy, HER2 status, and trimester at diagnosis. Multivariate analysis confirmed only AJCC stage and chemotherapy as significant predictive factors for

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Table 2. Univariate and multivariate Cox regression models for DFS.

	Disease-free (n=49)	Recurrence/ metastases (n=12)	Univariate analysis	Multivariate analysis	
			P value	HR (95% CI)	P value
Age			0.36		
20–29	22 (44.9%)	5 (41.7%)			
30–40	27 (55.1%)	7 (58.3%)			
AJCC stage			0.01	3.45 (1.46–5.32)	0.00
1	20 (40.8%)	1 (8.3%)			
2	21 (42.8%)	4 (33.3%)			
3	8 (16.4%)	7 (58.4%)			
ER/PR positivity			0.27		
Yes	24 (49%)	6 (50%)			
No	25 (51%)	6 (50%)			
HER2 positivity			0.04	0.94 (0.78–1.12)	0.16
Yes	22 (44.9%)	8 (66.7%)			
No	27 (55.1%)	4 (33.3%)			
Chemotherapy			0.02	2.17 (1.13–4.89)	0.03
Yes	32 (65.3%)	3 (25%)			
No	17 (34.7%)	9 (75%)			
Gestational age			0.04	1.06 (0.94–1.76)	0.20
Trimester I	5 (10.2%)	1 (8.3%)			
Trimester II	22 (44.9%)	5 (41.7%)			
Trimester III	22 (44.9%)	6 (50%)			

DFS – disease-free survival; HR – hazard ratio; CI – confidential interval; AJCC – American Joint Committee on Cancer.

DFS among selected factors in univariate analysis (Table 2). We also investigated the potential risk factors for overall survival. Univariate analysis showed that 3 factors – AJCC stage, chemotherapy, and HER2 status – had a significant effect on OS. Multivariate Cox regression models showed only AJCC stage was significant a prognostic factor (Table 3).

Discussion

Although the prognosis of early-stage breast carcinoma is good for most patients, cancer can complicate pregnancy. Breast carcinoma is one of the most common malignancies during pregnancy [11]. In addition, the diagnosis of breast carcinoma during pregnancy can be more complex since pregnancy-induced breast changes (e.g., engorgement) make it difficult to distinguish a concerning breast mass from a normal breast in a pregnant woman [12]. In addition, physiological hyperproliferative changes of the breast caused by gestational and puerperal hormones, can induce a false-positive or false-negative result with fine-needle aspiration biopsy [13]. Other diagnostic approaches such as MRI are controversial because the use of gadolinium during pregnancy, which can cross the placenta and increase the incidence of fetal abnormalities, is not widely accepted [14,15]. Apart from that, the treatment strategies for pregnancy-related breast cancer are different from those of nonpregnant patients. A previous study found that anhydramnios can lead to fetal adverse-effects [16]. Therefore, the use of trastuzumab is contraindicated for pregnant patients based on ESMO guidelines [11]. Because we performed breast-conversing surgery for all included patients according to the standard protocols, radiation therapy was necessary to reduce risk of recurrence. However, restriction of use of radiotherapy during pregnancy is controversial due to the teratogenic effects of ionizing radiation on the fetus [17]. Thus, in our study, all the patients received radiotherapy immediately after delivery.

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Table 3. Univariate and multivariate Cox regression models for OS.

	Survival (n=55)	Dead (n=6)	Univariate analysis	Multivariate analysis	
			P value	HR (95% CI)	P value
Age			0.81		
20–29	25 (45.5%)	2 (33.3%)			
30–40	30 (55.5%)	4 (66.7%)			
AJCC stage			0.02	3.17 (1.76–5.21)	0.00
1	21 (38.2%)	0			
2	25 (45.5%)	1 (16.7%)			
3	9 (163%)	5 (83.3%)			
ER/PR positivity			0.47		
Yes	25 (45.5%)	4 (66.7%)			
No	30 (55.5%)	2 (33.3%)			
HER2 positivity			0.03	0.92 (0.81–1.07)	0.22
Yes	26 (47.3%)	4 (66.7%)			
No	29 (52.7%)	2 (33.3%)			
Chemotherapy			0.02	1.93 (1.03–3.11)	0.02
Yes	34 (61.8%)	1 (16.7%)			
No	21 (38.2%)	5 (83.3%)			
Gestational age			0.89		
Trimester I	6 (10.9%)	0			
Trimester II	24 (43.6%)	3 (50%)			
Trimester III	25 (45.5%)	3 (50%)			

OS – overall survival.

Unlike the regular chemotherapy regimen for nonpregnant patients, cytotoxic agents such as methotrexate should be avoided at least in the first trimester of pregnancy [18,19].

We retrospectively reviewed the clinical data of patients, including demographics and pathological examination results, as well as genetic predisposition to breast cancer. In line with other reported results, we also found that most breast carcinomas diagnosed during pregnancy were ductal adenocarcinomas [20,21]. Genetics detection revealed that most pregnant patients had hormone receptor-negative cancer, and HER2 positivity was 42.8%, much higher than the 26.8% in nonpregnant patients. We also recorded morbidity and mortality in infants, finding that the rates were similar to those in the general population [22]. The data on liveborn infants showed the median birthweight was 2897 g and 3842 g at 4 weeks after delivery. Our results are similar to those of a previous report that recorded median birthweights of 2765g and 3590 g at 4 weeks after delivery [23].

Regarding long-term results, the prognosis of breast-conserving surgery for nonpregnant patients has been reported in several previous studies [24,25]. Here, we compared OS and DFS between pregnant and nonpregnant patients in this study. Our results showed that the 3-year DFS was 79.3% in the pregnant group and 81.7% in the nonpregnant group, which was in line with previous studies [23,26], and there was no significant difference between the 2 groups. OS was similar in pregnant and nonpregnant patients during 3-year follow-up (87.3% *vs.* 89%). Amant et al. [27] reported the 5-year OS rate in pregnant women with breast carcinoma was 78%, which was much lower than in our study. The discrepancy might be due to the different inclusion criteria and treatment strategies. We excluded the stage VI patients because the therapeutic approaches were different for these patients. We also aimed to focus on the effect of breast-conversing surgery in this study, so all the recruited patients underwent surgery plus radiotherapy with or without chemotherapy. To the best of our knowledge,

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few studies have reported predictive factors for long-term results of patients during pregnancy who underwent breast-conversing surgery. Voogd et al. [28] reported age 35 years and younger, extensive intraductal component, and vascular invasion are risk factors contributing to local recurrence in nonpregnant women. Another study confirmed that poorly differentiated ductal carcinoma-*in-situ* (DCIS) and positive margin status have prognostic value for predicting distant metastasis after breast-conserving surgery [29]. Here, we observed several factors, including AJCC stage and chemotherapy, contributing to the prognosis of OS and DFS of pregnant patients. In most previous studies, age was found to be one of the most effective predictors in predicting recurrence of breast cancer. However, we did not observe the prognostic value of age in pregnant patients. The range of childbearing age might explain these results. Pregnant patients are generally younger than nonpregnant patients. We also found an HR of 1.06 of gestational age, suggesting better outcome for late trimester patients; however, the confident intervals revealed no distinct difference between late pregnancy and early pregnancy.

Our study has several limitations. It was a retrospective study, there was scant data on potential confounding factors, and we could not control exposure or outcome assessment, which might have biased the study design.

Conclusions

In general, this study compared the long-term results between breast cancer patients with or without pregnancy and identified the potential predictive factors for survival of pregnant patients who underwent breast-conserving surgery. Conservative breast surgery had similar DFS and OS for breast cancer patients during pregnancy when compared to nonpregnant patients. Tumor stage and chemotherapy are independent risk factors for predicting the long-term prognosis of pregnant breast cancer patients who undergo conservative breast surgery. The clinical evidence of our results contributes to the therapy of pregnant breast carcinoma patients. Prospective observational studies are needed to provide a better understanding of breast cancer in pregnant women.

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