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Original Article

Study on the Effects of Fertility Preservation on the Timing of Breast Cancer Treatment and Oncological Outcomes

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ABSTRACT

Background: Breast cancer is the most common cancer among women of reproductive age. Although chemotherapy and endocrine therapy have improved the prognosis, they can induce chemotherapy-related amenorrhoea. Some guidelines recommend fertility preservation before breast cancer treatment. This study aimed to assess whether fertility preservation affects the timing of breast cancer treatment and oncological outcomes.

Methods: We performed a retrospective study of 249 patients under 45 years of age diagnosed with breast cancer between 2010 and 2021 at our institution. We compared the interval from breast cancer diagnosis to the start of breast cancer treatment and the prognosis among patients who did and did not undergo fertility preservation.

Results: Twenty-two patients (8.8%) underwent fertility preservation (FP group) and 227 (91.2%) did not undergo fertility preservation (non-FP group). The intervals from breast cancer diagnosis to initial treatment were 41.1 days in the FP group and 45.2 days in the non-FP group ($p = 0.87$). Cancer recurrence was noted in 5 patients in the FP group and in 22 in the non-FP group. Two patients in the FP group and eight in the non-FP group died. There were no differences in relapse-free or overall survival between the two groups ($p = 0.07/0.19$).

Conclusions: There were no differences in the interval from cancer diagnosis to the start of treatment or the oncological outcomes based on whether patients underwent fertility preservation. Fertility preservation should be considered before breast cancer treatment in young cancer patients.

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KEYWORDS: fertility preservation, adolescent and young adult, breast cancer, chemotherapy, amenorrhea

Introduction

Breast cancer is the most common cancer in women, and one in five women diagnosed with breast cancer is < 45 years at diagnosis.[1] The 5-year survival rate among women younger than 45 years who are diagnosed with breast cancer has been increasing since 1975, and the survival rate in 2008-2014 was 88.2%.[2] Consensus guidelines recommend neoadjuvant chemotherapy (NAC) or adjuvant chemotherapy for these patients, which improve both

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disease-free and overall survival.[3, 4] However, chemotherapy can induce a number of off-target effects, including temporary or permanent chemotherapy-related amenorrhoea.[5] The risk of chemotherapy-related amenorrhoea associated with alkylating agents or anthracyclines ranges from 53% to 89%.[6, 7] Further, an estimated 42% of all female cancer survivors develop ovarian failure because of the gonadotoxicity of chemotherapy and radiotherapy,[8–11] and adjuvant endocrine therapy, which is generally recommended for 5 years in patients with hormone receptor (HR)-positive breast cancer, can also delay parenthood, due to the potential teratogenicity of the treatment.[12] A recent study also recommended that endocrine therapy should extend for 7-10 years, depending on the cancer stage.[13]

Post-treatment pregnancy rates are highly dependent on the type of cancer, with the lowest rates reported in women with histories of breast and cervical cancer. Although no difference has been shown for the female partners of male cancer survivors, female cancer survivors have an increased risk of obstetric and birth complications, such as an increased risk of premature birth, low birthweight of the neonate, elective and emergency cesarean sections, assisted vaginal delivery, and postpartum haemorrhage.[14] Therefore, for patients who have not completed their family planning at the time of breast cancer diagnosis, the demand for fertility preservation (FP) and information about the feasibility, complications, and safety of pregnancy following breast cancer treatment are expected to increase. Therefore, FP before the introduction of breast cancer pharmacotherapy, including chemotherapy and endocrine therapy, should be considered for patients with breast cancer.

A number of FP techniques are available. Freezing embryos or oocytes after controlled stimulation for future in vitro fertilization procedures is the most frequently used FP technique .[15] If this is unfeasible, or if ovarian stimulation is contraindicated, ovarian tissue cryopreservation of vitrified oocytes or embryos after in vitro maturation of oocytes recovered from small antral follicles may be performed.[16] However, these FP techniques require time to collect embryos, oocytes, and ovarian tissues and depend on the patient's menstruation cycle. Thus, oncological treatment may be delayed in these patients, a fact which patients and oncologists are aware of and which may consequently compromise treatment outcome.[17]

This study aimed to compare the interval from breast cancer diagnosis to the start of breast cancer treatment in patients who did and did not undergo FP. We also compared breast cancer recurrence and survival based on FP treatment.

Methods

Study design

We analyzed a cohort of female patients diagnosed with breast cancer between 1 January, 2010 and 31 December, 2021. All patients were aged < 45 years at the time of diagnosis. Exclusion criteria were distant metastasis at diagnosis, refusal of treatment, treatment at other institutions, loss to follow-up, and FP after beginning of breast cancer treatment. A flowchart of patient selection is presented in Fig. 1. Patients were divided into two groups: those who underwent FP (FP group) and those who did not (non-FP group).

Details of this study are available on our website and potential participants were given the opportunity to decline to be further enrolled in the study (opt-out).

Patients

Patient data, including age at breast cancer diagnosis, family background, and breast cancer stage, were collected. In addition, the dates of the breast cancer diagnosis, initial visit to the reproductive specialists, breast cancer surgery, initial chemotherapy, and initial endocrine therapy were recorded.

Treatment

Patients were treated according to the Japanese Breast Cancer Society Clinical Practice Guideline.[18] The indications for NAC were determined at our institution. Before 2017, NAC was performed for patients with nodal positivity or T4 disease. After 2018, NAC was performed for patients with tumors > 4 cm regardless of nodal positivity.

FP consultation and procedure

After breast cancer diagnosis in our institution, the patient is asked whether she wishes to have children in the future. If the answer is yes, the oncologist refers her to the reproductive center, which is in the same institution.

We collected the following information from reproductive medical records: the date of the first visit to the reproduction center and the method of FP used (oocyte, embryo, or ovarian tissue cryopreservation).

In this study, we divided the relationship between the breast cancer and FP treatments into three patterns. Fig. 2 shows this temporal relationship. Type A was defined as FP treatment after breast cancer diagnosis followed by surgery and adjuvant therapy. Adjuvant ther-

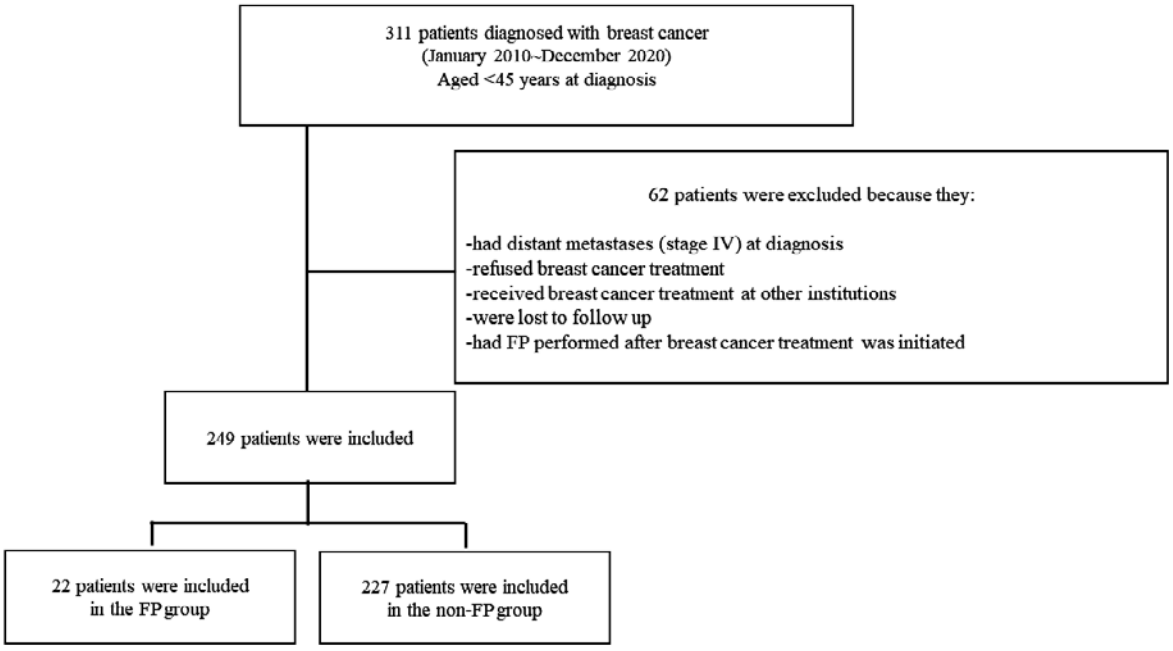

Fig. 1 Flowchart of patient selection
FP, fertility preservation.

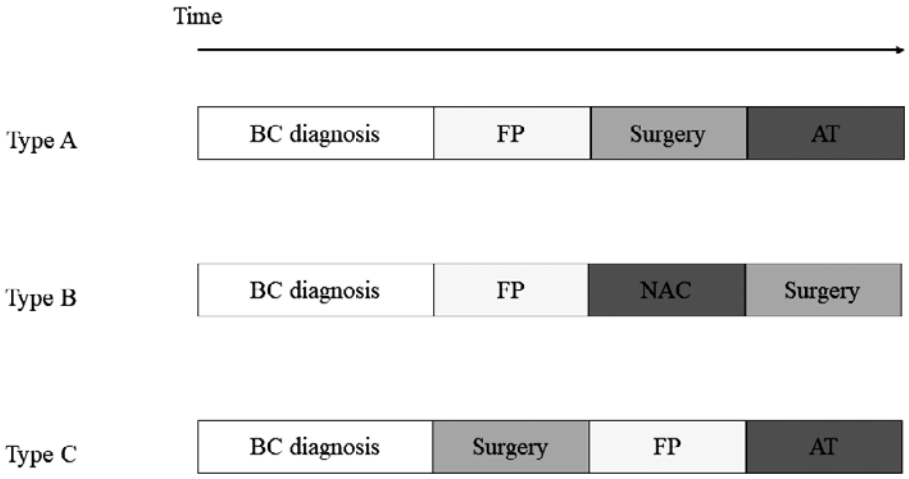

Fig. 2 Temporal relationship between breast cancer treatment and fertility preservation
AT, adjuvant therapy; BC, breast cancer; FP, fertility preservation; NAC, neoadjuvant chemotherapy.

apy included chemotherapy and endocrine therapy. Type B was defined as FP treatment after breast cancer diagnosis followed by NAC and surgery. Type C was defined as surgery after breast cancer diagnosis followed by FP and adjuvant therapy.

Statistical analysis

Statistical analyses were performed using JMP version 11.0 (SAS Institute, Inc., Cray, NC, USA). Characteristics of patients were reported for each study population using descriptive statistics. Categorical variables were analyzed using Pearson's chi-squared test. If continuous variables were normally distributed, then an independent t-test was used; a non-parametric Mann-Whitney U test was performed for variables that were not normally distributed. Relapse-free survival was defined as the date of breast cancer diagnosis to the date of recurrence, and overall sur-

vival was defined as the date of breast cancer diagnosis to the date of death or the last follow-up. Survival was calculated using the Kaplan-Meier method, and differences between the groups were calculated using the log-rank test. Statistical significance was set at $p < 0.05$.

Results

In total, 311 adult women aged <45 years were diagnosed with breast cancer between 2010 and 2021. Of these, 62 patients were excluded, as detailed in Fig. 1. The remaining 249 patients were included in this analysis. Twenty-two patients (8.8%) underwent FP before beginning breast cancer pharmacotherapy and were classified as the FP group. The non-FP group consisted of 227 patients (91.2%) who did not undergo FP. The median follow-ups were 42 months and 47 months in the FP and non-FP groups, respectively (NS).

Patient characteristics are summarized in Table 1. The average ages at breast cancer diagnosis were 34.8 years and 40.6 years in the FP and non-FP groups, respectively. The age at breast cancer diagnosis was significantly lower in the FP group than in the non-FP group ($p < 0.01$).

With regard to family background, 14 patients (63.6%) in the FP group and 152 patients (67.0%) in the non-FP group had a husband or partner. There was no significant difference in clinical stage between the two groups. However, in the FP group, there were more patients with stage II/III disease than with Stage 0/I disease. HR status and HER2 amplification were not significantly different between the two groups.

As an initial treatment for breast cancer, NAC was performed significantly more frequently in the FP group than in the non-FP group ($p < 0.05$). However, there was no difference in the combination of chemotherapy and endocrine therapy between the two groups.

FP treatment

Details on FP treatment and outcomes are shown in Table 2. In terms of the temporal relationship between FP and breast cancer treatments, seven patients had a type A, eight had a type B, and seven had a type C. The time interval from breast cancer diagnosis to FP consultation was 36.3 ± 40.7 days (range: 0-142). The time interval from the date of the first visit to the reproduction center to the date of the start of FP was 10.4 ± 5.5 days (range: 0-31). The mean duration of FP treatment was 16.0 ± 3.0 days (range: 2-85).

Oocyte cryopreservation was performed in 12 patients, embryo cryopreservation in 8, and ovarian tissue cryopreservation in 2. Both one embryo and ovarian tissue cryopreservation were performed in one patient. One patient gave birth 3 years after breast cancer treatment: after undergoing surgical treatment, her cancer was determined to be at an early stage that did not need pharmacotherapy.

Interval from breast cancer diagnosis to initial treatment

The intervals between breast cancer diagnosis and initial treatment for breast cancer are shown in Table 3. The time intervals from breast cancer diagnosis to initial treatment of breast cancer were 41.1 ± 15.1 days in the FP group and 45.2 ± 20.7 days in the non-FP group. There were no significant differences between the two groups ($p = 0.87$). We also analyzed the time to treatment based on the type of breast cancer treatment after FP treatment. Regardless of whether the first treatment after FP treatment was surgery, NAC, or adjuvant therapy including chemotherapy and endocrine therapy, the time interval was not different between the two groups.

Oncological outcomes

Fig. 3 shows the relapse-free and overall survival in the two groups. Disease recurrence occurred in 5 patients in the FP group and 22 in the non-FP group during the follow-up period. There was no difference in relapse-free survival between the two groups ($p = 0.07$). Two patients in the FP group and eight patients in the non-FP group died during the follow-up period. There was no difference in overall survival between the two groups ($p = 0.19$). Table 4 shows the oncological characteristics of cases of recurrence and death.

Discussion

In this study, no differences were shown in time interval from breast cancer diagnosis to initiation of cancer treatment—either surgery or chemotherapy—in women who underwent FP and those who did not. There has been no paper that examined the timing until the start of treatment for each breast cancer treatment.

We observed no differences in the interval from breast cancer diagnosis to breast cancer treatment between the FP and non-FP groups, regardless of whether the initial treatment of breast cancer was surgery (type A + B) or NAC (type C). In addition, there was no difference between the two groups in the interval from breast cancer diagnosis and the first pharmacotherapy (NAC or adju-

Table 1 Characteristics of the patients

Characteristic	Overall n = 249 (100%)	FP group n = 22 (8.8%)	Non-FP group n = 227 (91.2%)	*p-value*
Age (years) mean ± SD		34.8 ± 5.9	40.6 ± 4.2	< 0.01[a]
Age (years)				[b]
～ 30	14 (5.7%)	4 (18.2%)	10 (4.4%)	
31 ～ 35	25 (10.0%)	8 (36.3%)	17 (7.5%)	
36 ～ 40	68 (27.3%)	6 (27.3%)	62 (27.3%)	
41 ～ 45	142 (57.0%)	4 (18.2%)	138 (60.8%)	
Year of BC diagnosis				[b]
2010 ～ 2014	90 (36.1%)	7 (31.8%)	83 (36.6%)	
2015 ～ 2019	159 (63.9%)	15 (68.2%)	144 (63.4%)	
Family background				
Has a child	115 (46.2%)	3 (13.6%)	112 (49.3%)	< 0.01[a]
With husband or partner	166 (66.7%)	14 (63.6%)	152 (67.0%)	0.68[a]
Clinical Stage				0.15[c]
Stage0/I	116 (46.6%)	7 (31.9%)	109 (48.0%)	
StageII/III	133 (53.4%)	15 (68.1%)	118 (52.0%)	
Subtype				[b]
DCIS	36 (14.5%)	1 (4.5%)	35 (15.4%)	
Luminal HR (+)/HER2 (−)	132 (53.0%)	8 (36.4%)	124 (54.6%)	
Luminal-HER2 HR (+)/HER2 (+)	48 (19.3%)	7 (31.8%)	41 (18.1%)	
HER2 HR (−)/HER2 (+)	15 (6.0%)	1 (4.5%)	14 (6.2%)	
TNBC HR (−)/HER2 (−)	18 (7.2%)	5 (22.8%)	13 (5.7%)	
Initial treatment				< 0.05[c]
NAC	39 (15.7%)	8 (36.4%)	31 (13.7%)	
Surgery	210 (84.3%)	14 (63.6%)	196 (86.3%)	
Treatment for BC				[b]
CT (+) ET (+)	99 (39.8%)	9 (41.0%)	90 (39.6%)	
CT (+) ET (−)	35 (14.1%)	7 (31.8%)	28 (12.3%)	
CT (−) ET (+)	65 (26.0%)	3 (13.6%)	62 (27.4%)	
CT (−) ET (−)	50 (20.1%)	3 (13.6%)	47 (20.7%)	

BC, breast cancer; DCIS, ductal carcinoma in situ; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NAC, neoadjuvant chemotherapy; SD, standard deviation; TNBC, triple-negative breast cancer.
CT, chemo therapy; ET, endocrine therapy.
[a] Mann-Whitney U test
[b] Assumptions for statistical analysis not met
[c] Peason Chi-square

vant chemotherapy). According to the Japanese guidelines, a delay of up to 12 weeks in starting adjuvant chemotherapy is acceptable.[19] In this study, we were able to start adjuvant therapy in the FP group (types A and B) without a large delay, as recommended in the guidelines.

NAC was significantly more common in the FP group than in the non-FP group. As the average age at breast cancer diagnosis was younger in the FP group than in the non-FP group, we considered that the FP group had more aggressive cases, for which NAC is indicated, than the non-FP group. Generally, the younger a patient is, the faster the progression of the cancer. It is said that younger patients tend to have more TNBC type.[20] However, there were no statistically significant differences in clinical stage and subtype between the two groups.

In the Japanese guidelines, NAC is not recommended

Table 2 Details regarding fertility preservation and outcome in the FP group

	Number
Temporal relationship between BC treatment and FP	
A	7
B	8
C	7
Time from BC diagnosis to FP consultation (days)	
Mean ± SD (range)	36.3 ± 40.7 (0–142)
Time from the first visit FP center to the biggening of FP treatment (days)[a]	
Mean ± SD (range)	10.4 ± 5.5 (0–31)
Time required for FP treatment (days)	
Mean ± SD (range)	16.0 ± 3.0 (2–85)
Type of FP (n)	
Oocyte	12
Embryo	9
Ovarian tissue	2
Childbirth (n)	1

BC, breast cancer; FP, fertility preservation; SD, standard deviation.
[a] n = 21 exclude ovarian tissue cryopreservation case

Table 3 Time from breast cancer diagnosis to initial treatment for cancer

Time interval	FP group n = 22	Non-FP group n = 227	*p-value*
Diagnosis to initial treatment (days)	41.1 ± 15.1	45.2 ± 20.7	0.87
Initial treatment is Surgery (type A and C)	41.4 ± 15.4[a]	46.2 ± 20.8[b]	0.85
Initial treatment is Chemotherapy (type B)	40.6 ± 15.8[c]	38.7 ± 19.9[d]	0.39
Diagnosis to first pharmacotherapy (days)	90.4 ± 61.3[e]	100.7 ± 52.5[f]	0.25

FP, fertility preservation.
Mann-Whitney U test
[a] n = 14
[b] n = 196
[c] n = 8
[d] n = 31
[e] n = 18
[f] n = 180

for patients undergoing FP treatment because of the lack of evidence of its safety.[19] Letourna et al. reported that there was no delay in the initiation of NAC, and they reported its efficacy and safety.[21]

In the FP group, 68.2% of the patients had HR-positive tumors. A temporary increase in estrogen levels was observed during the FP treatment procedure. Therefore, the safety of patients with HR-positive tumors should be considered. We observed no difference in the prognosis of patients with breast cancer who did and did not undergo FP whether ER positive or not. Goldrat et al. also reported that there was no difference in breast cancer prognosis between patients who did and did not use assisted reproductive technology.[22] In contrast, Bruinsma et al. reported an increased risk of breast cancer within 1 year after assisted reproductive technology.[23] As the safety of FP treatment in ER-positive patients remains controversial, long-term follow-up is required.

The timing of pregnancy after breast cancer treatment is a considerable problem. According to the European Society for Medical Oncology (ESMO) guidelines, the risk of pregnancy and childbirth complications is higher when the interval between the end of treatment and conception is short.[24] They recommend an interval of at least 1 year after completion of chemotherapy, and in patients receiving other anticancer treatments, a specific wash-out period

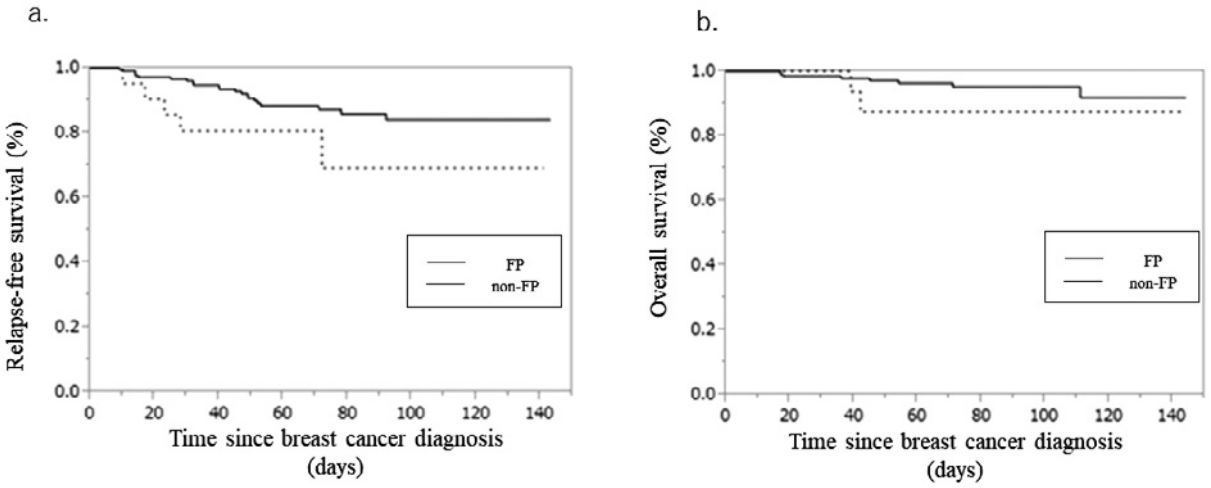

Fig. 3 Kaplan-Meier survival curves for relapse-free and overall survival
a: Recurrence in breast cancer patients who underwent FP or not (log-rank, p = 0.07)
b: Overall survival in breast cancer patients who underwent FP or not (log-rank, p = 0.19)

Table 4 Oncological characteristics of cases where recurrence and death occurred

Event			FP group	Non-FP group
Recurrence	Clinical Stage at diagnosis	I	-	3
		III	4	13
		III	1	6
	Subtype	Luminal	2	9
		TNBC	2	4
		HER2	-	2
		Luminal-HER2	1	5
		DCIS	-	2
Death	Clinical Stage at diagnosis	II	2	4
		III	-	4
	Subtype	Luminal	-	5
		TNBC	2	1
		Luminal-HER2	-	2

DCIS, ductal carcinoma in situ; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

should be considered before conception.[14] However, abortion, time to pregnancy, and breastfeeding do not appear to have any impact on oncological outcomes.[25] In young women with HR-positive breast cancer who are candidates for 5-10 years of adjuvant endocrine therapy, there are no reliable data on the safety of temporary treatment. The Pregnancy Outcome and Safety of Interrupting Therapy for women with Endocrine Responsive Breast Cancer (POSITIVE) trial (IBCSG 48-14/Breast International Group (BIG) 8-13/ALLIANCE A221405; NCT02308085) was designed as a single-arm prospective study to assess the risk of breast cancer relapse associated with temporary interruption of endocrine therapy to attempt conception. This ongoing trial is examining the safety of interrupting endocrine therapy temporarily for patients who wish to fall pregnant while they are undergoing prolonged endocrine therapy for breast cancer.

This retrospective study had some limitations. Since the cancer treatment and reproduction centers were in the same institution, this may have decreased the interval from breast cancer diagnosis to treatment initiation in patients undergoing FP treatment. Furthermore, oncologists may tend to hasten breast cancer treatment if the patient wanted to undergo FP treatment and if her age placed her at risk for fast progression of the breast cancer. Therefore, our conclusions should be confirmed in a larger study with

a longer follow-up period.

Conclusion

In younger women with breast cancer, FP treatment appears not to delay the initiation of breast cancer treatment, regardless of whether it was applied before NAC, surgery, or adjuvant therapy. Whether the patients underwent FP or not, there was no difference in the outcome of breast cancer.

For patients with breast cancer who wish to have a baby sometime in the future, FP is a treatment option that should be chosen before initiating breast cancer treatment.

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Authors' contribution: All authors (1) made substantial contributions to the study concept or the data analysis or interpretation; (2) drafted the manuscript or revised it critically for important intellectual content; (3) approved the final version of the manuscript to be published; and (4) agreed to be accountable for all aspects of the work.

Ethics statement: This retrospective cohort study was approved by the Ethics Committee of Toho University Omori Medical Center (M21050).

Conflicts of interest: None declared.

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