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Neoadjuvant Endocrine Therapy for Operable Breast Cancer: A Retrospective Analysis of Real-World Use

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Background: A retrospective study of the real-world use of neoadjuvant endocrine therapy (NET) is important for standardizing the role of NET in breast cancer care.

Methods: In a consecutive series of women with operable breast cancer who received NET for ≥28 days, associations of NET objectives, NET outcomes, adjuvant chemotherapy use after NET, and survival with clinicopathological factors were examined.

Results: NET objectives were reduction in surgical extent in 49 patients, avoidance of surgery in 31, and treatment until scheduled surgery in 8. The mean duration of NET was 349.5 (range, 34-1,923), 869.8 (range, 36-4,859), and 55.8 (range, 39-113) days, respectively, in these cohorts (success rate: 79.6%, 64.5%, and 100%, respectively), and the differences were significant. Among patients in the former two cohorts, progression-free survival was significantly better in patients with stage 0 or I disease, ductal carcinoma in situ or invasive ductal carcinoma, ≥71% estrogen receptor (ER) positivity, and the surgical extent reduction cohort than the other counterparts. Postoperative chemotherapy use was significantly associated with lymph node metastasis, a high Ki67 labeling index, lymphovascular invasion, and a high preoperative endocrine prognostic index at the time of surgery after NET. Better recurrence-free survival after surgery was significantly associated with high ER expression after NET or high progesterone receptor expression before or after NET.

Conclusions: NET can help reduce surgical extent or avoid surgery in women with early breast cancer, ductal carcinoma, or high ER expression. NET may also aid in decisions related to postoperative systemic therapy to improve survival. (J Nippon Med Sch 2021; 88: 448–460)

Key words: neoadjuvant endocrine therapy, breast cancer, progression, progression-free survival, recurrence-free survival

Introduction

Preoperative or neoadjuvant drug therapy is indicated for patients with operable breast cancer who want to undergo less extensive surgery. For example, after neoadjuvant therapy, breast-conserving surgery (BCS) could be indicated for cases that initially required total mastectomy (TM). Furthermore, axillary lymph node dissection (ALND) can be converted to sentinel lymph node biopsy (SLNB) alone, and removal of the nipple-areola complex can be converted to nipple-areola-complex-sparing sur-

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gery. Regarding preoperative drug therapy, chemotherapy rather than endocrine therapy is often used to effectively reduce the extent of surgery by reducing tumor size[1,2]. To date, neoadjuvant endocrine therapy (NET) has not been strongly recommended for women with operable breast cancer[3]. However, in older women with invasive breast cancer, studies have shown that NET, as well as neoadjuvant chemotherapy, reduces the extent of surgery[4]. In addition, randomized trials of NET using tamoxifen (followed by surgery for exacerbations) versus surgery alone in older women with breast cancer showed no significant difference in survival rates between the 2 groups[5,6]. Consequently, NET is considered effective for older women with breast cancer.

In premenopausal women with breast cancer, few studies have evaluated the impact of NET on tumor shrinkage or survival[7–10]. Endocrine therapy drugs for premenopausal women with breast cancer are tamoxifen with or without a luteinizing hormone-releasing hormone agonist (LHRH-a), or aromatase inhibitors (AIs) with an LHRH-a. The latter treatment is not covered by Japanese insurance, except for patients with relapsed cancer.

Appropriate treatment decisions regarding postoperative drug therapy, while considering the biology of the surgically resected tumor tissue after NET, are required for improving the survival rate of patients with breast cancer treated with NET. In this context, the preoperative endocrine prognostic index (PEPI) is an important predictive tool for survival after NET[11]. The PEPI score is based on 4 factors: post-treatment tumor size, lymph node metastasis, estrogen receptor (ER) expression, and the Ki67 labeling index, which can predict recurrence-free survival (RFS) and breast cancer-specific survival of postmenopausal women with invasive breast cancer[11]. However, there is no evidence that adding chemotherapy based on PEPI score improves survival.

The optimal duration of NET also needs to be resolved. In clinical trials involving postmenopausal women with invasive breast cancer, the duration of treatment was 3 to 12 months[12–22]. In these trials, increased NET duration led to an increased BCS rate, decreased tumor size, and an increased pathological response rate. In the United States, real-world data show that women with breast cancer who received NET for longer treatment durations had higher odds of BCS and downstaging than did women who did not receive NET[23].

NET helps to avoid surgery without tumor progression, which is even more important during the present coronavirus disease pandemic[24]. Hayashi et al. examined time to progression in patients with stage II or III breast cancer treated with NET in a multicenter study; median time to progression was approximately 3 years[25]. NET also helps determine the sensitivity of endocrine therapy, which can predict survival. PEPI scores at 3 to 4 months and Ki67 labeling index values at 2 weeks after NET initiation were significant predictors of survival[11,26]. A relatively short duration of NET is adequate to predict survival.

The effect of NET on ductal carcinoma in situ (DCIS) needs to be clarified. DCIS can be cured by complete surgical resection. It has been reported that survival of patients with low-grade DCIS did not differ between women who did and did not undergo surgery[27]. It is unclear whether AI or tamoxifen in postmenopausal women, and whether tamoxifen alone or tamoxifen with LHRH-a in premenopausal women, are optimal drugs of NET for DCIS. Meyerson et al.[28] used tamoxifen to treat premenopausal women with DCIS and AI for postmenopausal women as NET drugs.

This retrospective study analyzed real-world clinical use of NETs in women with operable breast cancer. This findings are important for standardizing the role of NET in breast cancer care.

Materials and Methods

Study Design

This study was approved by the Ethics Review Board of Nippon Medical School Hospital (Reception number, B 2020-130). We analyzed associations of NET objectives, NET drugs, NET duration, progression during NET, progression-free survival (PFS) after NET initiation, type of surgery after NET, achievement of NET objectives, postoperative systemic therapy, and postoperative RFS with clinicopathological factors in patients with operable breast cancer. The clinicopathological factors analyzed were age, menopausal status, tumor-node-metastasis (TNM) stage, histological type, nuclear grade (NG), lymphovascular invasion, ER, progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), and Ki67.

Purposes of NET

Purposes for the choice of NET as an initial treatment for breast cancer were classified as reduction of surgical extent, avoidance of surgery, and treatment until scheduled surgery. Reduction of surgical extent indicates performance of BCS or nipple-sparing mastectomy (NSM), or omission of ALND after SLNB. The purpose of NET was determined at the start of NET in a discussion be-

tween the doctor and patient. Surgical extent reduction was defined as successful when BCS or NSM was performed or ALND was avoided according to the purpose of NET. Avoidance of surgery was defined as successful when no surgery was performed, and there was no progression. However, avoidance of surgery was said to be successful if surgery was performed at the patient's revised request, despite absence of tumor progression during NET. Treatment until scheduled surgery was defined as successful when the patient continued treatment before the scheduled surgery.

Patients

A consecutive series of women with breast cancer who received NET for at least 28 days at Nippon Medical School Hospital between April 2013 and September 2020 were included in this study. NET drugs were tamoxifen with or without LHRH-a, and AIs, all of which were approved for preoperative and postoperative administration. Patients with inoperable breast cancer, distant metastases, or active cancer of another organ at the time of breast cancer diagnosis were excluded. For the informed consent of eligible patients, the study was posted on a website and patient consent was deemed to have been obtained if they did not decline to participate in the study.

TNM Stage, Histological Type, and NG

TNM staging was in accordance with the Union for International Cancer Control TNM classification[29]. Histological type was classified according to the World Health Organization classification (4th edition)[30]. Invasive ductal carcinoma (IDC) and invasive carcinoma of no special type were considered similar entities. NG was classified according to the Japanese Breast Cancer Society General Rules for Clinical and Pathological Recording of Breast Cancer[31].

ER, PgR, HER2, and Ki67

Expressions of ER, PgR, HER2, and Ki67 were evaluated by immunohistochemical staining. ER and PgR expressions were classified as 0%, 1-10%, 11-50%, 51-70%, and 71-100% according to the ratio of positive cells. HER 2 was scored as 0, 1+, 2+, and 3+, and classified as positive in case of 3+, or 2+ when the HER2/CEP17 ratio was $\geq$2.0 by in situ hybridization. Ki67 was classified as 0-5%, 6-15%, 16-30%, 31-50%, and 51-100% according to the percentage of positive cells.

Response, Progression, and No Change

Maximum tumor diameter was measured before NET initiation, during NET, and at surgery after NET, using one or more of the following modalities in addition to palpation: mammography, ultrasound, computed tomography, or magnetic resonance imaging. A response was defined as when tumor size decreased by $\geq$10% of the tumor size before NET. Progression was defined as an increase in tumor size by $\geq$10% of the smallest tumor size, appearance of a new lesion in the same breast or contralateral breast, appearance of lymph node metastases or distant metastases, or death from breast cancer. 'No change' was defined as cases not in the above categories.

Surgery and Postoperative Systemic Therapy

Breast surgery was classified as BCS, NSM, and TM (including skin-sparing mastectomy). Axillary surgery was classified as SLNB alone and ALND. Postoperative systemic therapy was categorized as endocrine therapy like NET, endocrine therapy unlike NET, and additional chemotherapy.

Survivals

PFS was the period from NET initiation to confirmed disease progression, as defined above. RFS was the time from surgery to recurrence or death from breast cancer.

PEPI

PEPI score was calculated in the manner reported by Ellis et al.[11] PEPI was originally for use in postmenopausal patients with invasive carcinoma; however, in this study it was also evaluated in premenopausal patients with invasive carcinoma.

Statistical Analysis

Associations between NET purposes, NET outcomes and clinicopathological factors were analyzed with the chi-square test, t-test, and analysis of variance. Survival was analyzed with the Kaplan-Meier method, log-rank test, and Cox proportional hazards model for multivariate analysis. P-values less than 0.05 were considered statistically significant. Statistical analyses were performed using BellCurve for Excel (SSRI. Inc. Japan).

Results

Of a total of 88 patients selected from the medical records were eligible in the analysis: 49 were in the cohort for the purpose of the surgical extent reduction, 31 were for the purpose of the surgery avoidance, and 8 were for the purpose of the treatment until scheduled surgery. Of the 49 patients in the cohort to reduce surgical extent, 38, 9, and 2 intended to undergo BCS, NSM, and avoid ALND, respectively. The 2 patients who intended to avoid ALND had slight enlargement of axillary lymph nodes at diagnosis, which suggested metastasis. Associations of NET purposes, NET duration, NET drugs, pro-

gression during NET, type of surgery after NET, and achievement of NET objective with other clinicopathological factors were analyzed (**Table 1**).

The mean age of patients at the NET initiation was oldest for patients in the cohort for the purpose to avoid surgery, followed by those for the purpose to reduce surgical extent and for the purpose to receive treatment until scheduled surgery (P=0.013). The proportions of postmenopausal patients, from highest to lowest, were also in the above order (P=0.088). The proportion of patients with stage IIA disease was higher in the cohort for the purpose to reduce the extent of surgery than in the cohort for the purpose to avoid surgery. All 4 patients with stage IIIB disease were in the cohort for the purpose to avoid surgery (P=0.045). Of the 5 cases of mucinous carcinoma, 4 were in the cohort for the purpose to avoid surgery (P=0.029).

The mean duration of NET was longest for patients in the cohort to avoid surgery and shortest for those in the cohort of treatment until scheduled surgery (P<0.001). The rate of successful NET was highest for patients in the cohort of treatment until scheduled surgery and lowest for those in the cohort to avoid surgery (P=0.0045).

The NET drugs were AIs alone in 32 patients, tamoxifen alone in 24 patients, tamoxifen in combination with LHRH-a in 32 patients, including 1 patient treated with LHRH-a alone (this patient with DCIS was not given tamoxifen because she had endometriosis). In the 24 patients treated with tamoxifen alone, 18 were postmenopausal and 6 were premenopausal. There was no significant association between the use of these drugs and the purpose of NET (**Table 1**).

Sixty-four patients underwent surgery: 40 underwent BCS, 14 underwent NSM, and 10 underwent TM. Of the 10 cases of TM, 1 underwent skin-sparing mastectomy. SLNB was performed in all 64 patients, and ALND was performed in 10 of these patients because of positive metastases in sentinel lymph nodes (SLNs). BCS or NSM was more often performed in the surgical extent reduction cohort and treatment until scheduled surgery cohort than in the surgery avoidance cohort (P<0.001) (**Table 1**).

Clinicopathological factors at the time of NET initiation are shown in **Table 1** and **Table 2**. Nineteen patients were classified as Tis N0 M0 stage 0, 30 patients as stage I (1 as T1mic, 3 as T1b, and 26 as T1c), 34 patients as T2 N0 M0 stage IIA, 1 patient as T2 N1 M0 stage IIB, and 4 patients as T4b N0 M0 stage IIIB; 87 of the 88 patients had a confirmed pathological diagnosis by core needle biopsy. One patient was diagnosed with IDC by fine needle aspiration cytology rather than core needle biopsy because she was receiving anticoagulants. DCIS was diagnosed in 18 patients, including 4 patients with intracystic papillary carcinoma.

Eight patients in the cohort of treatment until scheduled surgery were excluded from the analysis for presence or absence of progression or PFS because of the short treatment duration, which prevented assessment of treatment effect. Among the other 80 patients, 61 exhibited a response after NET initiation. Of the remaining 19 patients, 6 exhibited progression and 13 showed no change. Of the 61 patients who had an initial response to NET, 6 exhibited late progression: 3 had enlarged tumors and 3 had new lesions in the same breast. Ultimately, 12 patients exhibited progression during NET.

Progression was more frequent in patients of the cohort to avoid surgery than in those of the cohort to reduce surgical extent (p<0.001) (**Table 1**). Progression was more frequent for mucinous carcinoma and invasive lobular carcinoma (both categorized as invasive carcinoma special types) than for DCIS or IDC (p=0.0079) (**Table 2**). Progression was more frequent for patients who had tumors with an ER rate of $\leq$70% than for those with tumors with an ER rate of $\geq$71% (P=0.017) (**Table 2**).

PFS was better in patients in the cohort of surgical extent reduction (P=0.039) (**Fig. 1a**), those with stage 0 or stage I disease (P=0.0087) (**Fig. 1b**), those with an ER of $\geq$71% (P<0.001) (**Fig. 1c**), those with a histological type of DCIS or IDC (P<0.001) (**Fig. 1d**), and those with a Ki 67 labeling index of $\leq$5% (P=0.058) (figure not shown). There was no significant predictive factor for PFS in multivariate analysis (data not shown).

Postoperative systemic therapy was administered to 64 patients who underwent surgery: 20 received AIs, 14 received tamoxifen, 10 received tamoxifen in combination with an LHRH-a, and 15 received chemotherapy. Five patients received no adjuvant systemic therapy. Three patients were switched from tamoxifen to AIs. One patient was switched from tamoxifen plus LHRH-a to an AI. Two patients were switched from tamoxifen plus LHRH-a to tamoxifen alone.

Clinicopathological factors at the time of surgery were analyzed in relation to administration of adjuvant chemotherapy (**Table 3**). Pathological lymph node metastasis (P<0.001), Ki67 labeling index (P=0.0023), lymphovascular invasion (P=0.0046), and PEPI score (P=0.0020) were significantly associated with administration of adjuvant chemotherapy. Pathological tumor size had a borderline association with administration of adjuvant chemother-

Table 1 Clinicopathological characteristics, NET drugs, NET outcomes, and type of breast and axilla surgery in relation to purpose of NET in women with operable breast cancer

	Total		Purpose of NET						P value
			Reduction of surgery extent		Avoidance of surgery		Treatment until scheduled surgery		
No. and % of patients	88	100.0	49	100.0	31	100.0	8	100.0	
Age at treatment initiation, years									
mean±SD	59.4±14.3		57.0±13.8		65.1±14.6		51.7±9.5		0.013
Menopausal status									
Pre	38	43.2	22	44.9	10	32.3	6	75.0	
Post	50	56.8	27	55.1	21	67.7	2	25.0	0.088
TNM stage									
0	19	21.6	8	16.3	8	25.8	3	37.5	
I	30	34.1	15	30.6	13	41.9	2	25.0	
IIA	34	38.6	25	51.0	6	19.4	3	37.5	
IIB	1	1.1	1	2.0	0	0.0	0	0.0	
IIIB	4	4.5	0	0.0	4	12.9	0	0.0	0.045
Histological type									
DCIS	18	20.5	8	16.3	8	25.8	2	25.0	
IDC	59	67.0	37	75.5	17	54.8	5	62.5	
Mucinous	5	5.7	1	2.0	4	12.9	0	0.0	
ILC	5	5.7	3	6.1	2	6.5	0	0.0	
LCIS	1	1.1	0	0.0	0	0.0	1	12.5	0.029
NET drugs									
AI	32	36.4	18	36.7	13	41.9	1	12.5	
Tam	24	27.3	10	20.4	9	29.0	5	62.5	
Tam+LHRH-a	32	36.4	21	42.9	9	29.0	2	25.0	0.12
Progression									
Present	12	13.6	2	4.1	10	32.3	0	0.0	
Absent	68	77.3	47	95.9	21	67.7	0	0.0	
NE	8	9.1	0	0.0	0	0.0	8	100.0	<0.001
Successful NET									
Yes	67	76.1	39	79.6	20[a)]	64.5	8	100.0	
No	15	17.0	4	8.2	11[b)]	35.5	0	0.0	
Ongoing NET	6	6.8	6	12.2	0	0.0	0	0.0	0.0045
NET duration, days									
mean±SD	506.1±723.6		349.5±352.1		869.8±1,043		55.8±25.1		<0.001
median (range)	228 (34-4,859)		228 (34-1,923)		462 (36-4,859)		50 (39-113)		
Type of breast surgery									
BCS	40	62.5	31	72.1	4	30.8	5	62.5	
NSM	14	21.9	9	20.9	2	15.4	3	37.5	
TM	10	15.6	3[c)]	7.0	7	53.8	0	0.0	<0.001
Type of axilla surgery									
SLNB	54	84.4	34	79.1	13	100.0	7	87.5	
ALND	10	15.6	9	20.9	0	0.0	1	12.5	0.18

[a)] Three patients without progression underwent surgery during NET upon their personal request.

[b)] One patient refused surgery, although she had tumor progression.

[c)] One case of SSM was included in TM.

AI, aromatase inhibitor; ALND, axillary lymph node dissection; BCS, breast-conserving surgery; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LHRH-a, luteinizing hormone-releasing hormone agonist; LCIS, lobular carcinoma in situ; NE, not evaluated; NET, neoadjuvant endocrine therapy; NSM, nipple-sparing mastectomy; SLNB, sentinel lymph node biopsy; Tam, tamoxifen; TM, total mastectomy

Table 2 Clinicopathological factors correlated with tumor progression during NET in women with operable breast cancer

	Total		Progression						P value
			NE		Absent		Present		
No. and % of patients	88	100	8	100	68	100	12	100	
Age at treatment initiation, years									
≤55	43	48.9	7	87.5	28	41.2	7	58.3	
≥56	45	51.2	1	12.5	39	57.4	5	41.7	0.31
Mean ±SD	59.4±14.3		51.7±9.5		60.2±14.4		59.6±16.0		0.90
Menopausal status									
Pre	38	43.2	6	75.0	26	38.2	6	50.0	
Post	50	56.8	2	25.0	42	61.8	6	50.0	0.44
TNM stage									
0	19	21.6	3	37.5	14	20.6	2	16.7	
I	30	34.1	2	25.0	26	38.2	2	16.7	
IIA	34	38.6	3	37.5	25	36.8	6	50.0	
IIB	1	1.1	0	0.0	1	1.5	0	0.0	
IIIB	4	4.5	0	0.0	2	2.9	2	16.7	0.21
Histological type									
DCIS	18	20.5	2	25.0	14	20.6	2	16.7	
IDC	59	67.0	5	62.5	49	72.1	5	41.7	
Mucinous	5	5.7	0	0.0	2	2.9	3	25.0	
ILC	5	5.7	0	0.0	3	4.4	2	16.7	
LCIS	1	1.1	1	12.5	0	0.0	0	0.0	0.0079
Nuclear grade									
1	66	75.0	8	100.0	49	72.1	8	66.7	
2	11	12.5	0	0.0	10	14.7	1	8.3	
3	1	1.1	0	0.0	1	1.5	0	0.0	
Unknown	11	12.5	0	0.0	8	11.8	3	25.0	0.84
ER									
≥71%	81	92.0	8	100.0	65	95.6	8	66.7	
51-70%	1	1.1	0	0.0	0	0.0	1	8.3	
11-50%	3	3.4	0	0.0	2	2.9	1	8.3	
1-10%	0	0.0	0	0.0	0	0.0	0	0.0	
0%	0	0.0	0	0.0	0	0.0	0	0.0	
Unknown	3	3.4	0	0.0	0	0.0	0	0.0	0.017
PgR									
≥71%	57	64.8	6	75.0	47	69.1	4	33.3	
51-70%	11	12.5	1	12.5	8	11.8	2	16.7	
11-50%	8	9.1	0	0.0	6	8.8	2	16.7	
1-10%	9	10.2	1	12.5	6	8.8	2	16.7	
0%	0	0.0	0	0.0	0	0.0	0	0.0	
Unknown	3	3.4	0	0.0	1	1.5	2	16.7	0.14
HER2									
0	55	62.5	3	37.5	44	64.7	8	66.7	
1+	25	28.4	5	62.5	19	27.9	1	8.3	
2+[a)]	3	3.4	0	0.0	2	2.9	1[a)]	8.3	
Unknown	5	5.7	0	0.0	3	4.4	2	16.7	0.30
Ki67									
1-5%	29	33.0	2	25.0	26	38.2	1	8.3	
6-15%	30	34.1	5	62.5	22	32.4	3	25.0	
16-30%	8	9.1	0	0.0	6	8.8	2	16.7	
31-50%	6	6.8	0	0.0	4	5.9	2	16.7	
Unknown	15	17.0	1	12.5	10	14.7	4	33.3	0.13
NET drugs									
AIs	32	36.4	1	12.5	28	41.2	3	25.0	
Tam	24	27.3	5	62.5	15	22.1	4	33.3	
Tam+LHRH-a[b)]	32	36.4	2	25.0	25[b)]	36.8	5	41.7	0.52

[a)] One patient with a HER2 score of 2+ showed progression after initial response showed HER2 overexpression, detected using in situ hybridization (5.4 times).

[b)] One patient with ductal carcinoma in situ of the breast showing response after treatment with LHRH-a alone was included in the Tam+LHRH-a group.

AI, aromatase inhibitor; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ; LHRH-a, luteinizing hormone-releasing hormone agonist, NE, not evaluated; NET, neoadjuvant endocrine therapy; PgR, progesterone receptor; Tam, tamoxifen.

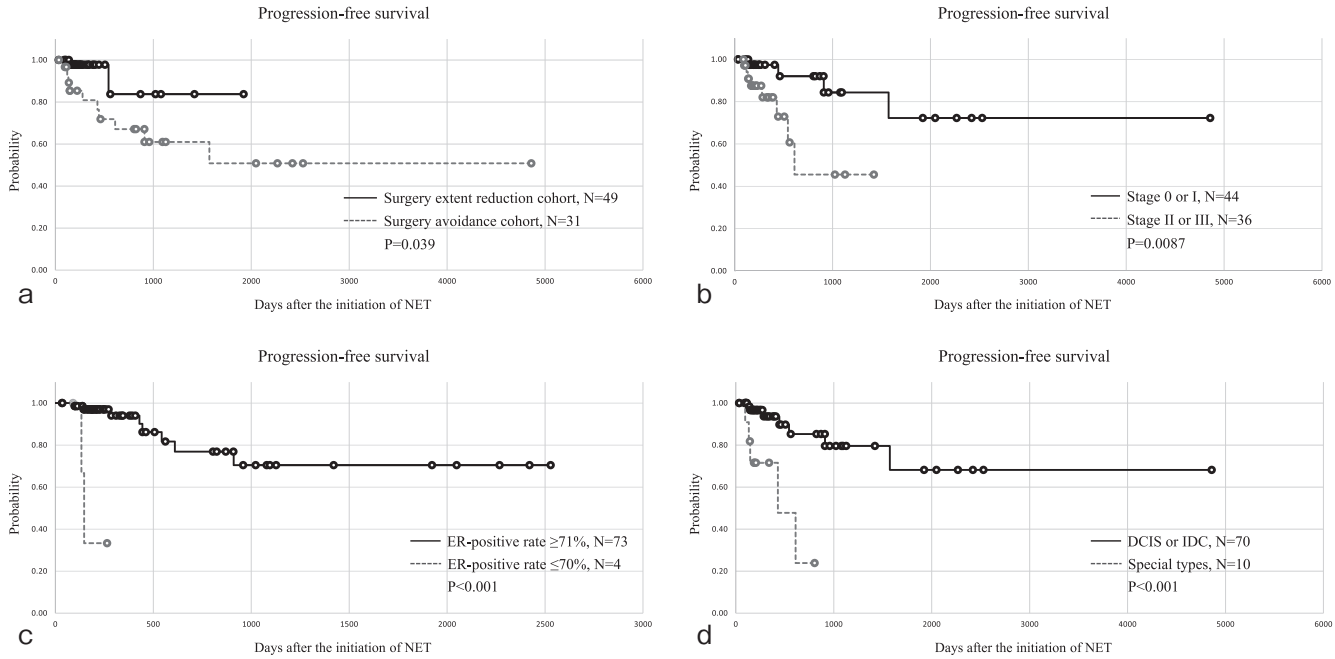

Fig. 1 Association of progression-free survival (PFS) with purpose of neoadjuvant endocrine therapy (NET) (a), clinical stage (b), estrogen receptor (ER) (c), and histological type (d).
PFS of patients in the surgical extent reduction cohort (black line) was significantly better than that of patients in the surgery avoidance cohort (dotted gray line) (P=0.039) (a). PFS of patients with stage 0 or I disease (black line) was significantly better than that of patients with stage II or III disease (dotted gray line) (P=0.0087) (b). PFS of patients with an ER-positive rate ≥71% (black line) was significantly better than that of patients with an ER-positive rate ≤70% (dotted gray line) (P<0.001) (c). PFS of patients with ductal carcinoma in situ or invasive ductal carcinoma (black line) was significantly better than that of patients with special types of invasive carcinoma (dotted gray line) (P<0.001) (d). The open circle represents a censored case.

apy (P=0.073).

In all 88 patients, no metastatic lesion was detected during NET administration. However, primary lung cancer was diagnosed at 2,065 days after initiation of tamoxifen in 1 patient. Five patients developed recurrences after surgery. One patient had an axillary lymph node recurrence on days 2,244 and 603 after NET initiation and surgery, respectively, and the other 4 patients developed distant organ recurrences at between 673 and 1,976 days after NET initiation and between 512 and 1,710 days after surgery. There were 2 postoperative deaths: 1 due to breast cancer metastasis on days 2,271 and 2,110 after NET initiation and surgery, respectively, and the other due to cerebral hemorrhage unrelated to breast cancer, on days 640 and 295 after NET initiation and surgery, respectively.

Among the 64 patients who underwent surgery, RFS was analyzed for associations with clinicopathological characteristics. ER expression (≤70% vs. ≥71%, P=0.027) at the time of surgery after NET (**Fig. 2a**), and PgR expression (≤50% vs. ≥51%) before NET (P=0.015) and at the time of surgery after NET (P=0.024) (**Fig. 2b**) were significantly associated with RFS. The Ki67 labeling index (≤5% vs. ≥6%) at the time of surgery after NET showed a borderline association with RFS (P=0.094) (figure not shown). Multivariate analysis was not performed because of the small number of recurrent cases.

We identified 18 cases of DCIS. NG was grade 1 in 14 cases, grade 2 in 3 cases, and of unknown grade in 1 case. ER-positive cell rates were ≥71% in 17 cases and 50% in 1 case. Mean age was 53.2 (range, 25-86) years. Ten patients were premenopausal and 8 were postmenopausal. In the 10 premenopausal patients, tamoxifen in combination with LHRH-a was administered in 8 patients, LHRH-a alone in 1, and tamoxifen alone in 1. In the 8 postmenopausal patients, tamoxifen was administered in 4 patients and AIs in 4.

Eight patients in the cohort for the purpose ofsurgical extent reduction, 8 in the cohort of surgery avoidance, and 2 in the cohort of treatment until scheduled surgery. In the 8 patients in the surgical extent reduction cohort, 4 successfully achieved it for a median NET duration of 237 (163 to 408) days, 3 remained on NET for a median duration of 258 (246 to 870) days, and 1 failed to achieve

Table 3 Clinicopathological factors at surgery correlated with administration of adjuvant chemotherapy in women with operable breast cancer treated with NET

	Total		Adjuvant chemotherapy				P value
			No		Yes		
No. and % of patients	64	100.0	49	100.0	15	100.0	
Age at surgery, years							
mean±SD	58.0±13.8		60.7±13.6		54.2±14.8		0.35
Progression during NET							
No	45	70.3	36	73.5	9	60.0	
Yes	11	17.2	7	14.3	4	26.7	
NE	8	12.5	6	12.2	2	13.3	0.51
Pathological tumor size							
ypTis	7	10.9	7	14.3	0	0.0	
ypT1	43	67.2	34	69.4	9	60.0	
ypT2-4	14	21.9	8	16.3	6	40.0	0.073
Pathological nodal status							
ypN0	47	73.4	43	87.8	4	26.7	
ypN1mi	6	9.4	2	4.1	4	26.7	
ypN1-3	11	17.2	4	8.2	7	46.7	<0.001
ER at surgery							
≥71%	54	84.4	41	83.7	13	86.7	
51-70%	5	7.8	3	6.1	2	13.3	
11-50%	3	4.7	3	6.1	0	0.0	
1-10%	1	1.6	1	2.0	0	0.0	
0%	1	1.6	1	2.0	0	0.0	0.68
PgR at surgery							
≥71%	14	21.9	10	20.4	4	26.7	
51-70%	12	18.8	10	20.4	2	13.3	
11-50%	16	25.0	13	26.5	3	20.0	
1-10%	14	21.9	10	20.4	4	26.7	
0%	8	12.5	6	12.3	2	13.3	0.92
Ki67 at surgery							
1-5%	38	59.4	33	67.3	5	33.3	
6-15%	16	25.0	13	26.5	3	20.0	
16-30%	7	10.9	2	4.1	5	33.3	
31-50%	3	4.7	1	2.0	2	13.3	0.0023
Lymphovascular invasion at surgery							
Absence	41	64.1	36	73.5	5	33.3	
Presence	23	35.9	13	26.5	10	66.7	0.0046
PEPI score							
0	14	21.9	14	28.6	0	0.0	
1-3	25	39.1	20	40.8	5	33.3	
≥4	19	29.7	9	18.4	10	66.7	0.0020

ER, estrogen receptor; NET, neoadjuvant endocrine therapy; PEPI, preoperative endocrine prognostic index; PgR, progesterone receptor; SD, standard deviation.

the purpose of NET because of tumor progression at 143 days after NET initiation. One patient whose objective was not met was a 33-year-old woman with intracystic papillary carcinoma accompanied by ductal spread with the following tumor characteristics: NG=1, ER=100%, PgR=100%, HER2=score 0, and Ki67=10%. She intended to undergo BCS at the start of tamoxifen combined with LHRH-a; however, because of tumor enlargement, NSM, SLNB and a tissue expander placement were performed. SLNB revealed micrometastases to SLNs. The resected tumor was pathologically diagnosed as encapsulated papillary carcinoma with microinvasion (maximum diameter, 42 mm) and had the following tumor characteristics: NG =1, ER=100%, PgR=80%, HER2=score 0, and Ki67=15%.

Of the 8 patients in the surgery avoidance cohort, 7 showed no tumor progression and are still on NET. Median NET duration was 959 (36 to 2,529) days. One patient failed to avoid surgery. She was a 55-year-old, post-

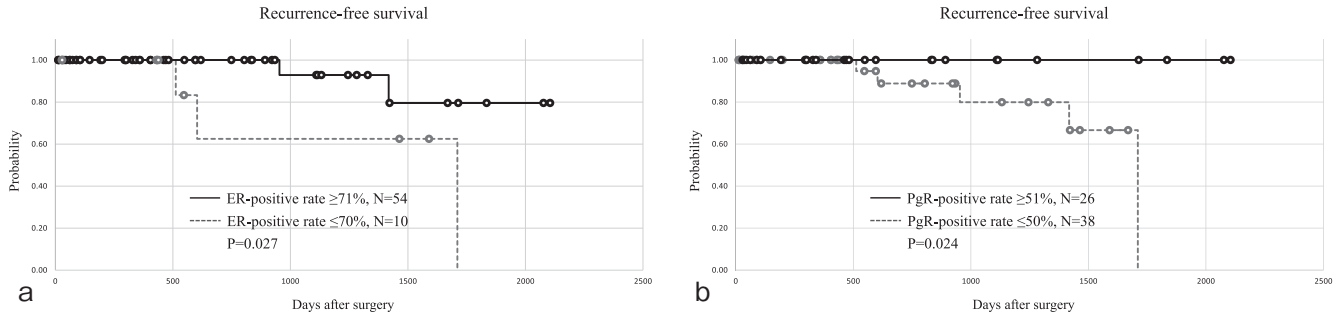

Fig. 2 Association of recurrence-free survival (RFS) with estrogen receptor (ER) (a) and progesterone receptor (PgR) (b) status at surgery after neoadjuvant endocrine therapy (NET).
RFS of patients with tumors with an ER-positive rate ≥71% (black line) at surgery after NET was significantly better than that of patients with an ER-positive rate ≤70% (dotted gray line) (P=0.027) (a). RFS of patients with tumors with a PgR-positive rate ≥51% (black line) at surgery after NET was significantly better than that of patients with a PgR-positive rate ≤50% (dotted gray line) (P=0.024) (b). The open circle represents a censored case.

menopausal woman with DCIS that had mammography-detected microcalcifications >50 mm in maximum diameter. The characteristics of DCIS were NG=1, ER=90%, PgR=40%, HER2=score 0, and Ki67=1%. She received tamoxifen, which resulted in no tumor change (minor response). A new mass was detected in the DCIS lesion area by ultrasound during a regular follow-up at 910 days after NET initiation and was diagnosed as IDC by core needle biopsy. She underwent NSM, SLNB and tissue expander placement. Pathologically, the 8-mm IDC was present in the DCIS lesion and had the following characteristics: NG=3, ER=0%, PgR=0%, HER2=score 3+, and Ki67=50%. The DCIS characteristics after NET were identical to those at diagnosis, as described above.

Discussion

This study indicates that NET was administered in practice for reduction of surgical extent, avoidance of surgery, and treatment until scheduled surgery, and NET was successful for about 80% of patients in the cohort of surgical extent reduction. Previous studies demonstrated the effectiveness of NETs in achieving a reduction in surgical extent, as shown by the possibility of switching from TM to BCS[12–22]. As most of these conversion rates were reported to be less than 80%, our result should be considered favorable. Accordingly, NET may be useful in reducing the extent of surgery.

NET for surgery avoidance was successful in 65% of patients. This success rate was the lowest of the 3 cohorts; however, surgery avoidance is the most difficult to achieve because NET is not stopped unless the patient intends to undergo surgery. The frequency of tumor progression in the cohort seeking to avoid surgery may increase during the longer treatment period; however, it remained low for patients with clinical stage 0 or I disease, those with an ER of ≥71%, and those with a histological type of DCIS or IDC. Therefore, use of NET to avoid surgery may be acceptable for breast cancer patients with the above characteristics.

Although the significance of treatment until scheduled surgery is unclear, it is thought to have been administered in clinical practice to relieve patient anxiety. Short-term Ki67 labeling index after NET administration was reported to be a significant postoperative predictor of survival[26]. Regardless of treatment period, evaluation of Ki67 in postoperative specimens after NET may be useful in determining postoperative treatment strategy. Therefore, short-term administration of NETs before scheduled surgery may have a clinical benefit.

Regarding NET drugs, the results of this study showed that tamoxifen in combination with LHRH-a, tamoxifen alone, and AIs alone were not significantly associated with progression, PFS, and RFS. In contrast, previous studies reported that AIs were more effective than tamoxifen for postmenopausal women with invasive breast cancer[32–34]. Furthermore, in premenopausal women with invasive breast cancer, an AI was more effective than tamoxifen when these drugs were used in combination with an LHRH-a in NET[10]. Thus, although there was no significant difference in efficacy between NET drugs in this study, it is difficult to draw conclusions from this study because of the small sample size and its retrospective design.

In this study, histological type and ER were significantly associated with tumor progression. In addition, PFS was significantly associated with clinical stage and had a borderline significant association with Ki67 labeling index. Early cancers and those with high ER expres-

sion and lower proliferative potential were assumed to be less biologically heterogeneous and consequently more hormone-dependent. Regarding histological type, tumor progression was more frequent for the invasive carcinoma special types, namely, mucinous carcinoma and invasive lobular carcinoma. There are few data on the effectiveness of NET for patients with mucinous carcinoma of the breast. For invasive lobular carcinoma, Dixon et al.[35] reported that NET with letrozole was effective for postmenopausal women. Therefore, because of the small number of cases and the fact that no significant predictor for PFS observed in multivariate analysis in this study, conclusions should be drawn with caution.

NET is also an in vivo drug susceptibility test and can provide information on the effectiveness of endocrine therapy drugs. In this study, lymph node metastasis, lymphovascular invasion, Ki67 labeling index, and PEPI score significantly influenced decisions regarding adjuvant chemotherapy indications after surgery. Therefore, it is assumed that physicians made decisions about postoperative systemic therapy based on an overall assessment of these factors. This would be expected to improve RFS. However, prospective clinical studies are needed in order to prove that adjuvant chemotherapy decisions after NET can improve survival[36].

In this study, ER and PgR were associated with RFS. ER and PgR are the most fundamental indicators of hormone sensitivity. In particular, PgR was a significant predictor of RFS, regardless of whether it was assessed before or after NET. Kurozumi et al.[37] reported that PgR was a significant predictive factor for survival even if it was added to PEPI score. In this study, the absence of factors affecting RFS other than these 2 factors suggests that an adequate choice of postoperative adjuvant chemotherapy may have improved RFS in high-risk patients.

The median treatment duration of NET in the cohort of surgical extent reduction was 228 days (about 8 months), and the mean was 350 days (about 12 months), which were similar to the results of a previous study by Hayashi et al.[22] in which the median duration of NET to achieve maximum tumor reduction was estimated to be 10 months. When combined with results from previous clinical studies[12–20], it can be assumed that NETs provide the greatest reduction in tumor size between 6 months and 1 year after the start of treatment.

In real-world clinical practice, to avoid surgery, NET duration was long, with a median of 462 days (about 15 months) and a mean of 870 days (29 months) in this study. The effect of these long-term NETs on survival has not been determined. However, considering that 10 years of treatment is recommended for tamoxifen as adjuvant therapy and 5 years or more for AIs, it can be assumed that long-term NET would not adversely affect survival if tumor shrinkage is confirmed. This study also found no significant association between tumor progression during NETs and RFS. As mentioned above, this result probably indicates that postoperative adjuvant therapy was appropriately administered, based on the risk of tumor recurrence after NET. As a result, survival might have been modified for better directions.

The clinical use of NETs in premenopausal breast cancer is limited; few clinical trials have compared NET with tamoxifen plus LHRH-a with neoadjuvant chemotherapy, which indicates inferior tumor reduction rates in NET[9]. Previous studies showed that the combination of tamoxifen and LHRH-a is more effective than tamoxifen alone as adjuvant therapy[38,39]. Therefore, it is likely that more premenopausal patients in this study received combination therapy. The menopausal status of patients in this study was not significantly correlated with NET, PFS, or RFS outcomes. These results suggest that NET is also effective for premenopausal women with breast cancer.

This study included 18 DCIS cases, most of which were low-grade tumors. The results of this study show that NET can contribute to reduction of surgical extent and avoidance of surgery in DCIS cases. Chen et al.[40] reported that NET may be effective for ER-positive DCIS, based on pathological and biological analyses. Meyerson et al.[28] reported that in 14 women with ER-positive DCIS, 6 remained on surveillance without evidence of invasive disease for a median of 31.8 (range 11.8-80.8) months. Similarly, in our study, of the 8 patients in the surgery avoidance cohort, 7 remain on NET, with a median duration of 32 months and a maximum duration of 84 months. Our study shows that there is a risk that NETs will be ineffective and that a new primary breast cancer will develop during NET; however, the risk seems to be low. Considering the above results, NET is recommended for patients with low-grade DCIS and high ER expression who wish to reduce surgical extent or avoid surgery.

Because this study is retrospective and the sample size is small, the results should be interpreted with caution. However, being different from previous studies, this study included premenopausal patients and patients with DCIS and analyzed different purposes of NET. Therefore, it yielded new insights on NET for breast cancer care.

In conclusion, NETs can help in reducing surgical ex-

tent or avoiding surgery in women with early breast cancer and with a histological type of IDC or DCIS and high ER expression, irrespective of menopausal status. In addition, regardless of NET duration, the characteristics of tumors at surgery allows for appropriate selection of adjuvant systemic therapy, which may result in improving postoperative survival. Further prospective clinical trials on NETs are warranted.

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