Table 3 Adjusted odds ratios of factors predicting pCR

Factor	pCR (ypT0/is + ypN0)			spCR (ypT0 + ypN0)		
	OR	95 % CI	*P* value	OR	95 % CI	*P* value
Whole dataset						
Age						
>40 vs. ≤40	0.97	(0.60–1.58)	0.907	1.45	(0.84–2.63)	0.191
BMI						
25≤ vs. <22	1.22	(0.78–1.91)	0.388	1.31	(0.80–2.11)	0.280
22≤, <25 vs. <22	1.38	(0.94–2.04)	0.100	1.47	(0.98–2.21)	0.062
Clinical tumor size						
T1–2 vs. T3–4	1.88	(1.27–2.79)	0.002	2.16	(1.39–3.41)	0.001
Clinical nodal status						
N0 vs. N2–3	0.65	(0.40–1.07)	0.093	0.98	(0.57–1.71)	0.942
N1 vs. N2–3	0.83	(0.53–1.31)	0.435	1.44	(0.88–2.39)	0.152
ER/PgR status						
Negative vs. positive	3.42	(2.42–4.86)	<0.001	2.27	(1.55–3.35)	<0.001
Histological/Nuclear grade						
3 vs. 1&2	1.39	(0.99–1.95)	0.060	1.29	(0.90–1.88)	0.169
ER/PgR-positive dataset						
Age						
>40 vs. ≤40	0.74	(0.40–1.39)	0.343	1.22	(0.56–2.89)	0.622
BMI						
25≤ vs. <22	1.65	(0.85–3.20)	0.140	1.27	(0.56–2.81)	0.559
22≤, <25 vs. <22	1.43	(0.77–2.61)	0.253	1.46	(0.71–2.97)	0.296
Clinical tumor size						
T1–2 vs. T3–4	1.76	(0.94–3.43)	0.078	2.95	(1.28–7.72)	0.010
Clinical nodal status						
N0 vs. N2–3	0.98	(0.46–2.11)	0.954	0.89	(0.36–2.32)	0.810
N1 vs. N2–3	0.80	(0.39–1.67)	0.547	0.93	(0.39–2.35)	0.869
Histological/Nuclear grade						
3 vs. 1&2	1.22	(0.73–2.05)	0.454	1.00	(0.54–1.86)	0.991
ER/PgR-negative dataset						
Age						
>40 vs. ≤40	1.43	(0.68–2.94)	0.344	1.73	(0.80–4.08)	0.170
BMI						
25≤ vs. <22	0.95	(0.52–1.76)	0.871	1.29	(0.69–2.36)	0.422
22≤, <25 vs. <22	1.35	(0.81–2.27)	0.248	1.47	(0.89–2.43)	0.132
Clinical tumor size						
T1–2 vs. T3–4	1.93	(1.17–3.20)	0.010	1.89	(1.13–3.24)	0.016
Clinical nodal status						
N0 vs. N2–3	0.48	(0.24–0.92)	0.027	0.98	(0.49–1.95)	0.943
N1 vs. N2–3	0.89	(0.48–1.61)	0.692	1.75	(0.97–3.26)	0.065
Histological/Nuclear grade						
3 vs. 1&2	1.53	(0.97–2.42)	0.068	1.50	(0.94–2.40)	0.087

BMI body mass index, *ER/PgR* estrogen receptor/progesterone receptor, *pCR* pathologic complete response, *spCR* strict pathologic complete response, *OR* odds ratio

(30–67 %) [7–10, 12–15]. In our study, ER/PgR status was the strongest predictor for pCR or spCR. Our results were consistent with those of two meta-analyses in which the pCR rate of NAC with trastuzumab was about 50 % for patients with ER/PgR-negative disease and 30 % for those with ER/PgR-positive disease [6, 16].

In the TECHNO trial, a phase-II trial of 217 patients with HER2-positive disease who received NAC with trastuzumab, failure to achieve pCR was a significant predictor for DFS in the multivariate analysis [10]. Kim et al. [12] retrospectively investigated the prognostic value of pCR using data from 229 patients with HER2-positive

tumor who were treated with NAC with trastuzumab. They reported that pCR, clinical tumor stage, and lymphovascular invasion were independent predictors for DFS. In our study, pCR and spCR were predictors for DFS; in addition, conventional prognostic factors such as nodal stage and histological/nuclear grade were predictors for DFS.

In this study, the association of age with DFS was not statistically significant in the whole dataset, consistent with the results of the TECHNO trial and Kim et al. Partridge et al. [17] reported that young age was not associated with worse DFS in patients with HER2-positive disease using large cohort data from the HERA trial. When we divided the patients into ER/PgR-positive and -negative groups, multivariate analysis showed that young age (age ≤40) was an independent predictor for poorer DFS in the ER/PgR-positive dataset. Our result was consistent with earlier studies showing that younger age is an independent predictor for worse DFS, especially in patients with ER/PgR-positive disease [18, 19].

After dividing the patients into ER/PgR-positive and -negative datasets, we performed multivariate analysis for DFS using each dataset. About 30–40 % of HER2-enriched subtype tumors are reported to be ER positive [20, 21]. Among clinically HER2-positive tumors, up to 60 % are classified as the HER2-enriched subtype, with the rest classified as luminal B, luminal A, or basal-like [22]. Adjuvant systemic therapy differs according to ER/PgR status [23]. Therefore, it seemed reasonable to perform the analysis based on ER/PgR status; however, the results should be interpreted carefully because of the relatively small event rate in each dataset.

In relation to the two aforementioned meta-analyses, pooled analysis from the German study group [6] indicated that pCR was a prognostic factor for the HER2-positive non-luminal subgroup, but not for those in the HER2-positive luminal subgroup. In the meta-analysis from the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) [16], there was a stronger association of pCR with event-free survival in the HER2-positive non-luminal subgroup compared with those in the HER2-positive luminal subgroup. In our study, pCR was an independent predictor for DFS in the ER/PgR-negative dataset, but not ER/PgR-positive dataset, and spCR was an independent predictor for DFS regardless of ER/PgR status.

The limitations of this study include its retrospective design. Adjustment using multivariate analysis is mandatory to minimize selection bias. The relatively short observation period may also limit the interpretation of our results. The median follow-up period of our study (42 months) covered the time when recurrence risk is high in HER2-positive disease [24]. Strength of our study was the large number of patients, which allowed us to conduct multivariate analysis separately according to ER/PgR status.

In conclusion, pCR/spCR, nodal status, and grade were predictors for DFS in patients with HER2-positive disease treated with NAC plus trastuzumab. Response to therapy and prognostic impact of the factors differed according to ER/PgR status. Our results may help identify patients who are not likely to achieve pCR or whose outcome would otherwise be unfavorable. New treatment approaches, such as the incorporation of novel anti-HER2 drugs, are needed for patients with high-risk disease.

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ORIGINAL ARTICLE

Incidence of contralateral breast cancer in Japanese patients with unilateral minimum-risk primary breast cancer, and the benefits of endocrine therapy and radiotherapy

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Abstract
Background: Tamoxifen is recommended as adjuvant endocrine therapy for patients with minimum-risk breast cancer. It is primarily effective at prevention of contralateral and ipsilateral breast cancer recurrence after breast-conserving surgery. The incidence of contralateral breast cancer and the absolute benefit of endocrine therapy among patients with unilateral minimum-risk breast cancer in Japan, where the incidence of breast cancer is low, are unknown.
Patients and methods We retrospectively studied the incidence of contralateral breast cancer, and the efficacy of endocrine therapy, in a cohort of 2074 Japanese women with unilateral breast cancer whose primary tumor was pTis ($n = 1905$) or pT1mic ($n = 169$) (unknown for endocrine therapy, $n = 4$; unknown for radiotherapy, $n = 2$). We also assessed the efficacy of endocrine therapy and radiotherapy for prevention of ipsilateral and contralateral breast cancer recurrence in 1205 patients who underwent breast-conserving surgery (unknown for endocrine therapy, $n = 2$; unknown for radiotherapy, $n = 2$).
Results The incidence of contralateral breast cancer per 1000 person-years was 5.1 (95 % confidence interval (CI), 3.7–7.1) among patients without endocrine therapy ($n = 1364$) and 3.6 (95 % CI 2.1–6.1) among those with endocrine therapy ($n = 706$). The incidence of ipsilateral breast cancer recurrence after breast-conserving surgery per 1000 person-years was 9.2 (95 % CI 6.5–13) among patients without endocrine therapy ($n = 753$) and 4.2 (95 % CI 2.2–8.1) among those with endocrine therapy ($n = 450$). The incidence of ipsilateral breast cancer recurrence after breast-conserving surgery per 1000

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person-years was 9.9 (95 % CI 6.3–15.6) among patients without radiotherapy ($n = 380$) and 5.9 (95 % CI 3.9–9.0) among those with radiotherapy ($n = 823$).
Conclusion The incidence of contralateral breast cancer among minimum-risk breast cancer patients in Japan, where the incidence of breast cancer is low, was similar to that in Western countries. Endocrine therapy is indicated for this population.

Keywords Adjuvant therapy · Aromatase inhibitor · Contralateral breast cancer · Ethnic difference · Tamoxifen

Introduction

The benefit of adjuvant systemic therapy for breast cancer patients with minimum risk of development of distant metastasis, for example ductal carcinoma in situ (DCIS) or pT1mic, is limited to reduction of the risk of contralateral or ipsilateral breast cancer recurrence after the breast-conserving surgery. Chemotherapy is generally not indicated for this population, whereas endocrine therapy is considered when tumors are hormone-sensitive. The guidelines of the Japanese Breast Cancer Society and the National Comprehensive Cancer Network both suggest the use of tamoxifen for this population [1, 2].

Two large randomized controlled trials investigated the benefit of tamoxifen as adjuvant endocrine therapy in Western countries. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial, 1804 patients with DCIS were randomized either to breast-conserving surgery followed by radiotherapy and placebo or to breast-conserving surgery followed by radiotherapy and tamoxifen. The 5-year breast cancer incidence of 8.2 % in the tamoxifen arm was statistically significantly lower than that of 13.4 % observed in the placebo arm. Tamoxifen significantly reduced the incidence of ipsilateral and contralateral breast cancer recurrence by approximately 40 and 50 %, respectively. Overall survival was not improved by use of tamoxifen [3]. The UK/Australia, and New Zealand (UK/ANZ) trial used a 2 × 2 factorial design for 1701 patients with DCIS treated with breast-conserving surgery who were randomized to radiotherapy and tamoxifen, radiotherapy alone, tamoxifen alone, or no treatment. The hazard ratio for ipsilateral breast cancer recurrence for tamoxifen versus no tamoxifen was 0.78 (95 % confidence Interval (CI), 0.62–0.99) over the median follow-up period of 12.7 years. Tamoxifen reduced the incidence of contralateral breast cancer by half and that of all breast cancer by approximately 30 %, but it did not improve overall survival [4].

The incidence of breast cancer in Asian women, including Japanese, is lower than that in women in the West [5]. However, it is unclear if the incidence of contralateral breast cancer in Japanese patients with unilateral breast cancer is lower than in Western patients. The incidence of contralateral breast cancer in patients with breast cancer in Taiwan has been reported to be similar to that in Western countries, but the cohort mainly comprised patients with invasive cancer who received systemic therapy [5]. Therefore, it is hard to estimate from existing data the absolute benefit of endocrine therapy for Japanese patients with primary breast cancer who are at minimum risk of development of distant metastasis.

In this retrospective study we investigated the incidence of contralateral breast cancer in Japanese women with unilateral minimum-risk breast cancer, and the efficacy of endocrine therapy. We also assessed the efficacy of endocrine therapy and radiotherapy for prevention of ipsilateral and contralateral breast cancer recurrence in patients who underwent breast-conserving surgery.

Methods

Patients

This was a historical cohort study of Japanese patients in eight hospitals with unilateral primary breast cancer whose primary tumor was pTis or pT1mic. The eligibility criteria for this cohort were patients who underwent surgery for primary breast cancer that was histopathologically diagnosed as pTis or pT1mic and had no axillary lymph node metastasis. We retrospectively identified all eligible patients consecutively treated at the hospitals through December 2010. A total of 1905 patients with pTis and 169 patients with pT1mic were identified and included in this analysis. The institutional distribution was as follows: Saitama Cancer Center, $n = 257$ (12 %); Jichi Medical School, $n = 289$ (14 %); Kansai Rosai Hospital, $n = 76$ (4 %); Sagara Hospital, $n = 543$ (26 %); Aihara Hospital, $n = 27$ (1 %); Aichi Cancer Center, $n = 452$ (22 %); Osaka Medical Center, $n = 197$ (9 %); and Kyushu Cancer Center, $n = 233$ (11 %). The study protocol was approved by the Ethics Committee of Osaka Medical Center in December 2010. Because of the retrospective enrollment, written informed consent was not obtained from the patients, which is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare of Japan. The following data were collected by using a standardized electronic data-collection form: date and age at the time of surgery, type of surgery, given endocrine therapy or not, given postoperative radiotherapy or not, development of contralateral breast cancer, and ipsilateral tumor recurrence for patients who underwent breast-conserving surgery.

Table 1 Patient demographics

	Total ($n = 2074$)	Without endocrine therapy ($n = 1364$)	With endocrine therapy ($n = 706$)	p*
Mean age and SD at surgery (years)	54.1 ± 12.2	54.3 ± 12.2	53.9 ± 12.2	0.04
Type of surgery				<0.01
Breast-conserving	1205 (58 %)	753 (63 %)	450 (37 %)	
Mastectomy	869 (42 %)	611 (70 %)	256 (30 %)	
Histology				<0.01
pTis	1905 (92 %)	1281 (67 %)	621 (33 %)	
pT1mic	169 (8 %)	83 (49 %)	85 (51 %)	
Family history				0.86
No	1109 (53 %)	674 (61 %)	435 (39 %)	
Yes	150 (7 %)	90 (60 %)	60 (40 %)	
Unknown	815 (39 %)	600 (74 %)	211 (26 %)	
Endocrine therapy				–
No	1364 (66 %)	1364 (100 %)	0 (0 %)	
Tamoxifen	594 (29 %)	0 (0 %)	594 (100 %)	
Aromatase inhibitors	112 (5 %)	0 (0 %)	112 (100 %)	
Unknown	4 (0 %)	0	0	
Radiotherapy				<0.01
No	1224 (59 %)	886 (73 %)	335 (27 %)	
Yes	848 (41 %)	477 (56 %)	371 (44 %)	
Unknown	2 (0 %)	1 (100 %)	0 (0 %)	

SD standard deviation

* Fisher's exact test was used for comparison of patients with and without endocrine therapy

The demographics of the patients are shown in Table 1. Patients aged ≤55 years, those who received breast-conserving surgery, those with pT1mic, and those who received radiotherapy tended to receive endocrine therapy. Administration of endocrine therapy was not affected by family history. There were 1364 (66 %) patients who did not receive endocrine therapy. Among the 706 patients who received endocrine therapy, tamoxifen was given to 594 (29 %) and aromatase inhibitors were given to 112 (5 %). The proportion of patients who received endocrine therapy was larger among those who received radiotherapy than among those who did not. Ipsilateral breast cancer recurrence was assessed in 1205 patients who underwent breast-conserving surgery (unknown status for endocrine therapy, $n = 2$; unknown status for radiotherapy, $n = 2$). We could not collect the following data: detailed pathological features of the primary tumor, including the presence of comedo-type necrosis, cut-surface margin status, and menopausal status. Data on endocrine therapy from four patients and on radiotherapy from two patients could not be retrieved.

Statistical methods

The outcomes studied were: the incidence of contralateral breast cancer, recurrence of ipsilateral cancer, and total incidence of breast cancer (sum of ipsilateral breast cancer recurrence and incidence of contralateral breast cancer) after surgery. The person-year method was used to estimate the incidence, recurrence, and 95 % CI. The Kaplan–Meier method was used to estimate survival curves. The Cox model, which has an adjustment for pTis/pT1mic, type of surgery, and age at surgery as confounding factors, was used to estimate the hazard ratio (HR) with 95 % CI for endocrine therapy and radiotherapy. Missing data were collected by complete-case analysis. All reported p values for statistical tests are two-tailed, and the significance level was set at $p < 0.05$. SAS version 9.2 (SAS Institute, Cary, NC, USA) was used by a biostatistician (ST) to perform all of the statistical analysis.

Results

The estimated contralateral breast cancer incidence and Kaplan–Meier curves according to endocrine therapy and radiotherapy are shown in Table 2 and Fig. 1a. Among those who did not receive endocrine therapy ($n = 1364$), there were 35 cases of contralateral breast cancer after a mean follow-up period of 5.0 years, equivalent to an incidence per 1000 person-years of 5.1 (95 % CI 3.7–7.1). The probabilities of living event-free at 5 years and 10 years were 97.5 % (95 % CI 96.4–98.6 %) and 94.2 % (95 % CI 92.0–96.4 %), respectively. Among those who received endocrine therapy ($n = 706$), there were 14 cases of contralateral breast cancer after a mean follow-up period

Table 2 Contralateral breast cancer incidence ($n = 2074$)

	Contralateral breast cancer incidence ($n = 2074$)					
	No. of cases	No. of patients	Mean follow-up period (years)	Annual incidence (per patient-year)	95 % CI	
Total	49	2074	5.2	0.0045	0.0034	0.0060
Endocrine therapy						
No	35	1364	5.0	0.0051	0.0037	0.0071
Yes	14	706	5.5	0.0036	0.0021	0.0061
TAM	13	594	5.8	0.0038	0.0022	0.0065
AI	1	112	3.8	0.0023	0.0003	0.0165
Radiotherapy						
No	30	1224	5.7	0.0043	0.0030	0.0062
Yes	19	848	4.5	0.0049	0.0031	0.0077
No adjuvant treatment	21	886	5.4	0.0044	0.0029	0.0068
Endocrine treatment only	9	335	6.4	0.0042	0.0022	0.0081
Radiotherapy only	14	477	4.4	0.0066	0.0039	0.0112
Endocrine treatment and radiotherapy	5	371	4.7	0.0029	0.0012	0.0069

TAM tamoxifen, *AI* aromatase inhibitor, *CI* confidence interval

Excluded patients: unknown for endocrine therapy, $n = 4$; unknown for radiotherapy, $n = 2$

of 5.5 years, equivalent to an incidence per 1000 person-years of 3.6 (95 % CI 2.1–6.1). The probabilities of living event-free at 5 years and 10 years were 98.7 % (95 % CI 97.8–99.7 %) and 97.1 % (95 % CI 95.3–99.0 %), respectively. The incidence of contralateral breast cancer among those who received tamoxifen was 3.8 (95 % CI 2.2–6.5) after a mean follow-up period of 5.8 years; the incidence among those who received aromatase inhibitors was 2.3 (95 % CI 0.3–16.5) after a mean follow-up period of 3.8 years. Four patients for whom we could not retrieve endocrine therapy data were excluded from this analysis. Among those who did not receive radiotherapy ($n = 1224$), there were 30 cases of contralateral breast cancer after a mean follow-up period of 5.7 years, which was equivalent to an incidence per 1000 person-years of 4.3 (95 % CI 3.0–6.2). The probabilities of living event-free at 5 years and 10 years were 98.1 % (95 % CI 97.1–99.0 %) and 95.8 % (95 % CI 94.0–97.6 %), respectively. Among those who received radiotherapy ($n = 848$), there were 19 cases of contralateral breast cancer at a mean follow-up period of 4.5 years, which was equivalent to an incidence per 1000 person-years of 4.9 (95 %CI 3.1–7.7). The probabilities of living event-free at 5 years and 10 years were 97.8 % (95 % CI 96.5–99.1 %) and 94.5 % (95 % CI 91.7–97.3 %), respectively.

Ipsilateral breast cancer recurrence after breast-conserving surgery and Kaplan–Meier curves according to endocrine therapy and radiotherapy are shown in Table 3a and Fig. 1b. Among those who did not receive endocrine therapy ($n = 753$), there were 32 cases of ipsilateral breast cancer recurrence after breast-conserving surgery after a mean follow-up period of 4.6 years, equivalent to an incidence per 1000 person-years of 9.2 (95 % CI 6.5–13). The probabilities of living event-free at 5 years and 10 years were 95.6 % (95 % CI 93.7–97.5 %) and 89.9 % (95 % CI 85.0–94.8 %), respectively. Among those who received endocrine therapy ($n = 450$), there were 9 cases of ipsilateral breast cancer recurrence after breast-conserving surgery after a mean follow-up period of 4.8 years, equivalent to an incidence per 1000 person-years of 4.2 (95 % CI 2.2–8.1). The probabilities of living event-free at 5 years and 10 years were 97.9 % (95 % CI 96.2–99.6 %) and 95.2 % (95 % CI 90.5–99.8 %), respectively. Two patients for whom we could not retrieve endocrine therapy data were excluded from this analysis. Among those who did not receive radiotherapy ($n = 380$), there were 19 cases of ipsilateral breast cancer recurrence after breast-conserving surgery after a mean follow-up period of 5.0 years, equivalent to an incidence per 1000 person-years of 9.9 (95 % CI 6.3–15.6). The probabilities of living event-free at 5 years and 10 years were 94.6 % (95 % CI 91.7–97.5 %) and 89.4 % (95 % CI 83.4–95.5 %), respectively. Among those who received radiotherapy ($n = 823$), there were 22 cases of ipsilateral breast cancer recurrence after breast-conserving surgery after a mean follow-up period of 4.5 years, equivalent to an incidence per 1000 person-years of 5.9 (95 % CI 3.9–9.0). The probabilities of living event-free at 5 years and 10 years were 97.4 % (95 % CI 96.0–98.8 %) and 93.2 % (95 % CI 88.9–97.5 %), respectively. Two patients for whom we could not retrieve radiotherapy data were excluded from this analysis.

The total incidence of breast cancer and Kaplan–Meier curves according to endocrine therapy and radiotherapy are

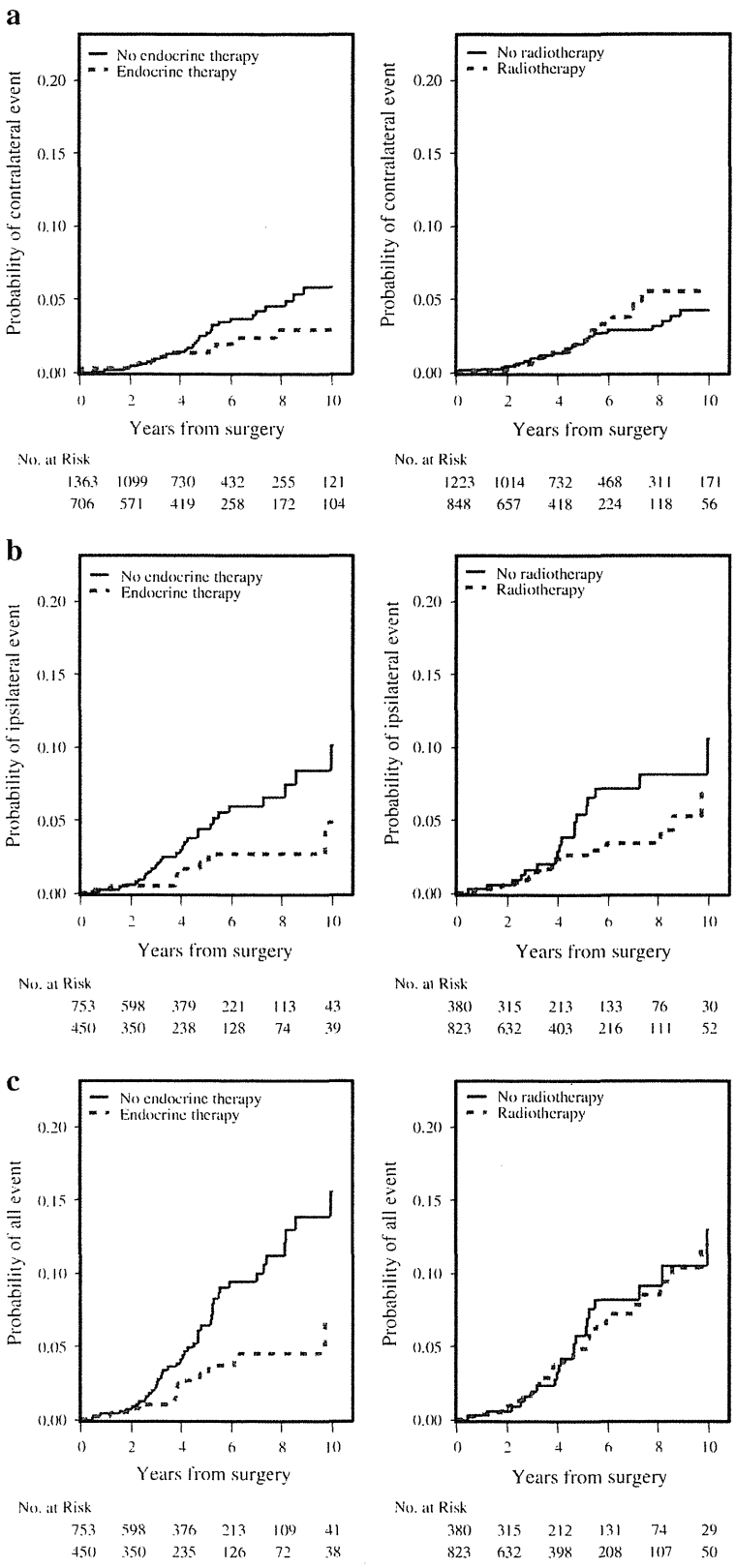

Fig. 1 **a** Kaplan–Meier curves for incidence of contralateral breast cancer among patients who received or did not receive endocrine therapy or radiotherapy. **b** Kaplan–Meier curves for recurrence of ipsilateral breast cancer after breast-conserving surgery among patients who received or did not receive endocrine therapy or radiotherapy. **c**. Kaplan–Meier curves for total incidence of breast cancer after breast-conserving surgery among patients who received or did not receive endocrine therapy or radiotherapy

Table 3 Ipsilateral breast cancer recurrence and total incidence of breast cancer after breast-conserving surgery ($n = 1205$)

	No. of cases	No. of patients	Mean follow-up period (years)	Annual incidence (per patient-year)	95 % CI	
Ipsilateral breast cancer recurrence						
Total	42	1205	4.7	0.0075	0.0055	0.0101
Endocrine therapy						
No	32	753	4.6	0.0092	0.0065	0.0130
Yes (TAM + AI)	9	450	4.8	0.0042	0.0022	0.0081
TAM	9	374	5.0	0.0048	0.0025	0.0093
AI	0	76	3.7	0.0000	0.0000	0.0000
Radiotherapy						
No	19	380	5.0	0.0099	0.0063	0.0156
Yes	22	823	4.5	0.0059	0.0039	0.0090
Total incidence of breast cancer						
Radiotherapy						
No	22	380	5	0.0116	0.0076	0.0176
Yes	40	823	4.4	0.0109	0.0080	0.0149
Total	63	1205	4.6	0.0113	0.0088	0.0145
Endocrine therapy						
No	48	753	4.6	0.0139	0.0105	0.0185
Yes (TAM + AI)	14	450	4.7	0.0066	0.0039	0.0112
TAM	13	374	4.9	0.0071	0.0041	0.0122
AI	1	76	3.6	0.0036	0.0005	0.0256

TAM tamoxifen, *AI* aromatase inhibitor, *CI* confidence interval

Excluded patients: unknown for endocrine therapy, $n = 2$; unknown for radiotherapy, $n = 2$

shown in Table 3b and Fig. 1c. The incidence per 1000 person-years was 13.9 (95 % CI 10.5–18.5) among those who did not receive endocrine therapy and 6.6 (95 % CI 3.9–11.2) among those who received endocrine therapy. The probabilities of living event-free at 5 years and 10 years were 93.6 % (95 % CI 91.3–95.9 %) and 84.4 % (95 % CI 78.9–90.0 %), respectively, for those without endocrine therapy and 96.9 % (95 % CI 94.9–98.9 %) and 93.4 % (95 % CI 88.4–98.4 %), respectively, for those with endocrine therapy. The incidence per 1000 person-years was 11.6 (95 % CI 7.6–17.6) among those who did not receive radiotherapy and 10.9 (95 % CI 8.0–14.9) among those who received radiotherapy. The probabilities of living event-free at 5 years and 10 years were 94.3 % (95 % CI 91.3–97.2 %) and 87.1 % (95 % CI 80.4–93.7 %), respectively, for those without radiotherapy and 95.2 % (95 % CI 93.3–97.1 %) and 88.1 % (95 % CI 83.2–93.0 %), respectively, for those with radiotherapy.

The effects of endocrine therapy and radiotherapy treatment on the incidence of contralateral breast cancer, estimated by Cox regression analysis after adjustment for age and type of surgery, are shown in Table 4a. The hazard ratios for developing contralateral breast cancer were 0.64 (95 % CI 0.34–1.19, $p = 0.16$) for endocrine therapy and 1.87 (95 % CI 0.80–4.39, $p = 0.15$) for radiotherapy, indicative of a nonsignificant trend toward improved outcome with endocrine therapy and deteriorated outcome with radiotherapy. The effects of endocrine therapy and radiotherapy treatment on ipsilateral breast cancer recurrence after breast-conserving surgery, estimated by Cox regression analysis after adjustment for age and pathology (pTis or pT1mic), are shown in Table 4b. Endocrine therapy significantly improved the outcome (hazard ratio 0.43; 95 % CI 0.20–0.92; $p = 0.03$). The effects of endocrine therapy and radiotherapy treatment on total breast cancer after breast-conserving surgery, estimated by Cox regression analysis after adjustment for age and pathology (pTis or pT1mic), are shown in Table 4c. Endocrine therapy again significantly improved the outcome (hazard ratio 0.42; 95 % CI 0.23–0.78; $p = 0.01$).

Discussion

In Western countries, the incidence of contralateral breast cancer after surgery in patients with minimum-risk breast cancers such as DCIS, when no systemic therapy was given, was reported to be 8.12 per 1000 person-years in the NSABP B24 trial [3] and 5.3 per 1000 person-years in the UK/ANZ trial [4]. Our study revealed that the incidence of

Table 4 Effects of endocrine therapy and radiotherapy on (a) contralateral breast cancer incidence estimated by multivariate Cox regression analysis ($n = 2067$), (b) ipsilateral breast cancer recurrence after breast-conserving surgery estimated by multivariate Cox regression analysis ($n = 1201$), and (c) total breast cancer incidence after breast-conserving surgery estimated by multivariate Cox regression analysis ($n = 1201$)

	Hazard ratio	95 % CI		*p*
(a)				
Endocrine therapy				
No	Reference			
Yes	0.64	0.34	1.19	0.16
Radiotherapy				
No	Reference			
Yes	1.87	0.80	4.39	0.15
(b)				
Endocrine therapy				
No	Reference			
Yes	0.43	0.20	0.92	0.03
Radiotherapy				
No	Reference			
Yes	0.70	0.37	1.34	0.28
(c)				
Endocrine therapy				
No	Reference			
Yes	0.42	0.23	0.78	0.01
Radiotherapy				
No	Reference			
Yes	1.15	0.67	1.97	0.62

CI confidence interval

Hazard ratio <1 indicates efficacy of the treatment

contralateral breast cancer in Japanese patients with minimum-risk breast cancer without systemic therapy was 5.1 per 1000 person-years, which is similar to that in Western countries, although the incidence of development of breast cancer in Asian countries, including Japan, is much lower than that in Western countries. A study from Taiwan, in which the incidence of breast cancer is lower than in Japan, reported that the annual incidence of contralateral breast cancer was 4.6 per 1000 person-years [5], which is similar to that in our study. The population included in that study was quite different from ours. Most of the patients had invasive carcinomas and received endocrine therapy and/or chemotherapy. Therefore, our study is the first to demonstrate that the incidence of contralateral breast cancer in minimum-risk breast cancer patients in Japan, in which the incidence of breast cancer is low, was similar to that in Western countries when no systemic therapy was given. This information is of particular importance when the benefit of endocrine therapy is estimated for breast cancer patients with minimum risk of development of distant metastasis. This study showed that absolute risk reductions were 1.2 % at 5 years and 2.3 % at 10 years for contralateral breast cancer after endocrine therapy. For minimum-risk breast cancer patients in Japan, the risk reductions were 2.9 % at 5 years and 5.3 % at 10 years for ipsilateral breast cancer recurrence and 3.3 % at 5 years and 9.0 % at 10 years for total incidence of breast cancer after breast-conserving surgery followed by endocrine therapy. Because improved overall survival of unilateral minimum-risk breast cancer patients after tamoxifen therapy was not reported in the previous studies [3, 4], the decision of whether to give tamoxifen to this population should be made after considering the risks of adverse events, for example excess endometrial carcinoma or deep-vein thrombosis. A limitation of this study is that we could not investigate such adverse events. However, the incidence of tamoxifen-related adverse events seems to be low in Japanese breast cancer patients [6], and the risk–benefit ratio for tamoxifen may be higher for Japanese patients than for Western patients.

In our cohort, approximately 16 % of patients received an aromatase inhibitor as endocrine therapy, which is not currently recommended by the guidelines. The observed incidence and recurrence for this population were much lower than those for patients who received tamoxifen, but this result must be interpreted cautiously, because patients were not randomized and the number of events was very small. In addition, some aromatase inhibitors might have a negative effect on nonbreast cancer deaths [7]. A randomized controlled trial is necessary to examine whether an aromatase inhibitor has a better treatment profile than tamoxifen for breast cancer patients with a minimum risk of development of distant metastasis.

A weakness of this study for investigation of the efficacy of endocrine therapy or radiotherapy is that this was a nonrandomized study, which may have been subject to bias because of unadjusted confounding factors. For instance, ipsilateral breast cancer recurrence was not significantly different between patients with and without radiotherapy. This is attributable to the relatively small sample size and power needed to detect the effects of radiotherapy, so one should not interpret these results as a negation of efficacy of radiotherapy which is accepted as standard therapy in the guidelines. Also, the sample size was not determined on the basis of statistical considerations of the power needed to detect the effects. In addition, we could not collect data on the detailed pathological features of the primary tumor, including the presence of comedo-type necrosis, cut-surface margin status after breast-conserving surgery, and menopausal status. A prospective cohort is currently being assembled by the Japanese Breast Cancer Society that should provide more detailed data in the future.

In conclusion, we demonstrated that the incidence of contralateral breast cancer among minimum-risk breast cancer patients in Japan, where the incidence of breast cancer is low, was similar to that in Western countries. Endocrine therapy reduced the incidence of contralateral breast cancer and the recurrence of ipsilateral breast cancer. These findings enabled us to estimate the absolute benefit of endocrine therapy among these patients.

Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Pathological responses and survival of patients with human epidermal growth factor receptor 2-positive breast cancer who received neoadjuvant chemotherapy including trastuzumab

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Abstract
Background The effectiveness of neoadjuvant chemotherapy is evaluated on the basis of pathological responses and survival outcome, because achievement of a pathological complete response (pCR) is a good predictor of long-term survival. However, few studies have assessed the survival of breast cancer patients who received neoadjuvant chemotherapy including trastuzumab.
Methods The records of 161 breast cancer patients who received neoadjuvant chemotherapy between January 2006 and December 2011 were retrospectively reviewed. The patients were categorized into 4 subgroups on the basis of the status of the estrogen receptor (ER), the progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). HER2-positive patients received trastuzumab-based regimens. Pathological responses and survival were analyzed on the basis of breast cancer subtypes.
Results The pCR results obtained were: luminal A and B (ER and/or PR-positive, HER2-negative), 6.3 % (5/79 cases); luminal–HER2 hybrid (ER and/or PR-positive, HER2-positive), 25.0 % (5/20 cases); HER2-enriched (ER and PR-negative, HER2-positive), 63.0 % (17/27 cases); and triple-negative (ER and PR-negative, HER2-negative), 25.7 % (9/35 cases). Achievement of pCR was a good predictor of disease-free survival in the HER2-enriched group. Overall survival of patients with pCR was slightly, but not significantly, better in the HER2-enriched and triple-negative subgroups.
Conclusion Responses and survival after neoadjuvant chemotherapy including trastuzumab of patients with HER2-positive tumors differed among disease subtypes. Our findings suggest that disease subtype is an important determinant of the efficacy of neoadjuvant chemotherapy.

Keywords Neoadjuvant chemotherapy · HER2 · Trastuzumab · Pathological complete response · Neoadjuvant response index

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Introduction

Neoadjuvant chemotherapy is a general treatment strategy for breast cancer, but some clinical trials have shown no difference in response between neoadjuvant and adjuvant chemotherapy [1, 2]. In these trials, responses to neoadjuvant chemotherapy were based on the pathological complete response (pCR), which is a good predictor of long-term survival [1, 3]. Breast cancer subtypes also seem to be determinants of response to neoadjuvant chemotherapy. For example, significantly lower response has been reported for patients with estrogen receptor (ER)-positive tumors [4] and high pCR has been reported in patients with human epidermal growth factor receptor 2 (HER2)-positive tumors who received trastuzumab therapy [5]. However, only limited data are available on survival of patients with HER2-positive tumors treated with neoadjuvant chemotherapy including trastuzumab [6]. Correlation of pCR with survival benefits thus remains unclear for this patient subgroup.

Here we retrospectively reviewed data on the response to neoadjuvant chemotherapy including trastuzumab for patients with HER2-positive breast cancer treated in a single institution and report their pathological responses and survival.

Patients and methods

Patients

We retrospectively reviewed data for 161 consecutive patients who received neoadjuvant chemotherapy at Jichi Medical University Hospital (Tochigi, Japan) between January 2006 and December 2011. All patients had pathologically confirmed diagnosis of stage II or III invasive breast cancer, the longest diameter of the primary tumor exceeded 3 cm, or axillary lymph node metastases were indicated. During the study period, 2 patients with HER2-positive diseases did not receive trastuzumab as part of their neoadjuvant chemotherapy regimen because of cardiac diseases; they were, therefore, excluded from the study. Axillary node metastases were diagnosed by fine-needle aspiration or sentinel-node biopsy. These diagnostic procedures of the axilla were not performed for some patients because axillary node metastases were strongly suspected on the basis of clinical imaging.

Treatment

Neoadjuvant chemotherapy mainly comprised anthracycline-based regimens followed by taxane-based regimens. Three anthracycline-based regimens were used: 3 or 4 cycles of FEC (fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 every 3 weeks); 4 cycles of AC (adriamycin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks); and 4 cycles of EC (epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks). Three taxane-based regimens were used: 3 or 4 cycles of docetaxel (100 mg/m^2 every 3 weeks); 4 cycles of docetaxel (75 mg/m^2 every 3 weeks); and 12 cycles of paclitaxel (80 mg/m^2 every weeks). A small proportion of patients received other anthracycline-based or taxane-based regimens. One patient received 6 cycles of a regimen combining an anthracycline and a taxane (docetaxel 80 mg/m^2, adriamycin 50 mg/m^2, and cyclophosphamide 500 mg/m^2 every 3 weeks). Patients with HER2-positive diseases received trastuzumab regimens (4 mg/kg as a loading dose and 2 mg/kg from the second dose onward every week) concomitantly with a taxane-based regimen. Surgery was performed 3–4 weeks after the final dose of the neoadjuvant chemotherapy. After surgery, patients with ER-positive tumors were scheduled to receive adjuvant endocrine therapy for 5 years. Postmenopausal women received endocrine therapy with tamoxifen or an aromatase inhibitor. The endocrine therapy for premenopausal women included tamoxifen or a combination of LH–RH agonist plus tamoxifen. Patients with HER2-positive diseases were administered additional trastuzumab cycles to complete 1 year of treatment. All patients who received breast-conservation therapy were also treated with radiation therapy. Women who underwent mastectomies and had tumors >5 cm in diameter before chemotherapy or ≥4 positive nodes received postmastectomy chest-wall irradiation.

Pathological evaluation

All patients had a histologically confirmed diagnosis of invasive carcinoma via core-needle biopsy before neoadjuvant chemotherapy. The biopsy specimens were routinely assessed for immunohistochemical markers for estrogen receptor (ER; SP1; Roche Diagnostics, Mannheim, Germany), progesterone receptor (PR; 1E2; Roche Diagnostics), and HER2 (4B5; Roche Diagnostics). The cut-off values for ER and PR were 10 % positive cells. HER2 expression was scored 0–3+, in accordance with the scoring system recommended by the manufacturer. A score of 0–1+ was considered negative, whereas the score 3+ was positive. For 2+ cases, HER2 amplification was verified by fluorescence in-situ hybridization (PathVysion HER2 test; Abbott/Vysis, Des Plaines, IL, USA). We categorized tumors into 4 subtypes on the basis of ER, PR, and HER2 status in the biopsy specimens as surrogate markers: luminal A and B (ER and/or PR-positive, HER2-negative); luminal–HER2 hybrid (ER and/or PR-positive, HER2-positive); HER2-enriched (ER and PR-negative, HER2-positive); and triple-negative (ER and PR-negative, HER2-negative) (Table 1).

After surgery, the resected specimens were evaluated for residual tumors and responses to neoadjuvant chemotherapy. Pathological complete response (pCR) was defined as no pathological evidence of residual invasive cancer in the breast, irrespective of the remaining intraductal components in the breast and axillary tumors.

In addition to evaluating pCR, we calculated the neoadjuvant response index (NRI) as described by Rodenhuis et al. [7], with slight modifications. In brief, the NRI comprises breast and axillary response scores derived from the differences between the clinical stage before chemotherapy and the pathological stage on evaluation of surgical specimens (Table 2). One point was awarded for each decrease in the T stage, except for the transition from cT1 to pT0 and for achievement of a near pCR (invasive tumor <5 mm in diameter), and 2 points for pCR. The axillary response score was calculated on the basis of the change in stage. Again, 1 point was awarded for every stage decrease.

Table 1 Classification of breast cancer subtypes on the basis of immunohistochemical markers

Subtypes used in this study	Status of immunohistochemical markers	Corresponding subtypes (Goldhirsch et al. [10])
Luminal A and B	ER and/or PR positive, HER2 negative	Luminal A, Luminal B (HER2 negative)
Luminal–HER2 hybrid	ER and/or PR positive, HER2 positive	Luminal B (HER2 positive)
HER2-enriched	ER and/or PR negative, HER2 positive	HER2 positive (non luminal)
Triple-negative	ER and/or PR negative, HER2 negative	Triple-negative (ductal)

ER, PR positive, more than 10 % positive cells; HER2 positive, score 3+ or FISH amplified; *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

Table 2 Definition of stage for calculation of neoadjuvant response index

	Clinical stage before chemotherapy		Pathological stage according to surgical specimen
cT1	Tumor 2 cm or less	pT0	No evidence of residual invasive cancer in breast
cT2	Tumor more than 2 cm but not more than 5 cm	pT1	Tumor 2 cm or less
cT3	Tumor more than 5 cm	pT2	Tumor more than 2 cm but not more than 5 cm
cT4	Tumor of any size with direct extension to skin	pT3	Tumor more than 5 cm
cA0	No LN metastasis on SLNB	pT4	Tumor of any size with direct extension to skin
cA1	LN metastasis only on SLNB before chemotherapy	pA0	No LN metastasis
cA2	No palpable nodes, but LN metastasis proved by FNAC or suspected strongly on imaging studies	pA1	Only microscopic (<2 mm) LN metastasis
cA3	Palpable axillary nodes and proved LN metastasis on FNAC	pA2	One or more nonpalpable LN containing metastatic disease >2 mm in diameter
		pA3	At least one positive LN still palpable before surgery

LN lymph node, *SLNB* sentinel lymph node biopsy, *FNAC* fine-needle aspiration cytology

The NRI was defined as the sum of the breast and axillary response scores divided by the sum of achievable points, resulting in a number between 0 (no response) and 1 (complete response in both breast and axilla).

Statistical analysis

The chi-squared test was used to compare categorical data. The Kruskal–Wallis test was used to compare quantitative data. Survival was estimated by use of the Kaplan–Meier method. Survival results were compared among the 4 breast cancer subtypes by use of the log-rank test. The generalized Wilcoxon test was used to compare survival results between the 2 groups. All statistical analysis was performed with Prism 5 software version 5.0d (GraphPad Software, La Jolla, CA, USA).

Results

Patient characteristics

A total of 161 women with stage II/III breast cancer were studied. Table 3 summarizes the clinical data before neoadjuvant chemotherapy. Luminal A and B, luminal–HER2 hybrid, HER2-enriched, and triple-negative subtypes were diagnosed in 79 (49.1 %), 20 (12.4 %), 27 (16.8 %), and 35 patients (21.7 %), respectively. The median age at diagnosis was 50 years (range 27–83). The patients with ER-negative tumors (HER2-enriched and triple-negative) were older than those with ER-positive tumors (luminal A and B and luminal–HER2 hybrid) ($p < 0.01$). Median tumor size, clinical axillary node status, and clinical stage did not differ among subtypes ($p = 0.71$, 0.70, and 0.18, respectively). Overall, 147 patients (91.3 %) received an anthracycline-based regimen followed by a taxane-based regimen. All patients with HER2-positive tumors (luminal–HER2 hybrid and HER2-enriched) received an anthracycline-based regimen followed by a taxane-based regimen concomitantly with trastuzumab. Clinical responses differed significantly among subtypes ($p < 0.01$).

Pathological evaluation

The results from pathological evaluation are shown in Table 4. Among the 161 patients, 36 (22.4 %) achieved pCR. pCR was highest (63.0 %) for the HER2-enriched subtype and lowest (6.3 %) for luminal A and B. For the luminal–HER2 hybrid and triple-negative subtypes pCR was 25.0 and 25.7 %, respectively, which was significantly different ($p < 0.01$). The axillary node status also differed significantly among the subtypes ($p = 0.01$).

Table 3 Patient characteristics

	Luminal A and B	Luminal–HER2 hybrid	HER2-enriched	Triple-negative	Total
Number of patients	79	20	27	35	161
Median age (range)	46 (31-66)	49 (33-66)	58 (31-83)	52 (27-77)	50 (27-83)
Median tumor size (range) (cm)	3.5 (1.6-7.5)	3.1 (1.3-6.8)	3.5 (1.2-6.5)	3.1 (1.5-7.5)	3.3 (1.2-7.5)
Clinical axillary node status					
Metastasis	59 (74.7 %)	14 (70.0 %)	21 (77.8 %)	29 (82.9 %)	123 (76.4 %)
No metastasis	20 (25.3 %)	6 (30.0 %)	6 (22.2 %)	6 (17.1 %)	38 (23.6 %)
Clinical stage					
2	56 (70.9 %)	16 (80.0 %)	16 (59.3 %)	26 (74.3 %)	114 (70.8 %)
3	23 (29.1 %)	4 (20.0 %)	11 (40.7 %)	9 (25.7 %)	47 (29.2 %)
Regimen of neoadjuvant chemotherapy					
Anthracycline based (without taxane)	5 (6.3 %)	0 (0 %)	0 (0 %)	4 (11.4 %)	9 (5.6 %)
Taxane based (without anthracycline)	0 (0 %)	1 (5 %)	2 (7.4 %)	1 (2.9 %)	4 (2.5 %)
Anthracycline followed by taxane	73 (92.4 %)	19 (95 %)	25 (92.6 %)	30 (85.7 %)	147 (91.3 %)
Anthracycline concurrently with taxane	1 (1.3 %)	0 (0 %)	0 (0 %)	0 (0 %)	1 (0.6 %)
Trastuzumab concurrently with taxane	0 (0 %)	20 (100 %)	27 (100 %)	0 (0 %)	47 (29.2 %)
Clinical response					
Complete response	5 (6.3 %)	3 (15.0 %)	11 (40.7 %)	8 (22.9 %)	27 (16.8 %)
Partial response	60 (76.0 %)	15 (75.0 %)	16 (59.3 %)	21 (60.0 %)	112 (69.6 %)
Stable disease	14 (17.7 %)	2 (10.0 %)	0 (0 %)	4 (11.4 %)	20 (12.4 %)
Progressive disease	0 (0 %)	0 (0 %)	0 (0 %)	2 (5.7 %)	2 (1.2 %)

Complete response, disappearance of target lesion; Partial response, at least 30 % decrease in the longest diameters of target lesion; Progressive disease, at least 20 % increase in the longest diameter of target lesion; Stable disease, neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease

Table 4 Pathological evaluation

	Luminal A and B	Luminal–HER2 hybrid	HER2-enriched	Triple-negative	Total
Evaluation of pCR					
No pCR	74 (93.7 %)	15 (75.0 %)	10 (37.0 %)	26 (74.3 %)	125 (77.6 %)
pCR	5 (6.3 %)	5 (25.0 %)	17 (63.0 %)	9 (25.7 %)	36 (22.4 %)
Axillary node status					
Metastasis	29 (36.7 %)	7 (35.0 %)	3 (11.1 %)	18 (51.4 %)	57 (35.4 %)
No metastasis	50 (63.3 %)	13 (65.0 %)	24 (88.9 %)	17 (48.6 %)	104 (64.6 %)
Evaluation of breast and axilla					
Invasive component remaining	74 (93.7 %)	16 (80.0 %)	12 (44.4 %)	29 (82.9 %)	131 (81.4 %)
No invasive component	5 (6.3 %)	4 (20.0 %)	15 (55.6 %)	6 (17.1 %)	30 (18.6 %)

pCR pathological complete response

Neoadjuvant response index

The mean NRI for all patients was 0.45. Thirty patients (18.6 %) had an NRI of 1 and 36 (22.4 %) had an NRI of 0. Figure 1 shows a waterfall plot of the NRI according to each subtype. Distribution of the NRI differed among subtypes ($p < 0.01$). Patients with the HER2-enriched subtype and those who received trastuzumab had a higher mean NRI, reflecting a high pCR. The luminal A and B subtype was associated with a lower NRI (mean 0.27), and approximately one-third (27 of 79) of the patients had an NRI of 0.

Survival analysis

The mean follow-up period was 2.45 years (median 2.25 years). The follow-up periods did not differ among subtypes ($p = 0.15$) or between pCR cases and no pCR cases ($p = 0.58$). Five-year disease-free survival (DFS) and overall survival (OS) for all 161 patients were 75.6 and

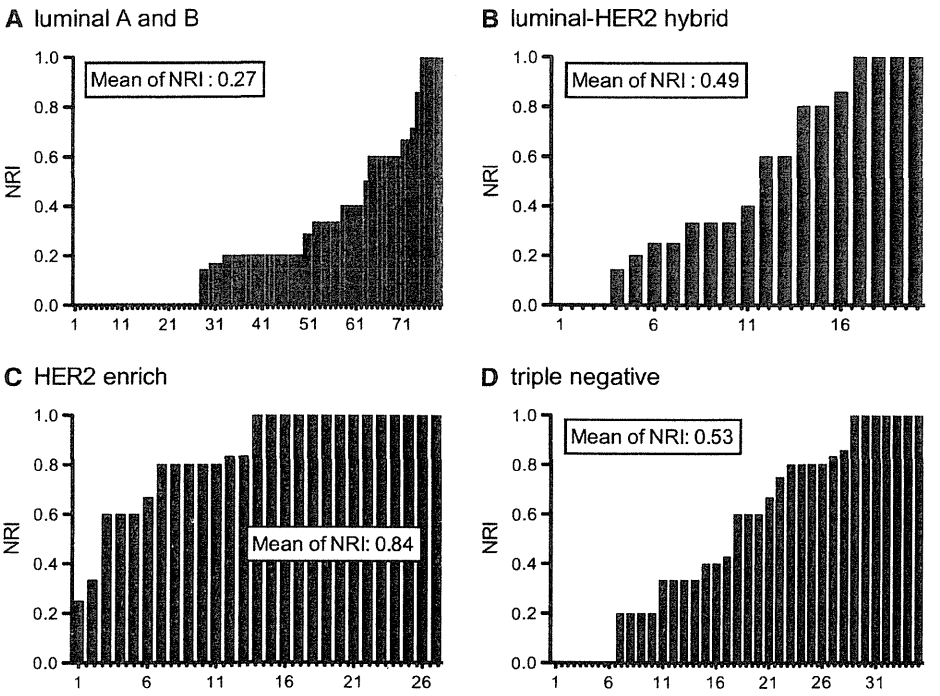

Fig. 1 Distribution of neoadjuvant response index markers

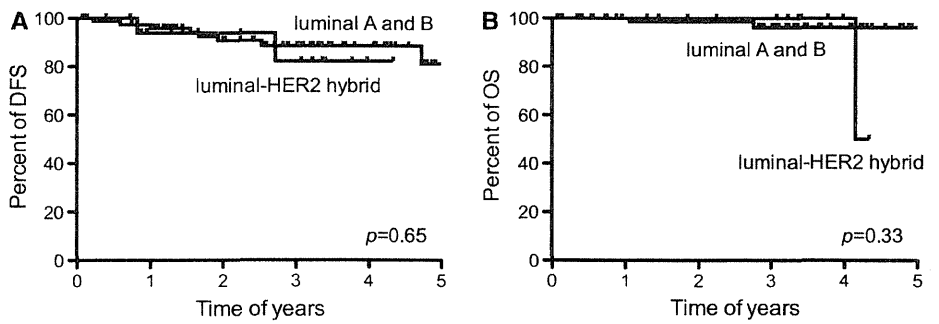

Fig. 2 Kaplan–Meier estimates of disease-free and overall survival for the ER-positive subtype. **a** Disease-free survival for the luminal A and B and luminal–HER2 hybrid subtypes ($p = 0.65$). **b** Overall survival for the luminal A and B and luminal–HER2 hybrid subtypes ($p = 0.33$)

86.9 %, respectively. To examine the effect of trastuzumab, we compared the survival results separately on the basis of ER status. Figures 2 and 3 show the Kaplan–Meier survival estimates for each subtype. Estimated DFS and OS for luminal A and B were 81.0 and 96.2 %, respectively, and those for luminal–HER2 hybrid were 82.0 and 50.0 %, respectively (Fig. 2). Survival was no different for patients with luminal A and B tumors and those with luminal–HER2 hybrid tumors. Estimated DFS and OS for HER2-enriched were 77.6 and 84.0 %, respectively, and those for triple-negative were 62.5 and 71.9 %, respectively (Fig. 3). Although DFS and OS were slightly better for patients with HER2-enriched tumors than for those with triple-negative tumors, the differences were not significant ($p = 0.33$ and 0.18, respectively). Next, we examined the correlation between pCR and clinical outcomes on the basis of DFS and OS. Achievement of pCR was not correlated with clinical outcome for patients with ER-positive tumors (luminal A and B and luminal–HER2 hybrid) (Fig. 4), whereas clinical outcome for patients with ER-negative tumors (HER2-enriched and triple-negative) seemed better for patients achieving pCR (Fig. 5), but the difference was statistically significant only for DFS for the HER2-enriched subtype ($p = 0.04$).

Discussion

Our study showed that pathological and survival results differed substantially among breast cancer subtypes. Addition of trastuzumab to conventional neoadjuvant chemotherapy regimens for patients with HER2-positive diseases resulted in a high pCR, especially for the HER2-enriched subtype. The discussion below will focus on

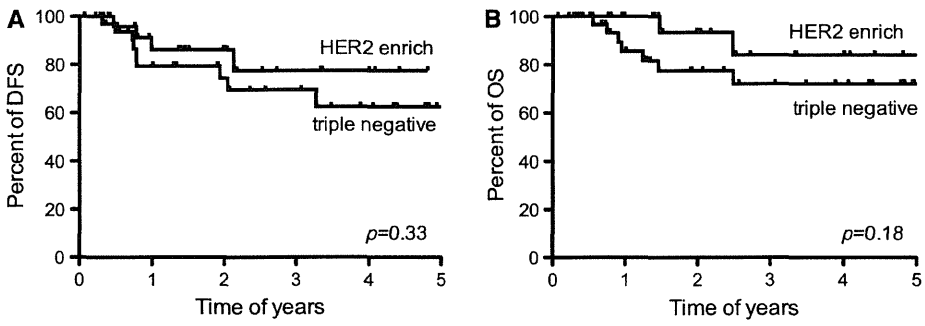

Fig. 3 Kaplan–Meier estimates of disease-free and overall survival for ER-negative subtypes. **a** Disease-free survival for the HER2-enriched and triple-negative subtypes ($p = 0.33$). **b** Overall survival for the HER2-enriched and triple-negative subtypes ($p = 0.18$)

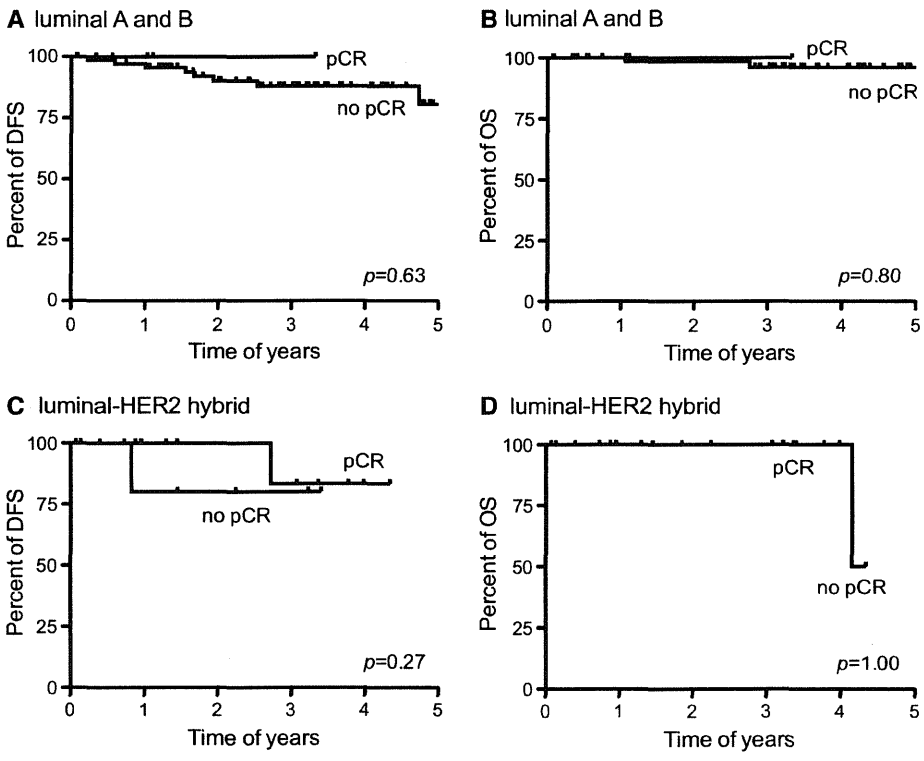

Fig. 4 Correlations between pCR and disease-free and overall survival for the ER-positive subtypes. **a** Disease-free survival for the luminal A and B subtype ($p = 0.63$). **b** Overall survival for the luminal A and B subtype ($p = 0.80$). **c** Disease-free survival for the luminal–HER2 hybrid subtype ($p = 0.27$). **d** Overall survival for the luminal–HER2 hybrid subtype ($p = 1.00$)

neoadjuvant chemotherapy combined with trastuzumab for HER2-positive breast cancer.

Trastuzumab combined with chemotherapy has improved survival in HER2-positive breast cancer in both adjuvant [8] and metastatic settings [9]. The choice of neoadjuvant chemotherapy should be based on the same criteria as those used for the selection of postoperative adjuvant treatments [10]. It is reasonable to treat HER2-positive cases with an anti-HER2 drug in a neoadjuvant setting. Several trials have reported that addition of trastuzumab to neoadjuvant chemotherapy regimens resulted in pCR of 31.7–66.7 % [6, 11–13]. pCR for patients with HER2-positive diseases who received trastuzumab was higher than for those in control groups [6, 11].

In our study, pCR was different for the 2 HER2-positive subgroups. Patients with HER2-enriched tumors had the highest pCR (63.0 %), compared with only 25.0 % for patients with luminal–HER2 hybrid tumors. Previously, ER status has been shown to be correlated with pCR in some studies but not in others. Buzdar et al. [11, 14] reported that pCR was similar for ER-positive and ER-negative tumors, in contrast with their previous experience. Other studies have obtained different pCR for different ER status [15]. Among Japanese women with HER2-positive breast cancer, pCR differed between ER-positive and ER-negative tumors, although the study group did not receive trastuzumab [16]. Although these results suggested that ER status affects the chemosensitivity of HER2-positive tumors, several clinical trials in adjuvant and metastatic settings have demonstrated that additional trastuzumab treatment had a survival benefit irrespective of hormonal status [17, 18]. Thus, addition of trastuzumab to neoadjuvant chemotherapy should be

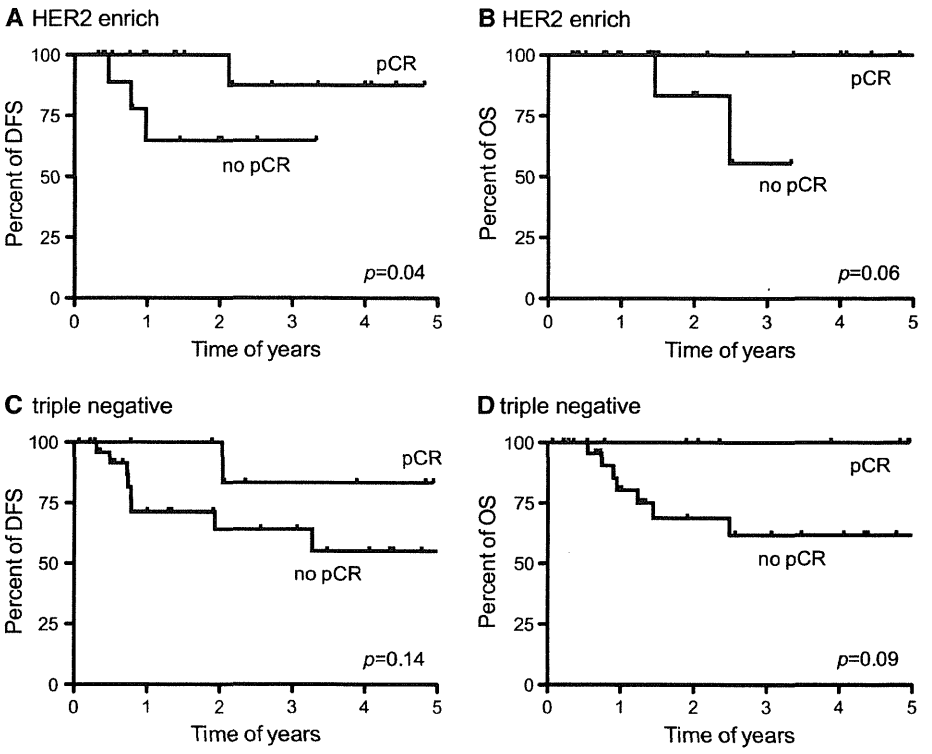

Fig. 5 Correlation between pCR and disease-free and overall survival for the ER-negative subtypes. **a** Disease-free survival for the HER2-enriched subtype ($p = 0.04$). **b** Overall survival for the HER2-enriched subtype ($p = 0.06$). **c** Disease-free survival for the triple-negative subtype ($p = 0.14$). **d** Overall survival for the triple-negative subgroup ($p = 0.09$)

considered for patients with HER2-positive tumors, irrespective of ER status.

In addition to pCR, we also calculated the NRI as a measure of response to neoadjuvant chemotherapy. The NRI is a continuous scale based on a simple scoring system developed by Rodenhuis et al. [7]. The NRI can be used to estimate the degree of downstaging on the basis of a score of 0–1. A minimum score of 0 suggests no response whereas the maximum score, 1, indicates pCR of both the breast and axilla. Although race of patients and chemotherapy regimens differed, NRI distribution of the 161 patients, shown in Fig. 1, resembled that of the study by Rodenhuis et al.

There are several theoretical advantages of neoadjuvant chemotherapy, including tumor shrinkage, which could potentially increase the feasibility of breast-conserving surgery for women with operable breast cancer. Other advantages include acquisition of information on in-vivo tumor responses and the ability to define putative short-term surrogate response markers to predict long-term outcomes. Evaluation of the effectiveness of neoadjuvant chemotherapy should be based on not only pCR but also on survival.

Few studies have documented survival after neoadjuvant chemotherapy with trastuzumab for patients with HER2-positive breast cancer. Although randomized trials have established the effect of neoadjuvant chemotherapy and demonstrated that pCR is a surrogate marker of better long-term survival [1, 3], the subjects in these studies were enrolled without regard to HER2 status.

The Kaplan–Meier survival analyses in our study suggested there were some differences among ER status. In patients with ER-negative tumors (HER2-enriched and triple-negative), clinical outcomes for the HER2-enriched group were slightly, but not significantly, better than those for the triple-negative group. Patients with HER2-positive diseases were given additional trastuzumab cycles to complete 1 year of treatment in accordance with the herceptin adjuvant trial protocol [19]; this must be one of the reasons for the survival benefit in addition to the efficacy of trastuzumab-containing neoadjuvant chemotherapy. A survival benefit of additional trastuzumab was unclear for patients with ER-positive tumors (luminal A and B and luminal–HER2 hybrid groups). The correlation between pCR and survival benefit also seemed to differ with ER status. Achieving pCR was a good predictor of better survival for patients with ER-negative tumors, but whether pCR could be used to predict survival was unclear for patients with ER-positive tumors. One possible reason for this difference is that adjuvant endocrine therapy can also improve clinical outcome for patients who do not achieve pCR. In the luminal–HER2 hybrid group, endocrine therapy was administered as an adjuvant therapy in addition to chemotherapy and trastuzumab; however, the therapeutic benefits of the additional endocrine therapy remain uncertain. Although several clinical studies have suggested a low response of HER2-positive tumors to endocrine therapy, consistent evidence is lacking. Physiological cross-talk

between the HER2 and ER signaling pathways might be involved. It has been hypothesized that the HER2-signaling network may affect the sensitivity of estrogen-dependent tumors to antiestrogen therapy. Although the reasons for these differences in response and survival remain unclear, future studies should investigate appropriate combinations of endocrine therapy, chemotherapy, and trastuzumab.

There were some limitations in our study. First, this study used a relatively small sample size because this was a retrospective study performed in a single institution. Second, recurrence and mortality were insufficient for multivariate analysis on the basis of classic clinicopathological factors (tumor size, nodal status, and grade). Therefore, our results should be interpreted cautiously. Although future clinical trials would overcome these disadvantages, we believe our results could be useful in clinical practice.

In conclusion, our assessment of efficacy and survival for patients with HER2-positive breast cancer receiving neoadjuvant chemotherapy including trastuzumab suggested that treatment response differs among disease subtypes. Our findings suggest that the results of studies evaluating responses to neoadjuvant chemotherapy should be evaluated on the basis of disease subtype, particularly when assessing a correlation between pCR and outcome.

Conflict of interest The authors declare that they have no conflict of interest.

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