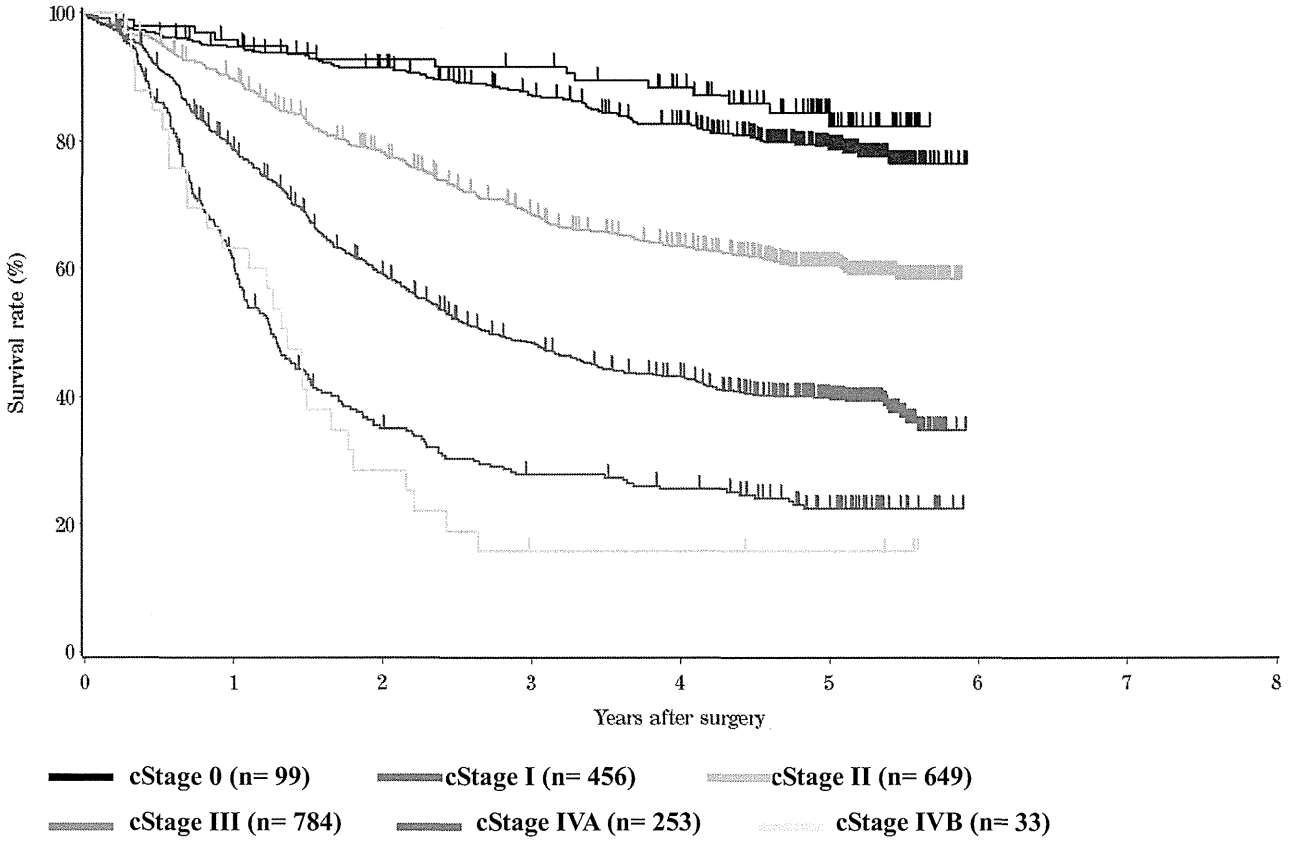
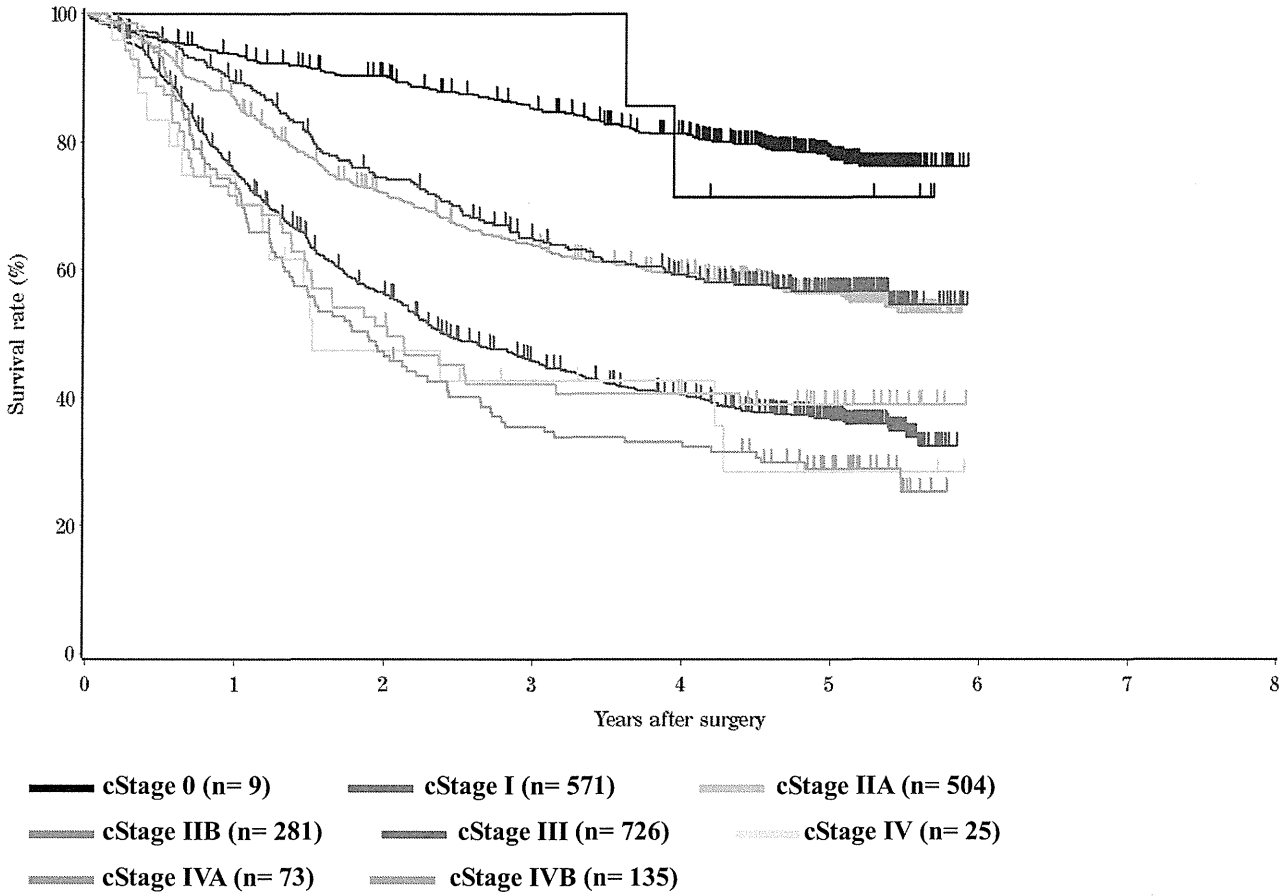


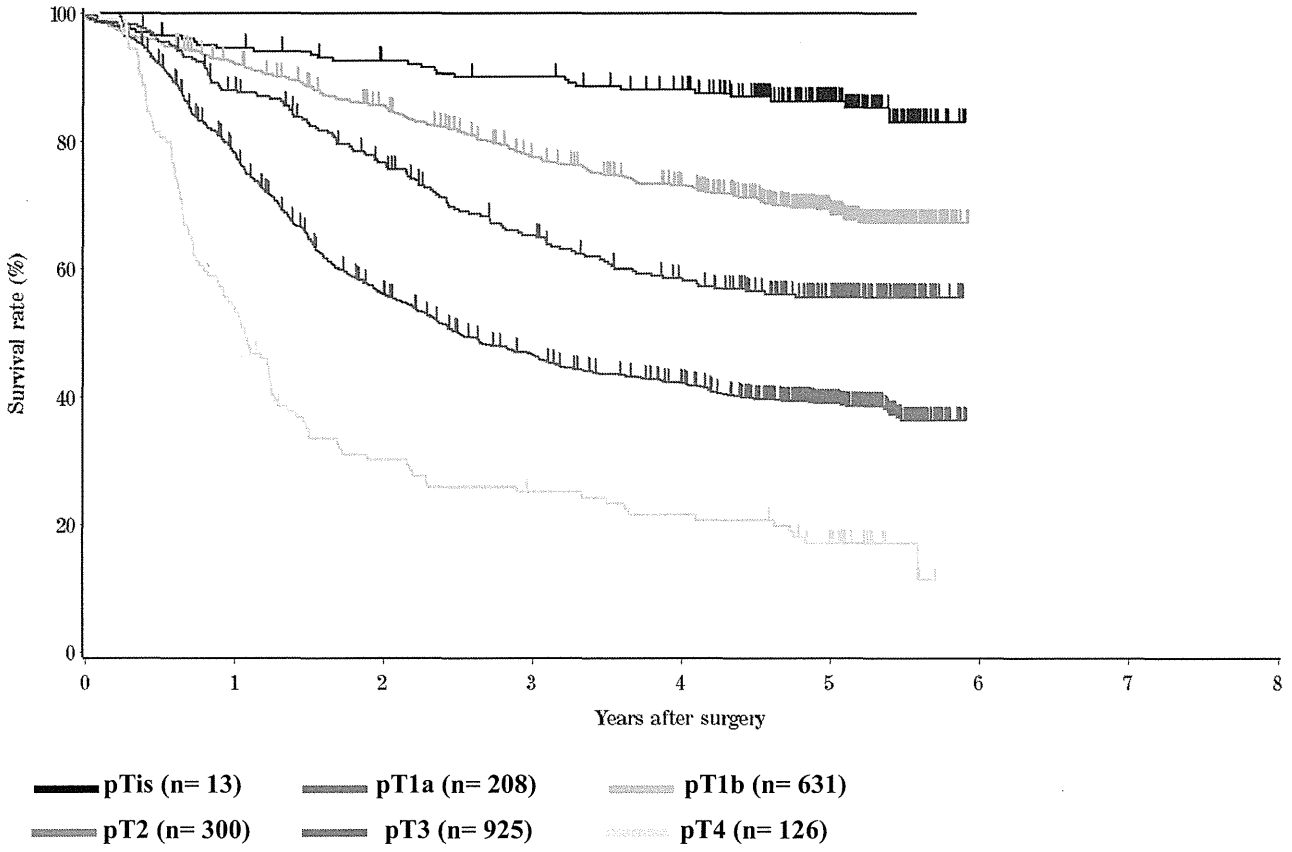
	Years after surgery							
	1	2	3	4	5	6	7	8
cStage 0	95.9%	92.7%	91.7%	88.4%	82.4%	-	-	-
cStage I	94.7%	91.5%	87.1%	82.7%	78.8%	-	-	-
cStage II	89.8%	78.2%	68.7%	63.6%	60.5%	-	-	-
cStage III	78.6%	59.2%	48.4%	43.2%	39.9%	-	-	-
cStage IVA	61.2%	35.0%	27.8%	25.6%	22.5%	-	-	-
cStage IVB	63.2%	28.5%	15.8%	15.8%	15.8%	-	-	-

Fig. 9 Survival of patients underwent esophagectomy according to clinical stage (JES TNM 10th)



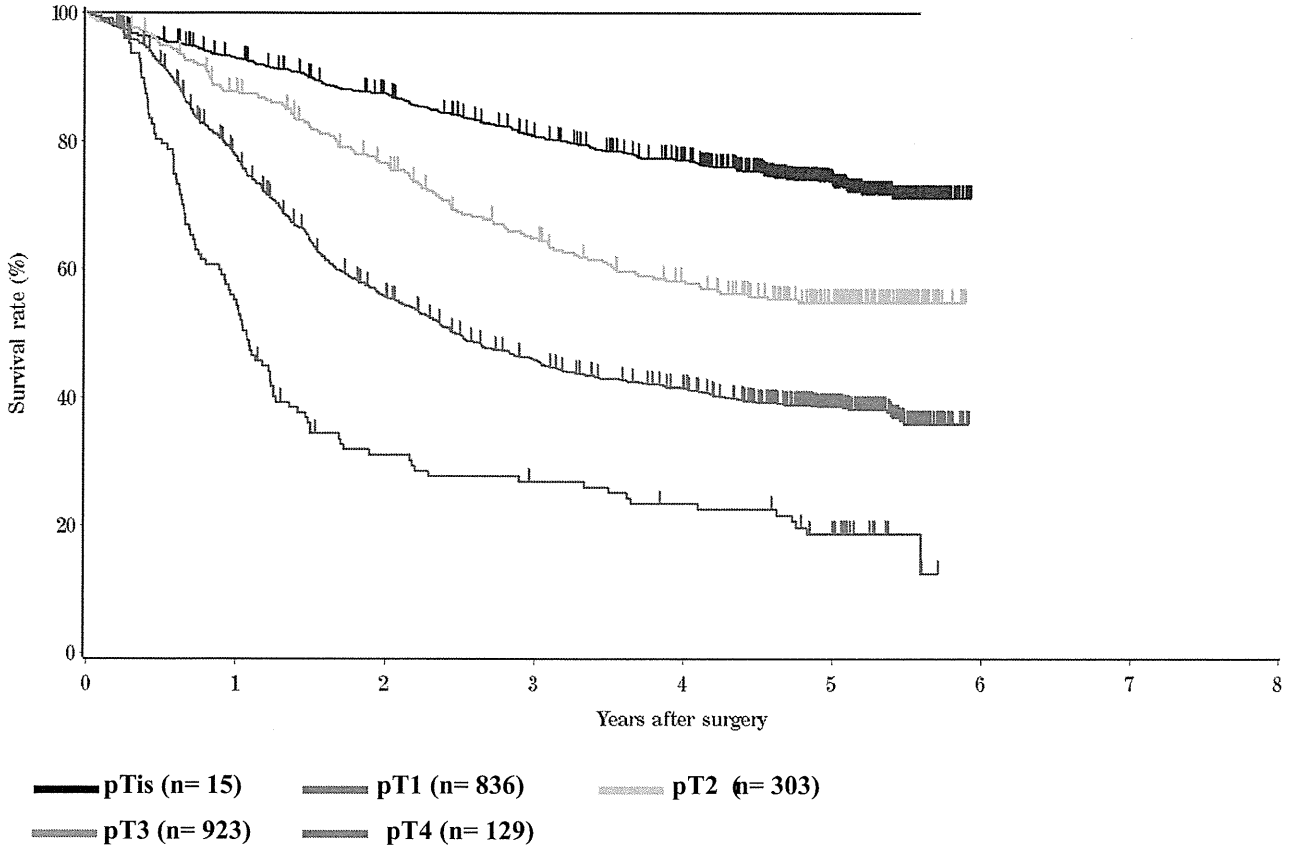
	Years after surgery							
	1	2	3	4	5	6	7	8
cStage 0	100.0%	100.0%	100.0%	71.4%	71.4%	-	-	-
cStage I	93.8%	90.4%	85.1%	81.3%	77.2%	-	-	-
cStage IIA	86.5%	72.0%	63.9%	59.5%	56.3%	-	-	-
cStage IIB	89.3%	74.5%	65.2%	59.3%	56.7%	-	-	-
cStage III	75.5%	56.2%	45.8%	40.6%	36.9%	-	-	-
cStage IV	70.5%	47.4%	42.7%	42.7%	28.5%	-	-	-
cStage IVA	71.7%	51.2%	42.2%	40.7%	39.0%	-	-	-
cStage IVB	73.6%	46.5%	35.5%	33.1%	29.0%	-	-	-

Fig. 10 Survival of patients underwent esophagectomy according to clinical stage (UICC TNM 6th)



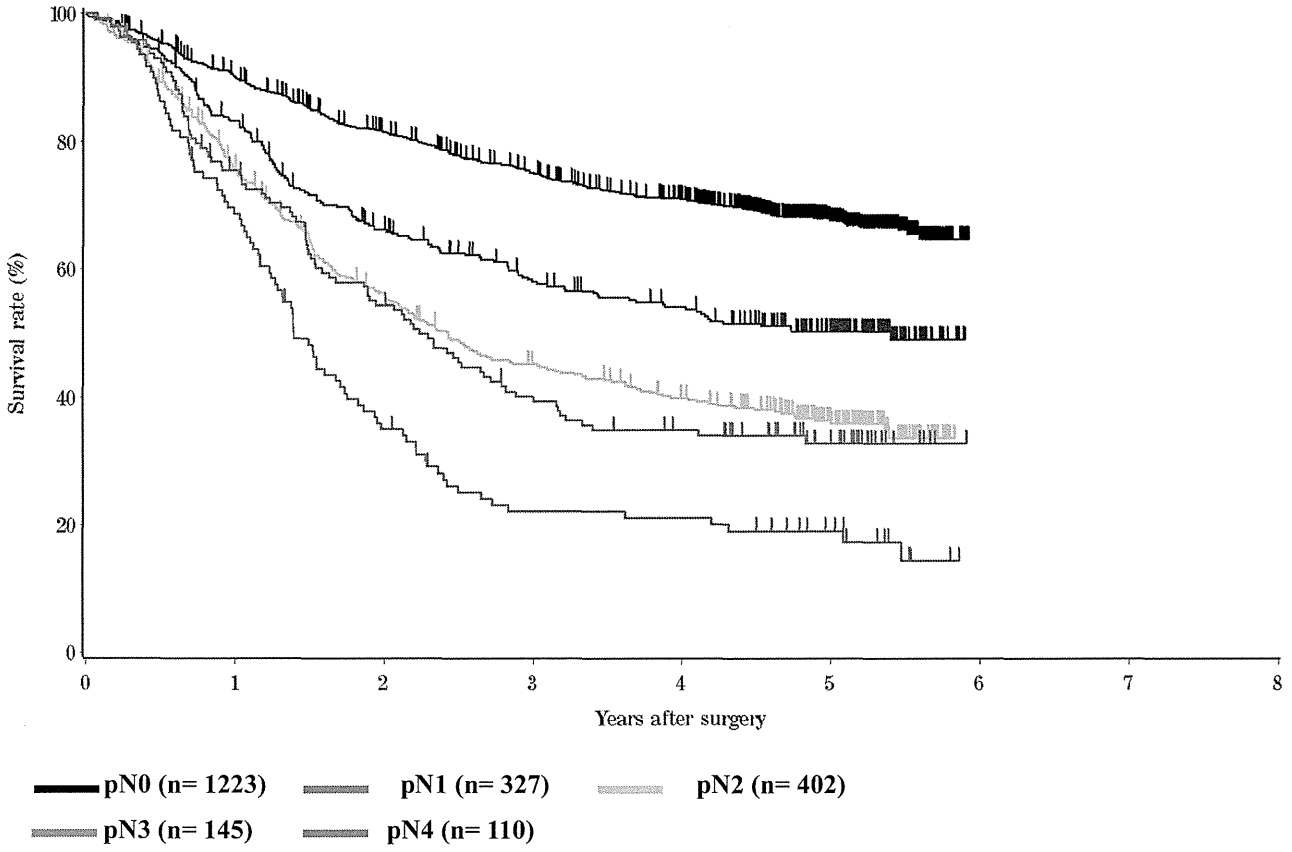
	Years after surgery							
	1	2	3	4	5	6	7	8
pTis	100.0%	100.0%	100.0%	100.0%	100.0%	-	-	-
pT1a	94.6%	92.7%	89.3%	88.1%	86.3%	81.1%	-	-
pT1b	92.1%	85.5%	77.4%	73.2%	68.8%	-	-	-
pT2	88.0%	76.7%	65.3%	58.5%	55.6%	-	-	-
pT3	78.1%	56.1%	46.5%	42.2%	39.1%	-	-	-
pT4	53.3%	30.2%	25.2%	21.7%	17.2%	-	-	-

Fig. 11 Survival of patients underwent esophagectomy according to the depth of tumor invasion: pT (JES TNM 10th)



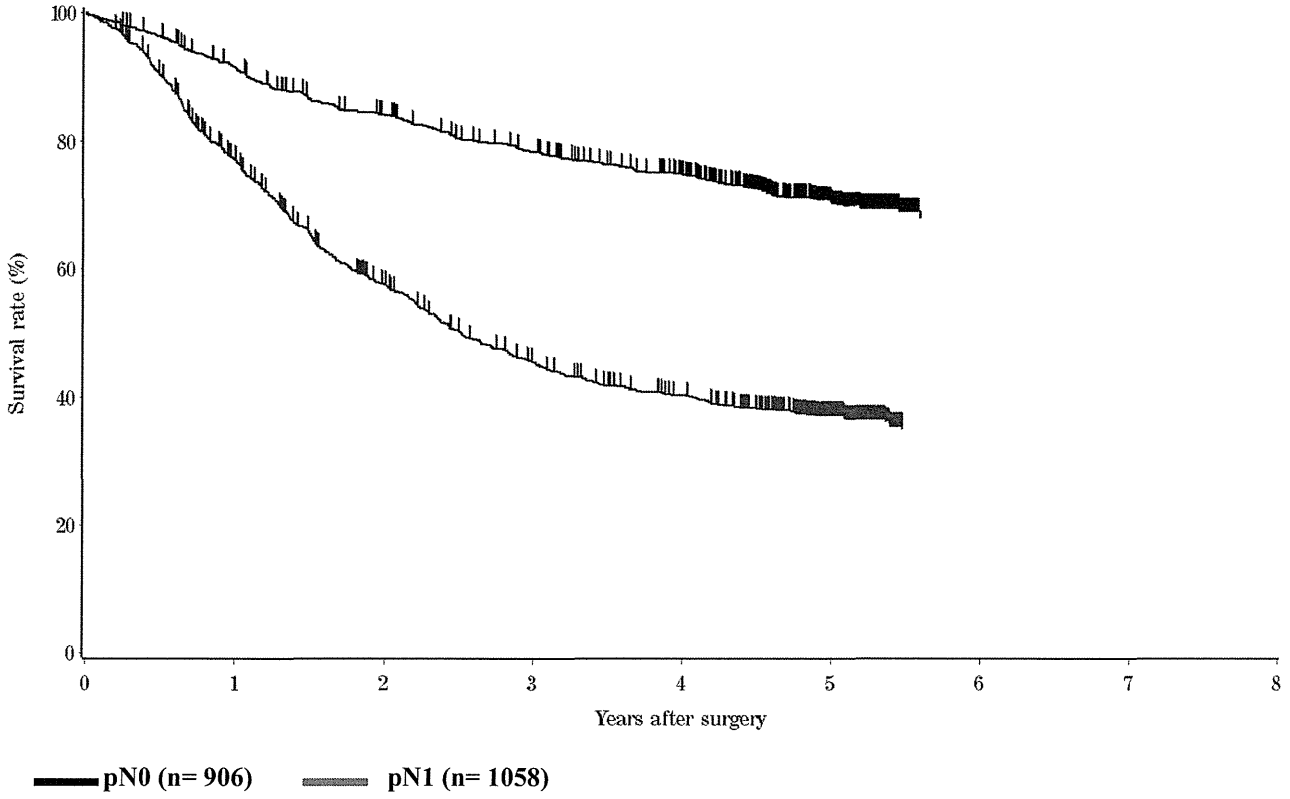
	Years after surgery							
	1	2	3	4	5	6	7	8
pTis	100.0%	100.0%	100.0%	100.0%	100.0%	-	-	-
pT1	92.8%	87.4%	80.7%	77.1%	73.2%	-	-	-
pT2	87.8%	76.6%	64.9%	58.1%	54.9%	-	-	-
pT3	77.6%	55.7%	45.8%	41.5%	38.6%	-	-	-
pT4	54.4%	31.0%	26.8%	23.4%	18.7%	-	-	-

Fig. 12 Survival of patients underwent esophagectomy according to the depth of tumor invasion: pT (UICC TNM 6th)



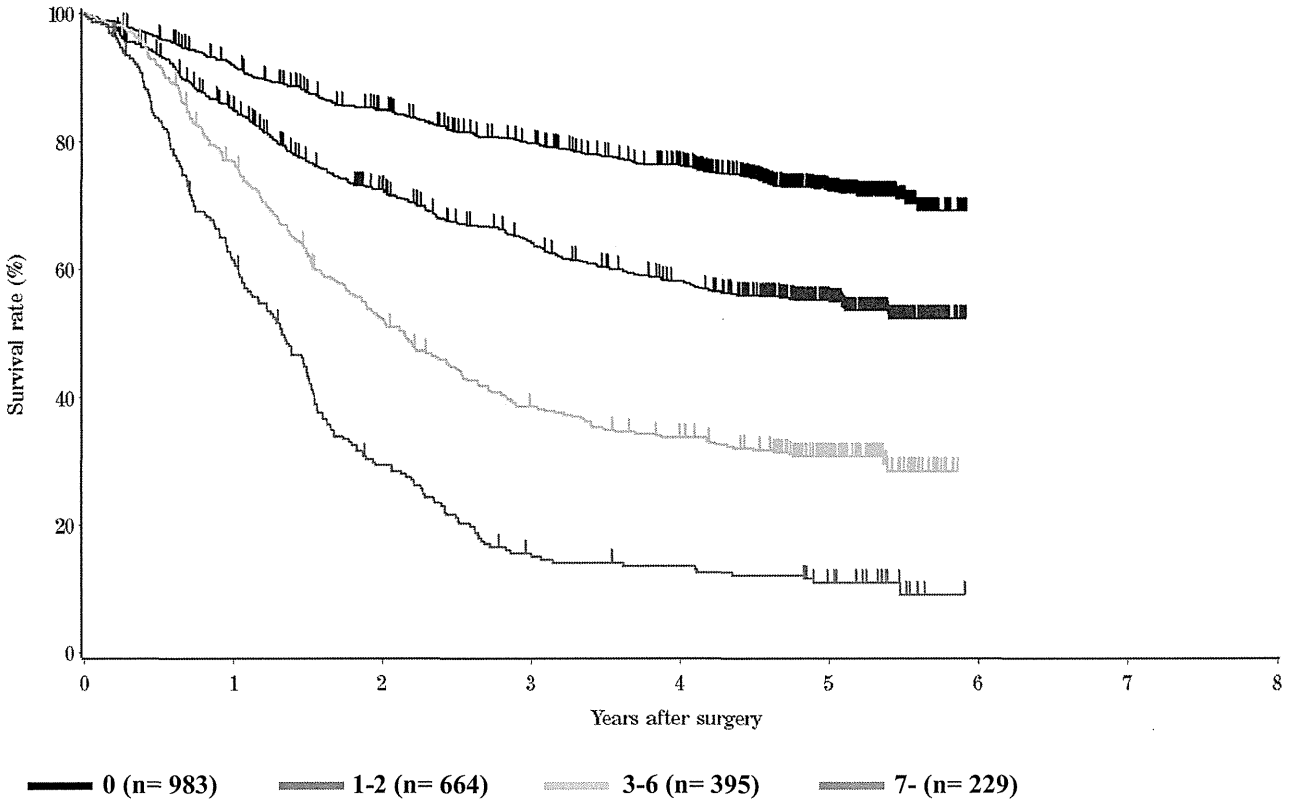
	Years after surgery							
	1	2	3	4	5	6	7	8
pN0	90.0%	81.5%	75.1%	71.1%	67.6%	-	-	-
pN1	83.2%	66.2%	58.0%	54.1%	50.2%	-	-	-
pN2	75.8%	56.0%	45.2%	39.9%	36.3%	-	-	-
pN3	75.5%	54.3%	39.4%	34.8%	32.7%	-	-	-
pN4	68.7%	35.0%	22.1%	21.1%	19.1%	-	-	-

Fig. 13 Survival of patients underwent esophagectomy according to lymph node metastasis: pN (JES TNM 10th)



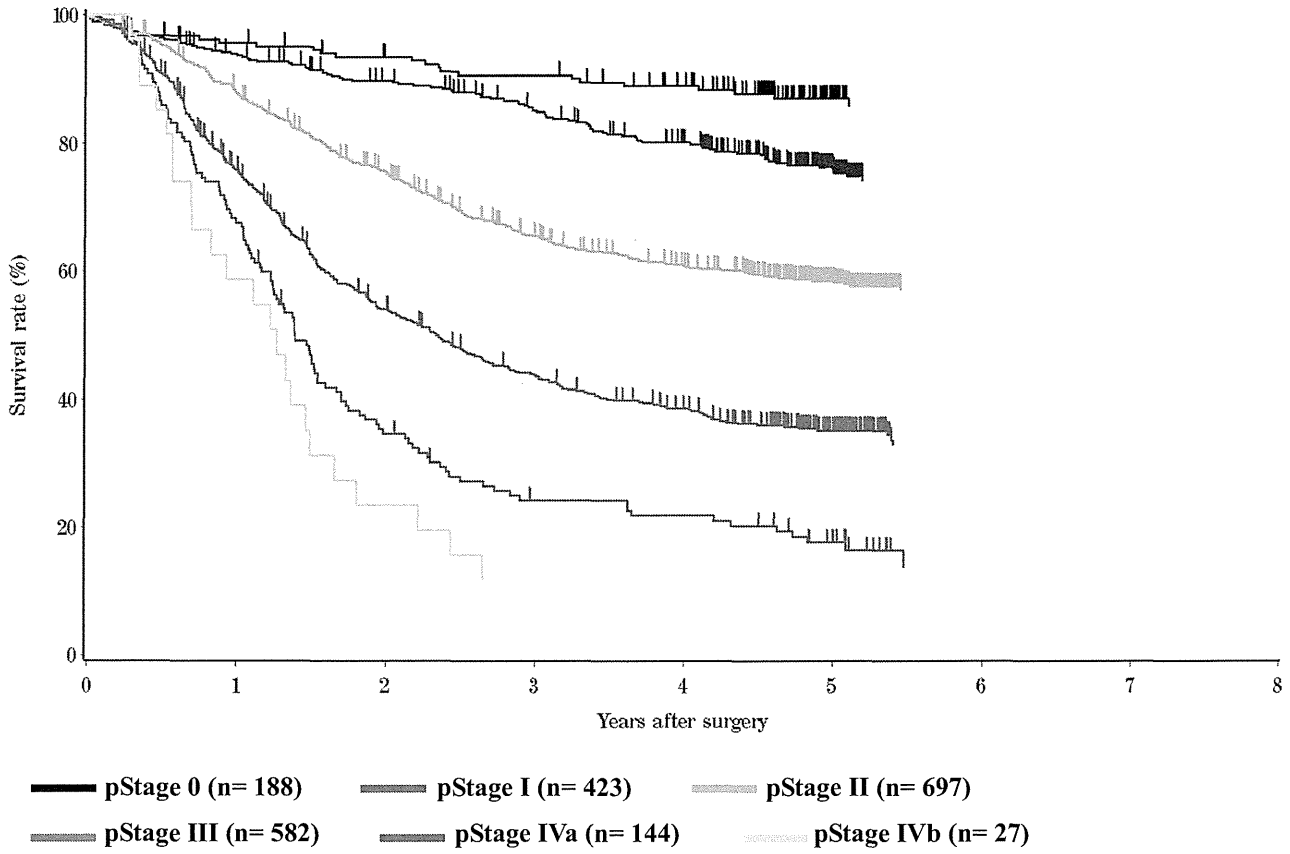
	Years after surgery							
	1	2	3	4	5	6	7	8
pN0	91.5%	84.0%	78.4%	74.9%	70.4%	-	-	-
pN1	77.2%	57.6%	45.4%	40.3%	37.2%	-	-	-

Fig. 14 Survival of patients underwent esophagectomy according to lymph node metastasis: pN (UICC TNM 6th)



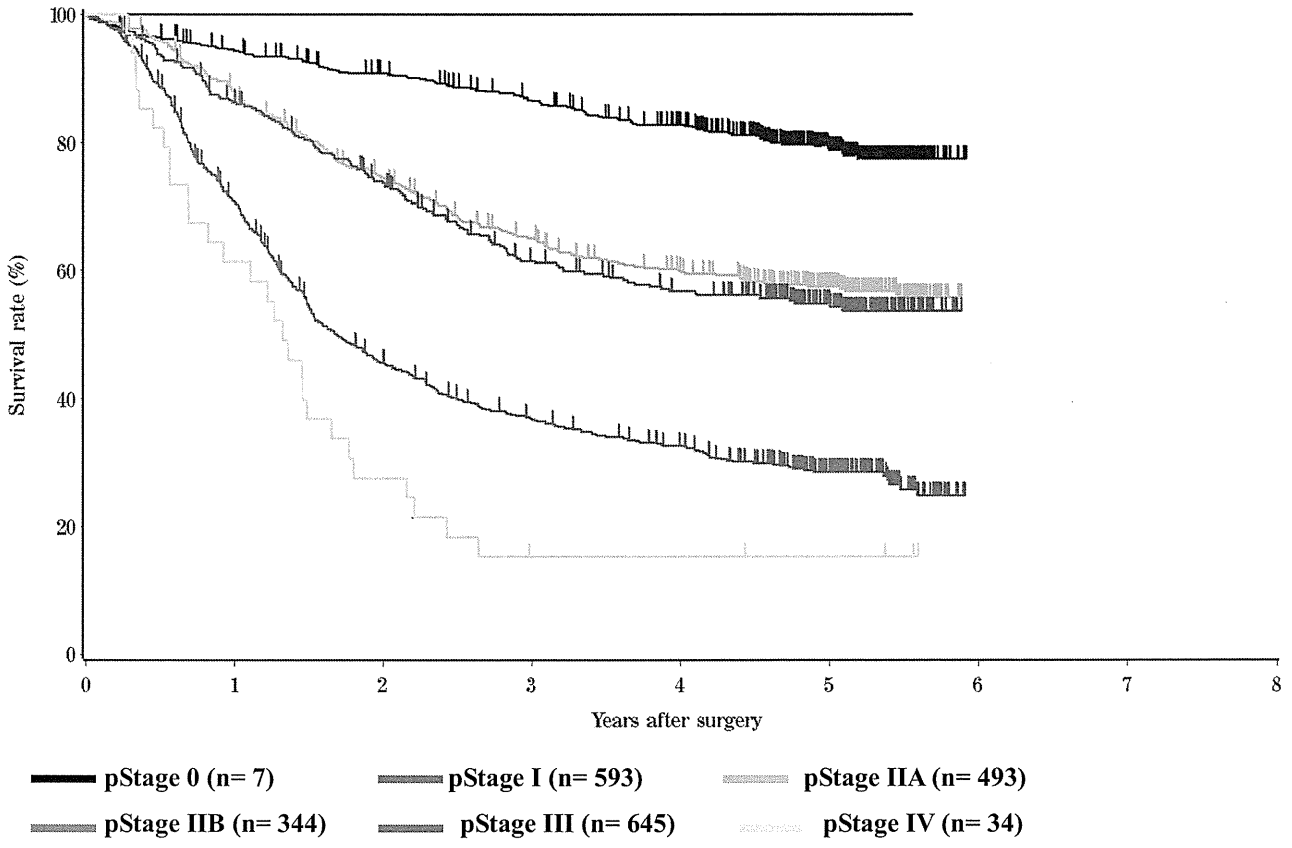
	Years after surgery							
	1	2	3	4	5	6	7	8
0	91.9%	84.9%	79.7%	76.3%	72.1%	-	-	-
1-2	84.8%	72.6%	64.2%	58.1%	55.2%	-	-	-
3-6	76.9%	52.3%	38.6%	33.8%	30.8%	-	-	-
7-	61.5%	29.4%	15.1%	13.6%	11.0%	-	-	-

Fig. 15 Survival of patients underwent esophagectomy according to number of metastatic node



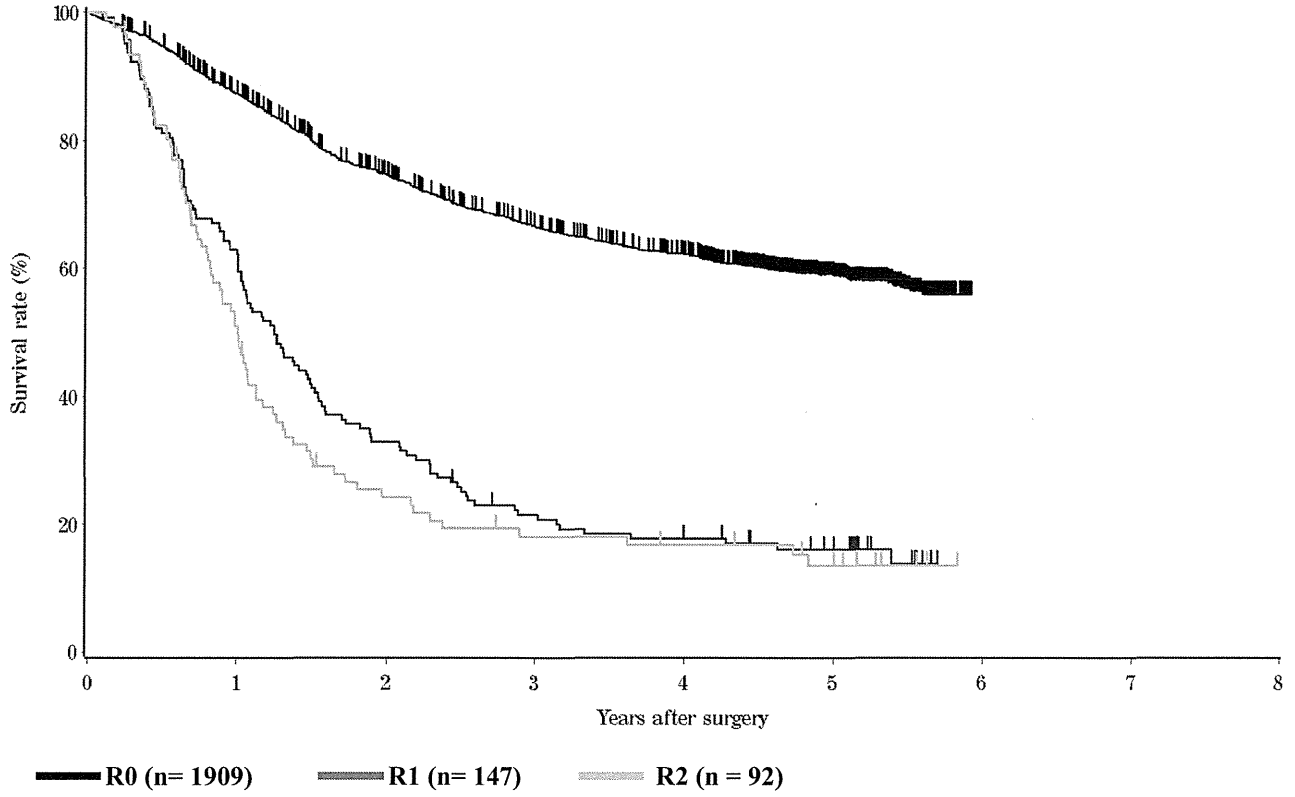
	Years after surgery							
	1	2	3	4	5	6	7	8
pStage 0	95.7%	93.5%	90.7%	89.0%	87.0%	-	-	-
pStage I	93.8%	89.8%	84.9%	80.2%	75.4%	-	-	-
pStage II	87.7%	75.3%	65.6%	60.9%	58.6%	-	-	-
pStage III	75.9%	54.1%	43.6%	38.6%	35.2%	-	-	-
pStage IVa	67.6%	34.7%	24.2%	21.8%	17.7%	-	-	-
pStage IVb	58.6%	23.5%	-	-	-	-	-	-

Fig. 16 Survival of patients underwent esophagectomy according to pathological stage (JES TNM 10th)



	Years after surgery							
	1	2	3	4	5	6	7	8
pStage 0	100.0%	100.0%	100.0%	100.0%	100.0%	-	-	-
pStage I	94.4%	90.8%	86.5%	82.8%	78.8%	-	-	-
pStage IIA	87.8%	74.5%	65.2%	60.0%	57.6%	-	-	-
pStage IIB	86.3%	73.7%	61.6%	56.8%	54.9%	-	-	-
pStage III	70.8%	45.7%	36.8%	32.7%	28.6%	-	-	-
pStage IV	61.4%	27.6%	15.3%	15.3%	15.3%	-	-	-

Fig. 17 Survival of patients underwent esophagectomy according to pathological stage (UICC TNM 6th)



	Years after surgery							
	1	2	3	4	5	6	7	8
R0	87.3%	74.7%	66.5%	62.3%	58.9%	-	-	-
R1	62.3%	32.9%	21.5%	17.8%	16.1%	-	-	-
R2	51.0%	24.2%	18.1%	16.8%	13.6%	-	-	-

Fig. 18 Survival of patients underwent esophagectomy according to residual tumor (R)

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Changes in tumor expression of HER2 and hormone receptors status after neoadjuvant chemotherapy in 21 755 patients from the Japanese breast cancer registry

N. Niikura[1*], A. Tomotaki[2], H. Miyata[2], T. Iwamoto[3], M. Kawai[4], K. Anan[5], N. Hayashi[6], K. Aogi[7], T. Ishida[8], H. Masuoka[9], K. Iijima[10], S. Masuda[11], K. Tsugawa[12], T. Kinoshita[13], S. Nakamura[14] & Y Tokuda[1]

[1]*Department of Breast and Endocrine Surgery, Tokai University School of Medicine, Isehara;* [2]*Department of Healthcare Quality Assessment, Graduate School of Medicine, The University of Tokyo, Tokyo;* [3]*Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama;* [4]*Department of Breast Surgery, Miyagi Cancer Center, Natori;* [5]*Department of Surgery, Kitakyushu Municipal Medical Center, Kitakyushu;* [6]*Department of Breast Surgery, St Luke's International Hospital, Tokyo;* [7]*Department of Breast Surgery, Shikoku Cancer Center, Matsuyama;* [8]*Department of Surgical Oncology, Graduate School of Medicine, Tohoku University, Sendai;* [9]*Sapporo-kotoni Breast Clinic, Sapporo;* [10]*Department of Breast Oncology, Cancer Institute Hospital, Tokyo;* [11]*Department of Pathology, Nihon University School of Medicine, Tokyo;* [12]*Division of Breast and Endocrine Surgery, Department of Surgery, St Marianna University School of Medicine, Kawasaki;* [13]*Department of Breast Surgery, National Cancer Center Hospital, Tokyo;* [14]*Division of Breast Surgical Oncology, Department of Surgery, Showa University School of Medicine, Tokyo, Japan*

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Background: We investigate rates of pathologic complete response (pCR) and tumor expression of ER, PgR, HER2 discordance after neoadjuvant chemotherapy using Japanese breast cancer registry data.

Patients and methods: Records of more than 300 000 breast cancer cases treated at 800 hospitals from 2004 to 2013 were retrieved from the breast cancer registry. After data cleanup, we included 21 755 patients who received neoadjuvant chemotherapy and had no distant metastases. pCR was defined as no invasive tumor in the breast detected during surgery after neoadjuvant chemotherapy. HER2 overexpression was determined immunohistochemically and/or using fluorescence *in situ* hybridization.

Results: pCR was achieved in 5.7% of luminal tumors ($n = 8730$), 24.6% of HER2-positive tumors ($n = 4403$), and 18.9% of triple-negative tumors ($n = 3660$). Among HER2-positive tumors, pCR was achieved in 31.6% of ER-negative tumors ($n = 2252$), 17.0% of ER-positive ones ($n = 2132$), 31.4% of patients who received trastuzumab as neoadjuvant chemotherapy ($n = 2437$), and 16.2% of patients who did not receive trastuzumab ($n = 1966$). Of the 2811 patients who were HER2-positive before treatment, 601 (21.4%) had HER2-negative tumors after neoadjuvant chemotherapy, whereas 340 (3.4%) of the 9947 patients with HER2-negative tumors before treatment had HER2-positive tumors afterward. Of the 10 973 patients with ER-positive tumors before treatment, 499 (4.6%) had ER-negative tumors after neoadjuvant chemotherapy, whereas 519 (9.3%) of the 5607 patients who were ER-negative before treatment had ER-positive tumors afterward.

Conclusion: We confirmed that loss of HER2-positive status can occur after neoadjuvant treatment in patients with primary HER2-positive breast cancer. We also confirmed that in practice, differences in pCR rates between breast cancer subtypes are the same as in clinical trials. Our data strongly support the need for retest ER, PgR, HER2 of surgical sample after neoadjuvant therapy in order to accurately determine appropriate use of targeted therapy.

Key words: breast cancer, chemotherapy, HER2, *in situ* hybridization, neoadjuvant therapy

introduction

In breast cancer patients, neoadjuvant chemotherapy (i.e. presurgical systemic chemotherapy) is associated with rates of disease-free survival and overall survival comparable with those for adjuvant (post-surgical) chemotherapy [1]. It is standard in locally advanced and operable breast cancer, being intended to shrink the tumor and improve the chance for breast-conserving surgery [2]. Pathologic complete response (pCR) is the best predictor of patient outcome after neoadjuvant chemotherapy [2–4]; it is generally defined as the absence of residual invasive cancer in the

Correspondence to: Dr Naoki Niikura, Department of Breast and Endocrine Surgery, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan. Tel: +81-463-93-1121; Fax: +81-463-95-6491; E-mail: niikura@is.icc.u-tokai.ac.jp

breast [5]. Clinical trials have found that different breast cancer subtypes have different rates of pCR and that patients who show pCR have a different prognosis in each subtype. However, in an attempt to improve pCR, clinical trial investigators may use more frequent or standard doses of chemotherapeutic agents than would be used in a routine clinical setting.

The *HER2/neu* gene is amplified in 10%–20% of primary breast cancer cases. In HER2-positive patients, HER2-targeting therapies such as neoadjuvant trastuzumab result in better rates of pCR than non-HER2-targeting therapies [6, 7], as might be expected, HER2-positive patients who show pCR have a better prognosis than those who do not. In the latter, HER2 status may be discordant between the primary breast tumor and those remaining after chemotherapy [8–12]. Some studies suggest that trastuzumab in particular can convert disease status from HER2-positive in a primary tumor to HER2-negative in residual tumors [13–15]. Mittendorf et al. found that according to fluorescence *in situ* hybridization (FISH) analysis, approximately one-third of their patients with sufficient residual disease to warrant repeat HER2 testing had lost *HER2* gene amplification. Furthermore, patients who have lost *HER2* gene amplification have significantly lower relapse-free survival than those whose tumors retain *HER2* gene amplification [15]. Patients with such HER2 status discordance between primary tumors and residual or metastatic ones may also have shorter survival than those without [15, 16]. However, the prevalence of such discordance in patients who have undergone neoadjuvant chemotherapy has not been conclusively established, and it is unclear if trastuzumab increases its likelihood; if so, the treatment may not be suitable for such patients. Using data from the Japanese national breast cancer registry, we aimed to investigate pCR and discordance rates after neoadjuvant chemotherapy in relation to positivity for estrogen receptor (ER), progesterone receptor (PgR), and HER2.

materials and methods

data collection

The Breast Cancer Registry (BCR) in Japan's National Clinical Database (NCD) contains records on more than 300 000 cases of breast cancer from more than 800 hospitals. Affiliated institutes voluntarily provide the BCR with data on newly diagnosed primary breast cancer patients through a Web-based system, covering more than 50 demographic and clinicopathological categories. TNM classification is registered according to the 6th edition of the Unio Internationalis Contra Cancrum (UICC) staging system [17].

The BCR was originally maintained by the Registration Committee of the Japanese Breast Cancer Society (JBCS) and supported by the Public Health Research Foundation (Tokyo). Until 2012, annual reports on this registry were published in Japanese and made accessible to active JBCS members through the JBCS homepage (http://www.jbcs.gr.jp/Member/tourokusyukei.html). Since 2012, this dataset has been part of the NCD, a nationwide project managed in cooperation with the certification board of the Japan Surgical Society [18]. For the year 2011 alone, data from more than 1.2 million surgical cases were collected from more than 3500 hospitals. The NCD is continuously updated by the data management departments of participating institutions and is evaluated annually using a Web-based data management system to ensure data traceability. All variables, definitions, and inclusion criteria for the NCD are accessible to participating institutions on its web site (http://www.ncd.or.jp); the database administrators also provide e-learning systems to teach participants how to input data consistently [18]. The administrators answer all inquiries regarding data entry, having taken ~80 000 inquiries in 2011, and a list of frequently asked questions is displayed on the web site.

For our study, we used the BCR to review 238 840 breast cancer cases treated between 2004 and 2011 and selected 21 755 patients who received neoadjuvant chemotherapy and had no distant metastases (Figure 1). Male patients, those with bilateral tumors, those who did not undergo surgery, and those with tumor stages of Tis or T0, were excluded. pCR was defined as no invasive tumor in the breast found during surgery after neoadjuvant chemotherapy. HER2 overexpression was defined as immunohistochemically 3+ and/or a positive FISH result. Hormone receptor positivity (ER or PgR positivity) was diagnosed if at least 1% of nuclei in the tumor were stained on immunohistochemical tests for ER or PgR. Immunohistochemical tests for ER, PgR, and HER on core biopsies were carried out before neoadjuvant therapy. Cases were categorized on the basis of their immunohistochemical status as follows: luminal (ER+ and HER2−); HER2-overexpressing (HER2+, regardless of ER status); and triple-negative (ER− and HER2−).

statistical analysis

The median and standard deviations were calculated for age at diagnosis. Associations between clinical categorical variables and HER2 status were analyzed using Pearson's χ^2. Fisher's exact test was also used to determine differences between patients who showed HER2 status discordance and those who did not. All analyses were carried out using SAS 9.3 (SAS Institute, Cary, NC).

results

A total of 21 755 patients who received neoadjuvant chemotherapy and developed no distant metastases were listed in Table 1. More than 80% of patients had a tumor of stage T2 or worse, and more than 60% were node-positive. Almost 70% received anthracyclines and taxanes as neoadjuvant chemotherapy.

rate of pCR

The rate of pCR was 5.7% for luminal cancer ($n = 8730$), 24.6% for HER2-positive ($n = 4403$), and 18.9% for triple-negative ($n = 3660$) (Figure 2). Thus, HER2-overexpressing tumors had a higher rate of pCR than triple-negative or luminal ones; however, within this category, the rate was 31.6% for ER-negative tumors ($n = 2252$), 17.0% for ER-positive ones ($n = 2132$), 31.4% for those who received trastuzumab as neoadjuvant chemotherapy ($n = 2437$), and 16.2% for those who did not receive trastuzumab ($n = 1966$) (Figure 2). In addition, HER2-positive patients who were ER-negative had a higher rate of pCR than those who were ER-positive ($P < 0.0001$), and those treated with trastuzumab had a higher rate of pCR than those not so treated ($P < 0.0001$).

rate of discordance after chemotherapy

Of the 2811 patients who were HER2-positive before treatment, 601 (21.4%) had tumors that showed HER2 negativity after neoadjuvant chemotherapy, whereas only 340 (3.4%) of the 9947 patients with HER2-negative pretreatment tumors developed HER2-positive tumors after neoadjuvant chemotherapy (Table 2). According to immunohistochemical testing, 499 (20.4%) of the 2447 patients with HER2-positive tumors lost HER2 positivity after neoadjuvant chemotherapy; with FISH,

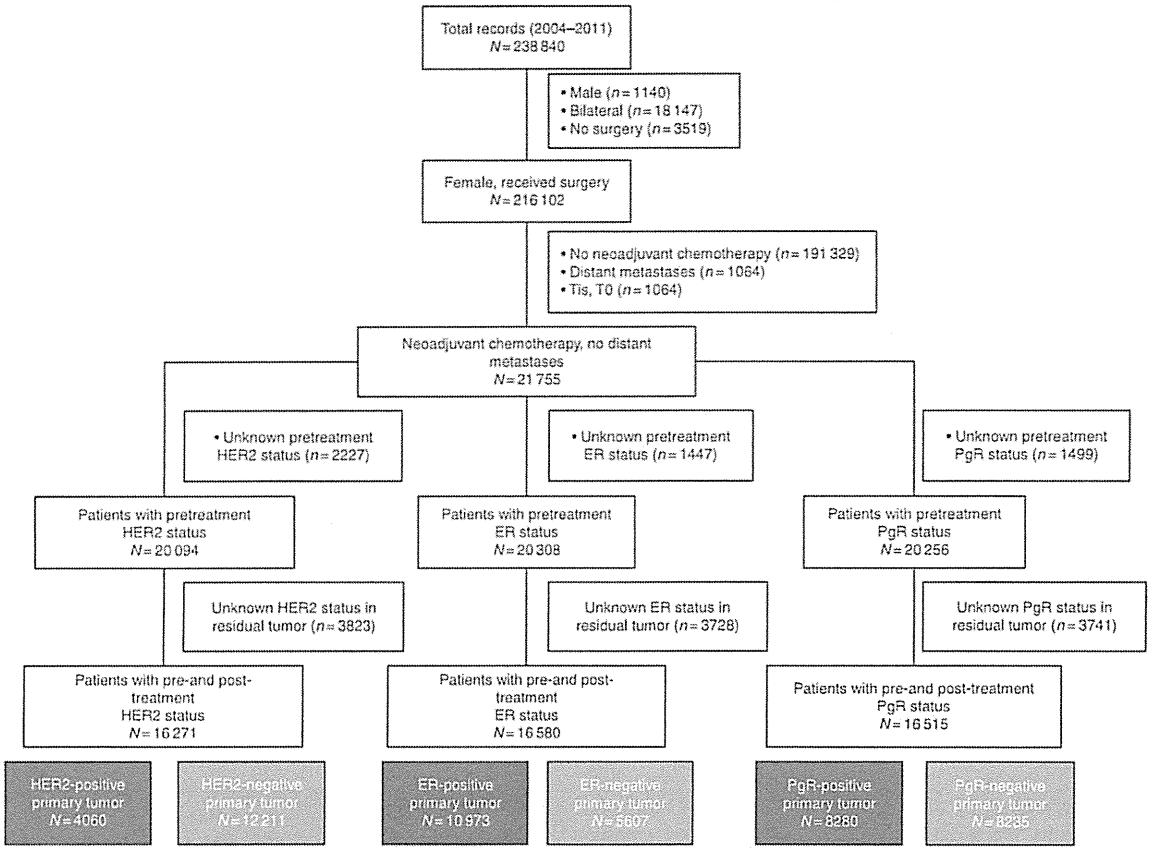

Figure 1. Study flow.

the rate was 8.4% (17/203). Of 342 patients whose tumors converted from HER2-positive to HER2-negative, who received neoadjuvant trastuzumab, 96 (28%) did not receive adjuvant trastuzumab therapy. Conversely, of 340 patients whose tumors converted from HER2-negative to HER2-positive, 206 (60%) received adjuvant trastuzumab therapy.

Of the 10 973 patients with ER-positive tumors before treatment, 499 (4.6%) had ER-negative tumors after neoadjuvant chemotherapy, whereas 519 (9.3%) of the 5607 patients with ER-negative tumors before treatment had ER-positive ones after neoadjuvant chemotherapy. Of the 499 patients whose tumors converted from ER-positive to ER-negative, 280 (56%) did not receive adjuvant endocrine therapy. Conversely, of 519 patients whose tumors converted from ER-negative to ER-positive, 333 (64%) received adjuvant endocrine therapy.

Of the 8280 patients with PgR-positive tumors before treatment, 1545 (18.7%) had PgR-negative ones after neoadjuvant chemotherapy, whereas 766 (9.3%) of the 8235 patients with PgR-negative tumors before treatment had PgR-positive tumors after neoadjuvant chemotherapy (Table 3).

clinicopathologic features associated with discordance

We evaluated HER2 concordance and discordance rates in relation to various clinical factors (Table 4). There were statistically significant differences in HER2 discordance rates between patients who received trastuzumab and those who did not ($P < 0.0001$). Of the 1385 patients who received trastuzumab as neoadjuvant therapy, 342 (24.7%) showed HER2 discordance. Similarly, of the 1426 patients who did not receive trastuzumab as neoadjuvant therapy, 259 (18.2%) showed HER2 discordance. Furthermore, there were statistically significant differences in discordance rates in relation to pretreatment ER status ($P < 0.0001$) and PgR status ($P < 0.0001$). In contrast, there were no statistically significant differences in HER2 discordance rates between premenopausal and menopausal women ($P = 0.440$) or among patients with residual tumors of different volumes ($P = 0.345$).

discussion

To the best of our knowledge, we use largest dataset to compare tumor expression of ER, PgR, HER2 discordance after neoadjuvant chemotherapy. Our pCR rates, obtained in a setting of clinical practice, were lower than those reported in clinical trials. One reason may be that in our study, almost 70% of patients were treated with anthracyclines and taxanes, whereas in clinical trials with a focus on pCR, investigators often test new agents and higher doses, patients in the real world have higher age, and poor performance status than in clinical trials. Another may be that 44% of HER-positive patients did not receive trastuzumab as neoadjuvant therapy; it was not until 2008 that trastuzumab was approved as an adjuvant therapy by the Ministry of Health,

Table 1. Patients Characteristic

		With pretreatment HER2 status ($n = 20\,094$)				With pretreatment ER status ($n = 20\,308$)				With pretreatment PgR status ($n = 20\,256$)			
		Positive ($n = 5535$)		Negative ($n = 14\,559$)		Positive ($n = 12\,938$)		Negative ($n = 7370$)		Positive ($n = 9720$)		Negative ($n = 10\,536$)	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Age	Median		54		51		51		55		49		55
Menopausal status													
	Premenopausal	2079	37.6	6928	47.6	6429	49.7	2679	36.4	5302	54.6	3779	35.9
	Post-menopausal	3289	59.4	7260	49.9	6183	47.8	4468	60.6	4152	42.7	6472	61.4
	Unknown	167	3.0	371	2.6	326	2.5	223	3.0	266	2.7	285	2.7
T stage													
	T1	587	10.6	1772	12.2	1578	12.2	804	10.9	1222	12.6	1157	11.0
	T2	3197	57.8	8288	56.9	7472	57.8	4112	55.8	5673	58.4	5876	55.8
	T3	893	16.1	2071	14.2	1837	14.2	1173	15.9	1346	13.9	1660	15.8
	T4	858	15.5	2428	16.7	2051	15.9	1281	17.4	1479	15.2	1843	17.5
N stage													
	N0	1725	31.2	4793	32.9	4304	33.3	2288	31.0	3353	34.5	3217	30.5
	N1	2807	50.7	7513	51.6	6805	52.6	3631	49.3	5116	52.6	5296	50.3
	N2	582	10.5	1356	9.3	1100	8.5	849	11.5	779	8.0	1169	11.1
	N3	411	7.4	859	5.9	699	5.4	583	7.9	452	4.7	825	7.8
	Unknown	10	0.2	38	0.3	30	0.2	19	0.3	20	0.2	29	0.3
Neoadjuvant chemotherapy													
	CMF alone	2	0.0	12	0.1	9	0.1	5	0.1	7	0.1	7	0.1
	Anthracycline regimen alone	547	9.9	1765	12.1	1502	11.6	851	11.6	1106	11.4	1235	11.7
	TC alone	81	1.5	265	1.8	265	2.1	82	1.1	219	2.3	127	1.2
	Taxane alone	532	9.6	586	4.0	634	4.9	510	6.9	464	4.8	681	6.5
	Anthracycline regimen and taxane	3891	70.3	10 191	70.0	9118	70.5	5097	69.2	6856	70.5	7316	69.4
	Others	482	8.71	1740	11.95	1410	10.90	825	11.19	1068	10.99	1170	11.10

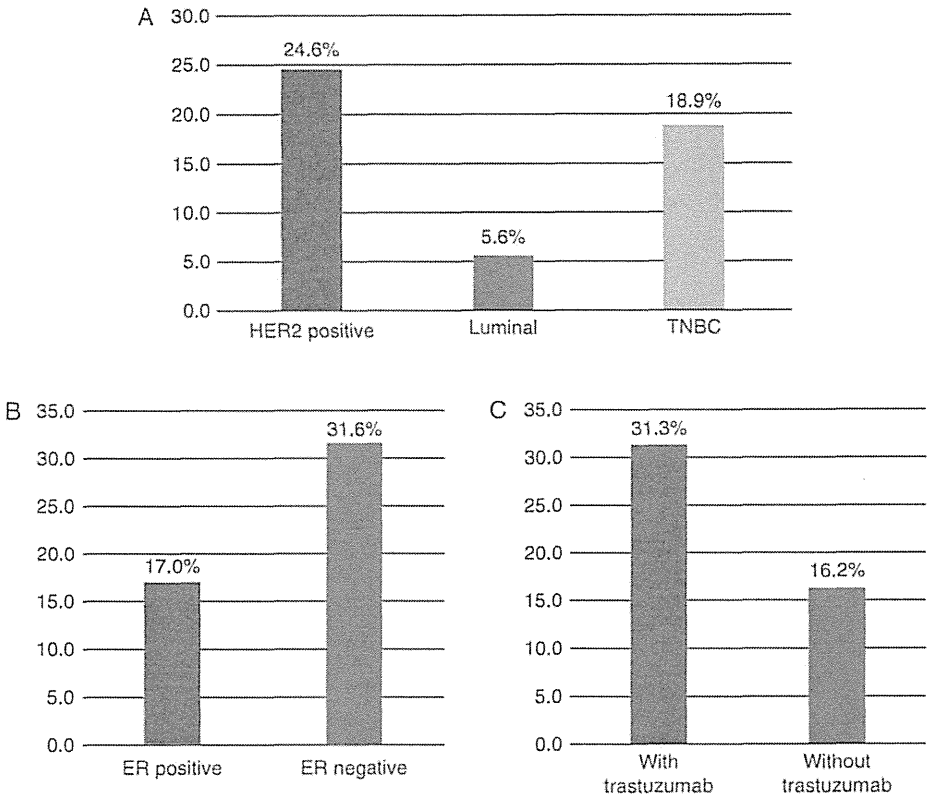

Figure 2. Rates of pathologic complete in response by (A) subtype (HER2-positive, luminal, triple-negative), (B) ER status (for HER2-positive tumors), and (C) treatment with trastuzumab as neoadjuvant therapy (HER2-positive tumors).

Table 2. Change in HER2 status of the primary tumor after neoadjuvant therapy

Primary tumor		Residual tumor	
HER2 status	n	HER2 status	n
Positive	2811	Positive	2210 (78.6%)
		Negative	601 (21.4%)
Negative	9947	Positive	340 (3.4%)
		Negative	9607 (96.6%)
Immunohistochemical analysis			
HER2 3+	2447	HER2 3+	1948 (79.6%)
		HER2 2+	203 (8.3%)
		HER2 1+	163 (6.6%)
		HER2 0	133 (5.4%)
HER2 2+	2077	HER2 3+	128 (6.2%)
		HER2 0, 1+, 2+	1949 (93.8%)
HER2 1+	3741	HER2 3+	68 (1.8%)
		HER2 0, 1+, 2+	3673 (98.2%)
HER2 0	4196	HER2 3+	45 (1.1%)
		HER2 0, 1+, 2+	4151 (98.9%)
FISH analysis			
Positive	203	Positive	186 (91.6%)
		Negative	17 (8.4%)
Negative	572	Positive	28 (4.9%)
		Negative	544 (95.1%)

Labour and Welfare in Japan. However, differences in pCR rates in our study with regard to cancer subtype and trastuzumab treatment were similar to those reported in clinical trials. For instance, patients with luminal tumors had lower pCR rates than those with HER2-positive or triple-negative tumors. Among HER2-positive tumors, tumors negative for hormonal receptors had higher pCR rates after neoadjuvant chemotherapy than those positive for hormonal receptors. HER2-positive, tumors that are negative for hormonal receptors are highly dependent on the *HER2* gene and respond well to therapies targeted against HER2 such as trastuzumab and pertuzumab [19]. As might be expected, HER2-positive, ER-negative patients who show pCR have better prognosis than those who do not [3, 4]. A previous study found that the use of trastuzumab as a neoadjuvant increased pCR rate (43% with trastuzumab, 26% without) in HER2-positive cancer [6]. Our data also showed this.

Our results also showed that HER2 status does not necessarily carry over between the original tumor and residual tumors. In 21.4% of HER2-positive patients, the tumor converted to HER2-negative; further, according to immunohistochemistry, 635 (17.9%) of the 3548 patients with HER2-positive tumors before neoadjuvant chemotherapy had HER2-negative tumors afterward. However, inconsistencies in immunohistochemical testing, for example, in antigen retrieval methods, fixation, and observer analysis, may affect the results [20]. Another study [14, 15] using FISH found a loss of HER2 amplification in paired pre- and post-treatment specimens from patients treated with neoadjuvant trastuzumab. FISH data are more easily reproducible than immunohistochemical data [21, 22], and in our study, although the sample size for FISH analysis was small, FISH data

were less likely to show discordance than immunohistochemical data.

We previously reported that trastuzumab therapy is not associated with an increased chance of loss of HER2 positivity in metastases, whereas chemotherapy is associated with an increase in the loss of such positivity [16]. Likewise, in a previous study of patients with residual disease treated with either chemotherapy alone or chemotherapy plus an anti-HER2 agent, HER2 expression loss was observed in 40% of the former group and 14.7% of the latter group [23]. We demonstrated that trastuzumab therapy is associated with increased odds of loss of HER2 positivity in residual tumors.

Table 3. Change in ER and PgR status of the primary tumor after neoadjuvant therapy

Primary tumor		Residual tumor	
ER status	*n*	ER status	*n*
Positive	10 973	Positive	10 474 (95.5%)
		Negative	499 (4.5%)
Negative	5607	Positive	519 (9.3%)
		Negative	5088 (90.7%)
PgR status			
Positive	8280	Positive	6735 (81.3%)
		Negative	1545 (18.7%)
Negative	8235	Positive	766 (9.3%)
		Negative	7469 (90.7%)

Nevertheless, it is unclear whether loss of HER2 amplification reflects response to therapy or a resistance mechanism and whether chemotherapy can promote clonal selection of *HER2/neu*-amplified cancers. In our study, 28% of patients whose cancer lost HER2 expression after neoadjuvant therapy did not receive trastuzumab, and 60% patients whose cancer developed HER2 expression after therapy did receive it. Possible explanations include true biological change, treatment-induced clonal selection, pre-analytical and analytical pitfalls, sampling errors, and tumor heterogeneity [24]. It is unclear if patients with HER2-negative tumors after neoadjuvant chemotherapy should receive anti-HER2 treatment, as sampling by core needle biopsy in pretreatment settings may not be representative of the character of the whole tumor. If the core needle biopsy proves to be a false positive, discontinuing the drug will avoid risking unnecessary treatment after loss of HER2 amplification after neoadjuvant therapy. However, if the core needle biopsy gives a false-negative result, anti-HER2 treatment should be started as soon as post-therapy HER2 amplification is detected.

We acknowledge several important limitations of this study. First, this study is retrospective, incurring the possibility of selection bias and precluding the determination of causal relationships. However, Japanese BCR data cover more than 50% of patients diagnosed with breast cancer in Japan [25], and therefore, we do not feel that this possibility would have substantially affected our findings. Secondly, our data were obtained through a web database, with no centralized reassessment of ER, PgR or HER2 status. Thirdly, several studies reported discordance ER,

Table 4. Discordance rates by clinical factors

	Post-treatment HER2 status ($N = 2811$)				*P*-value
	Negative (discordance)		Positive (concordance)		
	n	%	*n*	%	Pearson's χ^2
Pretreatment ER status					
Negative	169	13.0	1130	87.0	<0.0001
Positive	427	28.4	1075	71.6	
Pretreatment PgR status					
Negative	263	14.9	1501	85.1	<0.0001
Positive	330	32.0	701	68.0	
Menopausal status					
Pre	245	22.5	846	77.5	0.4626
Post	337	20.6	1301	79.4	
Unknown	19	23.2	63	76.8	
Neoadjuvant trastuzumab					
No	259	18.2	1167	81.8	<0.0001
Yes	342	24.7	1043	75.3	
Volume of residual tumor					
<50%	265	22.3	923	77.7	0.3436
>50%	313	20.8	1192	79.2	
Year of registration					
2004–2007	159	18.95	680	81.05	0.0405
2008–2011	442	22.41	1530	77.59	
Surgical cases at institution					
>100 cases/year	277	19.74	1126	80.26	0.0346
<100 cases/year	324	23.01	1084	76.99	

Volume of residual tumor: size of residual tumor divided by size of primary tumor.

PgR, HER2 status between core needle biopsy, and resection specimens without neoadjuvant chemotherapy [26]. Finally, our registry data did not include sufficient survival data to fully analyze the effects of pCR and tumor expression discordance on survival. However, the strength of our study is that it draws from more than 20 000 patients treated with neoadjuvant chemotherapy in a 'real-world' setting.

In conclusion, our findings demonstrate that although pCR rates in the real world have the same differences with regard to subtypes and trastuzumab treatment that are seen in clinical trials, they are also lower than those in clinical trials. Further, we have shown that HER2 status does not always carry over from the original tumor to residual tumors. In our study, more than 20% of patients with residual tumors after neoadjuvant therapy showed loss of HER2 expression. Our data strongly support the need for retest ER, PgR, HER2 of surgical sample after neoadjuvant therapy in order to accurately determine appropriate use of targeted therapy. Additional research should be conducted on biology and treatment in breast cancer patients whose tumors lose HER2 expression after neoadjuvant chemotherapy.

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disclosure

The authors have declared no conflicts of interest.

references

1. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst 2005; 97: 188–194.
2. Bonadonna G, Valagussa P, Brambilla C, Ferrari L. Preoperative chemotherapy in operable breast cancer. Lancet 1993; 341: 1485.
3. Cortazar P, Zhang L, Untch M et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384: 164–172.
4. von Minckwitz G, Untch M, Blohmer JU et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012; 30: 1796–1804.
5. Berruti A, Brizzi MP, Generali D et al. Presurgical systemic treatment of nonmetastatic breast cancer: facts and open questions. Oncologist 2008; 13: 1137–1148.
6. Gianni L, Eiermann W, Semiglazov V et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet 2010; 375: 377–384.
7. Buzdar AU, Ibrahim NK, Francis D et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 2005; 23: 3676–3685.
8. Simon R, Nocito A, Hubscher T et al. Patterns of her-2/neu amplification and overexpression in primary and metastatic breast cancer. J Natl Cancer Inst 2001; 93: 1141–1146.
9. Gancberg D, Di Leo A, Cardoso F et al. Comparison of HER-2 status between primary breast cancer and corresponding distant metastatic sites. Ann Oncol 2002; 13: 1036–1043.
10. Simmons C, Miller N, Geddie W et al. Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases? Ann Oncol 2009; 20: 1499–1504.
11. Thompson AM, Jordan LB, Quinlan P et al. Prospective comparison of switches in biomarker status between primary and recurrent breast cancer: the Breast Recurrence in Tissues Study (BRITS). Breast Cancer Res 2010; 12: R92.
12. Lower EE, Glass E, Blau R, Harman S. HER-2/neu expression in primary and metastatic breast cancer. Breast Cancer Res Treat 2008; 113: 301–306.
13. Burstein HJ, Harris LN, Gelman R et al. Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2 overexpressing stage II or III breast cancer: a pilot study. J Clin Oncol 2003; 21: 46–53.
14. Hurley J, Doliny P, Reis I et al. Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer. J Clin Oncol 2006; 24: 1831–1838.
15. Mittendorf EA, Wu Y, Scaltriti M et al. Loss of HER2 amplification following trastuzumab-based neoadjuvant systemic therapy and survival outcomes. Clin Cancer Res 2009; 15: 7381–7388.
16. Niikura N, Liu J, Hayashi N et al. Loss of human epidermal growth factor receptor 2 (HER2) expression in metastatic sites of HER2-overexpressing primary breast tumors. J Clin Oncol 2012; 30: 593–599.
17. Fl G. TNM Classification of Malignant Tumours. 6th ed. New York: Wiley 2002; 131–141.
18. Miyata H, Gotoh M, Hashimoto H et al. Challenges and prospects of a clinical database linked to the board certification system. Surg Today 2014; 44: 1991–1999.
19. Nagayama A, Hayashida T, Jinno H et al. Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. J Natl Cancer Inst 2014; 106.
20. Sauter G, Lee J, Bartlett JMS et al. Guidelines for human epidermal growth factor receptor 2 testing: biologic and methodologic considerations. J Clin Oncol 2009; 27: 1323–1333.
21. Press MF, Sauter G, Bernstein L et al. Diagnostic evaluation of HER-2 as a molecular target: an assessment of accuracy and reproducibility of laboratory testing in large, prospective, randomized clinical trials. Clin Cancer Res 2005; 11: 6598–6607.
22. Paik S, Bryant J, Tan-Chiu E et al. Real-world performance of HER2 testing—national surgical adjuvant breast and bowel project experience. J Natl Cancer Inst 2002; 94: 852–854.
23. Guarneri V, Dieci MV, Barbieri E et al. Loss of HER2 positivity and prognosis after neoadjuvant therapy in HER2-positive breast cancer patients. Ann Oncol 2013; 24: 2990–2994.
24. Pusztai L, Viale G, Kelly CM, Hudis CA. Estrogen and HER-2 receptor discordance between primary breast cancer and metastasis. Oncologist 2010; 15: 1164–1168.
25. Kurebayashi J, Miyoshi Y, Ishikawa T et al. Clinicopathological characteristics of breast cancer and trends in the management of breast cancer patients in Japan: based on the Breast Cancer Registry of the Japanese Breast Cancer Society between 2004 and 2011. Breast Cancer 2015; 22: 235–244.
26. Dekker TJ, Smit VT, Hooijer GK et al. Reliability of core needle biopsy for determining ER and HER2 status in breast cancer. Ann Oncol 2013; 24: 931–937.

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SPECIAL ARTICLE

Comprehensive prognostic report of the Japanese Breast Cancer Society Registry in 2005

Keisei Anan[1] · Naohito Fukui[2] · Takayuki Kinoshita[3] · Takayuki Iwamoto[4] · Naoki Niikura[5] · Masaaki Kawai[6] · Naoki Hayashi[7] · Kouichiro Tsugawa[8] · Kenjiro Aogi[9] · Takanori Ishida[10] · Hideji Masuoka[11] · Sinobu Masuda[12] · Kotaro Iijima[13] · Seigo Nakamura[14] · Yutaka Tokuda[5]

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Preface

A population-based cancer registry has been used for the planning and evaluation of cancer control activities based on administration and the care of individual cancer patients by those in the medical profession. The Japanese Breast Cancer Society (JBCS) registry was started in 1975. In 2004, the registry system was moved to a new system using web registration with the cooperation of the Non-Profit Organization Japan Clinical Research Support Unit and Public Health Research Foundation (Tokyo, Japan). Comprehensive individual patient data were recorded according to the Unio Internationalis Contra Cancrum (UICC) TNM classification [1] and the World Health Organization histological classification [2]. The details are described elsewhere [3]. Annual reports on this registry have since been published in Japanese and publicized through the JBCS web site to active members of the JBCS [4].

We herein report the results of a 5-year prognostic analysis of cases registered in 2005 (Figs. 1, 2, 3, 4, 5, 6, 7, 8 and 9; Supplementary Tables 1–9). The number of facilities involved in the 2005 registration was 354 and the total number of cases was 20,786. The estimated incidence of breast cancer was reported to be 50,695 cases in 2005 by the National Cancer Center [5]. Therefore, approximately

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✉ Yutaka Tokuda
tokuda@is.icc.u-tokai.ac.jp

[1] Department of Surgery, Kitakyushu Municipal Medical Center, Kitakyushu, Japan

[2] The Japan Clinical Research Support Unit and the Public Health Research Foundation, Tokyo, Japan

[3] Department of Breast Surgery, National Cancer Center Hospital, Tokyo, Japan

[4] Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan

[5] Department of Breast and Endocrine Surgery, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan

[6] Department of Breast Surgery, Miyagi Cancer Center, Natori, Japan

[7] Department of Breast Surgery, St. Luke's International Hospital, Tokyo, Japan

[8] Division of Breast and Endocrine Surgery, Department of Surgery, St. Marianna University School of Medicine, Kawasaki, Japan

[9] Department of Breast Surgery, Shikoku Cancer Center, Matsuyama, Japan

[10] Department of Surgical Oncology, Graduate School of Medicine, Tohoku University, Sendai, Japan

[11] Sapporo-kotoni Breast Clinic, Sapporo, Japan

[12] Department of Pathology, Nihon University School of Medicine, Tokyo, Japan

[13] Department of Breast Oncology, Cancer Institute Hospital, Tokyo, Japan

[14] Division of Breast Surgical Oncology, Department of Surgery, Showa University, Tokyo, Japan

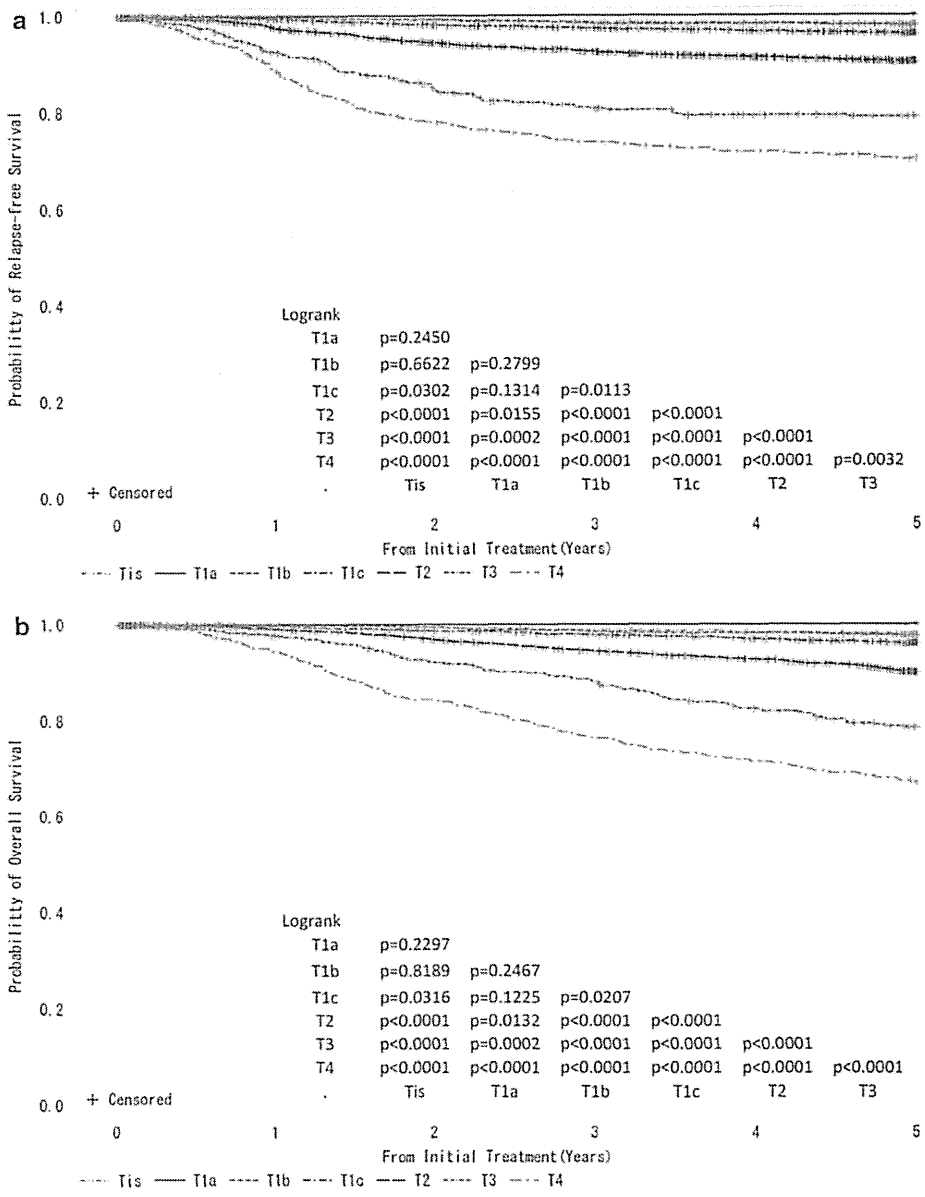

Fig. 1 a, b Kaplan–Meier curves for relapse-free and overall survival of all cases by tumor classification (cT-category). *P* values were calculated using the log rank test. Tis: Non-invasive ductal carcinoma, lobular carcinoma in situ, or Paget disease; T1a: ≤0.5 cm; T1b: 0.5< tumor ≤1.0 cm; T1c: 1.0< tumor ≤2.0 cm, T2: 2.0< tumor ≤5.0 cm; T3: >5.0 cm; T4: tumor of any size with direct extension to the chest wall and/or skin (ulceration or skin nodules) or inflammatory carcinoma

41 % of newly diagnosed breast cancer patients were included in the JBCS registry in 2005. In this prognostic study, we analyzed 9971 cases in which the survival data were available from 161 facilities. The background characteristics of the patients are summarized in Table 1. The median follow-up period was 60.0 months (range 0.1–60.0 months). Note that during the study period, not only the cutoff levels of estrogen receptor and progesterone receptor but also their corresponding test procedures were non-standardized and that trastuzumab was rarely used because it was not covered by the Japanese National Health Insurance program as an adjuvant therapy for human epidermal growth factor receptor 2-positive breast cancer. On the whole, the survival data seem to be better than expected. However, it would be prudent to avoid commenting on any specific subject because the present study is part of an annual survival report. A data set spanning multiple years would be more suitable for addressing specific subjects, such as triple-negative type or HER2 type. This is planned for the next phase studies.

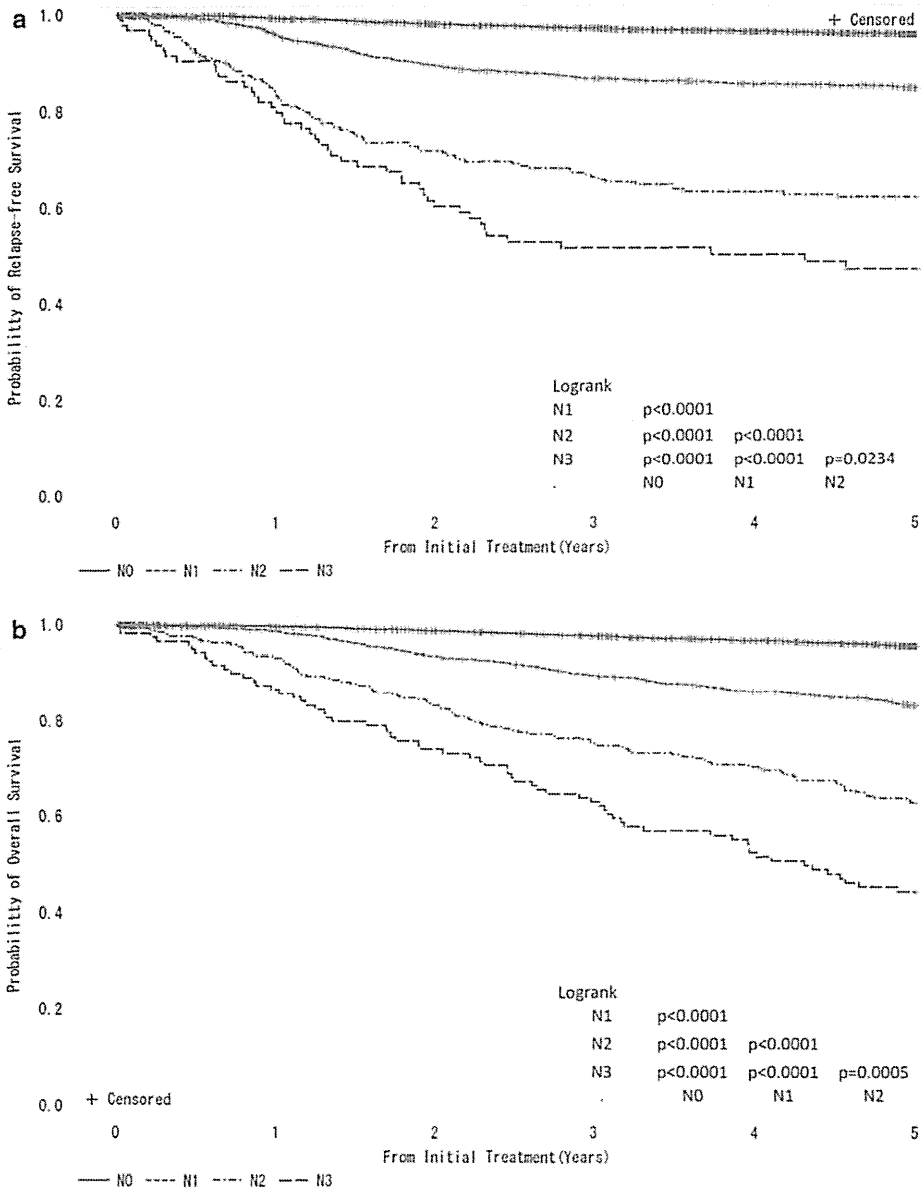

Fig. 2 a, b Kaplan–Meier curves for relapse-free and overall survival of all cases by regional lymph nodes status (cN-category). N0: no regional lymph node metastases; N1: metastases in movable ipsilateral level I, II axillary lymph node(s); N2: metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted OR metastases in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases; N3: metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement OR metastases in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases OR metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement. *P* values were calculated using the log rank test

Cancer control activities vary among nations and regional areas due to differences in population structures. The life expectancy for Japanese women, 87 years old in 2012, has been the longest worldwide for several years [6]. In addition, Japan is a super-aging society, with 25 % of citizens being 65 years of age or above as of October 2013, which is the highest number among all other nations [7]. We believe that the outcomes of our registry provide significant information for countries that are expected to have a similar population structure to that of Japan in the near future.