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ORIGINAL ARTICLE

The overall survival of breast cancer patients without adjuvant therapy

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Abstract

Purpose There are little data regarding the overall survival (OS) of patients without adjuvant systemic therapy, because most patients have been subject to standardized systemic therapies. We evaluated the baseline risk to facilitate making decisions about adjuvant therapy.

Patients and methods A total of 1835 breast cancer patients who did not receive adjuvant systemic therapy between 1964 and 1992 were retrospectively evaluated. We investigated the 10-year disease-free survival (DFS) and OS according to the number of metastatic lymph nodes, pathological T classification, stage, and estrogen receptor (ER) status.

Results Survival curves showed that as the number of metastatic lymph nodes, pathological T classification, and staging increased, the 10-year OS and DFS decreased. In univariate and multivariable analyses, the number of metastatic lymph nodes was significantly associated with the DFS and OS, while in a univariate analysis, the pathological T classification and stage were significantly associated with the DFS and OS. ER positivity was a good prognostic factor for the 5-year DFS. However, between 6 and 7 years after surgery, ER negativity was a better prognostic factor than ER positivity.

Conclusion We showed survival rates of patients without adjuvant therapy according to TNM classification and ER status. This information can aid in treatment selection for doctors and patients through a shared decision-making approach.

Keywords Breast cancer · Overall survival · Adjuvant therapy · Shared decision making

Introduction

Since the advent of systemic treatment for breast cancer, the prognosis of postoperative breast cancer patients has significantly improved worldwide [1–3]. At present, postoperative systemic therapy is recommended based on clinicopathological factors and biological factors, including estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor type-2 (HER2), and proliferation markers (Ki67 or multigene assay).

The systemic therapy regimen is usually determined based on a shared decision between the doctor and the patient, taking into consideration the baseline risk, risk reduction, and harm by treatment. The baseline risk of each patient is estimated by comparing prognostic factors, such as the number of metastatic lymph nodes, tumor size, stage, histological grade, hormone receptor, and HER2 overexpression, with the results of previous clinical trials or prognosis data [3, 4]. Recurrence prediction tools, such as Adjuvant! Online® and PREDICT®, have been used worldwide by inputting the data of each patient [5, 6]. However, caution should be practiced when using these tools, as ethnic differences can affect the results. In particular, a previous study showed that Adjuvant! Online was overoptimistic in predicting the survival of Asian breast cancer patients [7].

Several trials have shown a postoperative breast cancer survival of more than 10 years without systemic adjuvant

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therapy in Europe and the United States [2, 3]. However, there are little data on the survival of patients without systemic therapy in Japan. Therefore, we evaluated the influence of the true baseline risk on the prognosis of postoperative breast cancer patients who did not undergo adjuvant systemic therapy in Japan.

Patients and methods

We retrospectively reviewed survival data using the database of the Aichi Cancer Center Hospital for patients with primary breast cancer who underwent surgical resection between 1964 and 1992. We investigated the 10-year disease-free survival (DFS) and overall survival (OS) according to the number of metastatic lymph nodes, pathological T classification, stage, and ER status.

Study approval was obtained from the institutional review board of the Aichi Cancer Center Hospital.

Pathological review

The numbers of metastatic lymph nodes, tumor invasive diameter, pathological classification, and ER status of the primary tumors were determined. Tumors were categorized according to the UICC (Union for International Cancer Control) Six Edition 2002 [8] as follows: Tis, carcinoma in situ; T1, microinvasion, no more than 2 cm; T2, more than 2 cm but no more than 5 cm; T3, more than 5 cm; and T4, any size with direct extension to the chest wall or skin.

Staging of pTNM was also evaluated according to the UICC stage. The ER status was evaluated by the dextran-coated charcoal (DCC) ligand binding assay. The cutoff value of positivity was set at 5 fmol.

Statistical analyses

The DFS was defined as the time from the day of surgery to the day of the identification of cancer recurrence or death from any cause, while the OS was defined from the day of surgery to the day of death from any cause. The 10-year survival was estimated using the Kaplan–Meier method according to the number of metastatic lymph nodes, pathological T classification, stage, and ER status. The Cox proportional hazard model was used to identify prognostic factors independently associated with the DFS or OS and to estimate the hazard ratio (HR). A two-sided $p < 0.05$ was regarded as statistically significant. All data were analyzed using the STATA IC® software program, version 13 (Lightstone Corp., Tokyo, Japan).

Results

Patients

A total of 4323 breast cancer patients underwent surgical resection at the Aichi Cancer Center Hospital between 1964 and 1992. The Consolidated Standards of Reporting Trials (CONSORT) diagram is shown in Fig. 1. Patients who underwent adjuvant therapy were excluded. In that period, no standard adjuvant therapy existed. Hormone therapy was performed in 1067 patients for mostly early breast cancer (stage I: 55.1%, II: 34.9%, III: 5.1%), although ER positivity was assessed in only 376 patients (35.2%). Chemo-endocrine therapy was performed in 644 patients for mostly advanced breast cancer (stage I: 2.0%, II: 55.1%, III: 40.2%), and chemotherapy was performed in 619 patients (stage I: 23.4%, II: 45.2%, III: 23.6%). Patients with bilateral breast cancer or initially stage IV cancer were excluded to avoid bias. The final study population included 1835 patients.

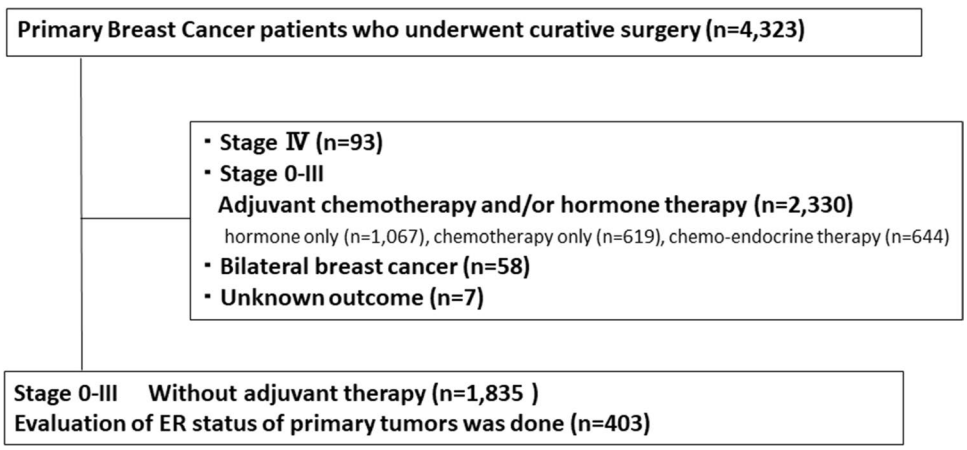

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) diagram

Patient characteristics

The patient characteristics are summarized in Table 1. Standard radical mastectomy and extended mastectomy were mainly performed as curative surgery between 1964 and 1988, after which modified radical mastectomy and breast conserving surgery were mainly performed. Axillary lymph node dissection was performed in all cases. The median number of resected lymph nodes of each patient was 21.1 (4–62). The stage of patients who did not receive adjuvant therapy was stage I in 39.3%, II in 39.1%, and III in 17.0%. A total of 252 out of 403 (62.5%) patients were ER-positive. The characteristics of the 403 patients who were tested for ER are shown in Table 2. There was no significant difference in the background between ER-positive and ER-negative patients. The median follow-up duration for the patients was 9.2 years.

The DFS

Survival curves showed that as the number of metastatic lymph nodes increased, the DFS decreased (Fig. 2). In node-negative patients, the 10-year DFS rate was 79.4%, whereas in patients with ≥ 10 metastatic lymph nodes, it was 12.5%. In univariate and multivariate analyses, the number of metastatic lymph nodes was significantly associated with the DFS ($p < 0.001$) (Tables 3, 4). Survival curves showed that as the invasive tumor diameter increased, the DFS decreased (Fig. 3). The 10-year DFS rate was 96.1% in Tis, 80.3% in T1, and 20.0% in T4. In a univariate analysis, the pathological T classification was significantly associated with the DFS ($p < 0.001$) (Table 3). In a multivariate analysis, T2 and T4 vs. T1 was significantly associated with the DFS ($p < 0.001$) (Table 4). Survival curves showed that the initial stage was associated with the DFS (Fig. 4). The 10-year DFS rate was 96.1% in stage 0 patients, 80.4% in stage I patients, and 12.5% in stage IIIC patients. In a univariate analysis, the initial stage was significantly associated with the DFS ($p < 0.001$–0.006) (Table 3).

We also investigated the relationship between the DFS and ER status except for in patients with noninvasive cancer (Fig. 5). The 5-year DFS was higher in ER-positive patients than in ER-negative ones (67.9% vs. 62.6%); however, the survival rate reversed from 6 to 7 years. Conversely, the 10-year DFS was lower in ER-positive patients than in ER-negative ones (52.8% vs. 58.5%).

The OS

Survival curves showed that as the number of metastatic lymph nodes increased, the OS decreased (Fig. 6). The 10-year OS rate was 81.6% in patients with no metastatic lymph nodes and 18.3% in patients with ≥ 10 metastatic lymph nodes. In univariate and multivariate analyses, the number of metastatic lymph nodes was significantly associated with the OS ($p < 0.001$) (Tables 3, 4). Survival curves showed that as the invasive tumor diameter increased, the OS decreased (Fig. 7). The 10-year OS rate was 97.4% in

Table 1 Patient characteristics ($n = 1835$)

	n (%)
Gender	
Female	1820 (99.1)
Male	15 (0.8)
Age (years)	18–87
< 35	112 (6.1)
35–54	1084 (59.0)
≥ 55	639 (34.8)
Menopause	
Pre	938 (51.5)
Post	882 (48.5)
Number of metastatic lymph nodes (pN)	
0	1175 (64.0)
1–3	412 (22.4)
4–9	128 (6.9)
≥ 10	120 (6.5)
Pathological tumor size (pT)	
Tis	81 (4.4)
T1	482 (26.2)
T2	1104 (60.1)
T3	153 (8.3)
T4	15 (0.8)
Stage	
0	81 (4.4)
I	722 (39.3)
IIA	364 (19.8)
IIB	355 (19.3)
IIIA	178 (9.7)
IIIB	14 (0.7)
IIIC	121 (6.6)
Breast surgery	
Radical mastectomy	1234
Extended radical mastectomy	396
Modified radical mastectomy	202
Breast-conserving surgery	1
Unknown	2
Histology	
Noninvasive carcinoma	81 (4.4)
Invasive carcinoma	1574 (85.7)
Special types	174 (9.5)
Unknown	6 (< 1)
Estrogen receptor (ER) status	
Positive	252 (13.7)
Negative	151 (8.2)
Unknown	1432 (78.0)

Table 2 Characteristics of the 403 patients whose ER status was evaluated

ER status	All ($n=403$) (%)	Positive ($n=252$) (%)	Negative ($n=151$) (%)
Number of metastatic lymph nodes			
0	196 (48.6)	124 (49.2)	72 (47.9)
1–3	122 (30.2)	75 (29.8)	47 (31.1)
4–9	43 (10.6)	29 (11.5)	14 (9.2)
≥ 10	42 (10.4)	24 (9.5)	18 (12.0)
Pathological T			
Tis	2 (0.5)	2 (0.8)	0 (0)
T1	68 (16.9)	42 (16.7)	26 (17.2)
T2	279 (69.2)	176 (69.8)	103 (68.2)
T3	52 (12.9)	30 (11.9)	22 (14.5)
T4	2 (0.4)	2 (0.8)	0 (0)
Stage			
0	2 (0.5)	2 (0.8)	0 (0)
I	88 (21.8)	63 (25.0)	25 (16.5)
IIA	98 (24.3)	98 (38.8)	47 (31.1)
IIB	110 (27.3)	70 (27.7)	40 (26.5)
IIIA	60 (14.8)	40 (15.8)	20 (13.2)
IIIB	2 (0.5)	2 (0.8)	0 (0)
IIIC	43 (10.6)	24 (9.52)	19 (12.6)

ER estrogen receptor

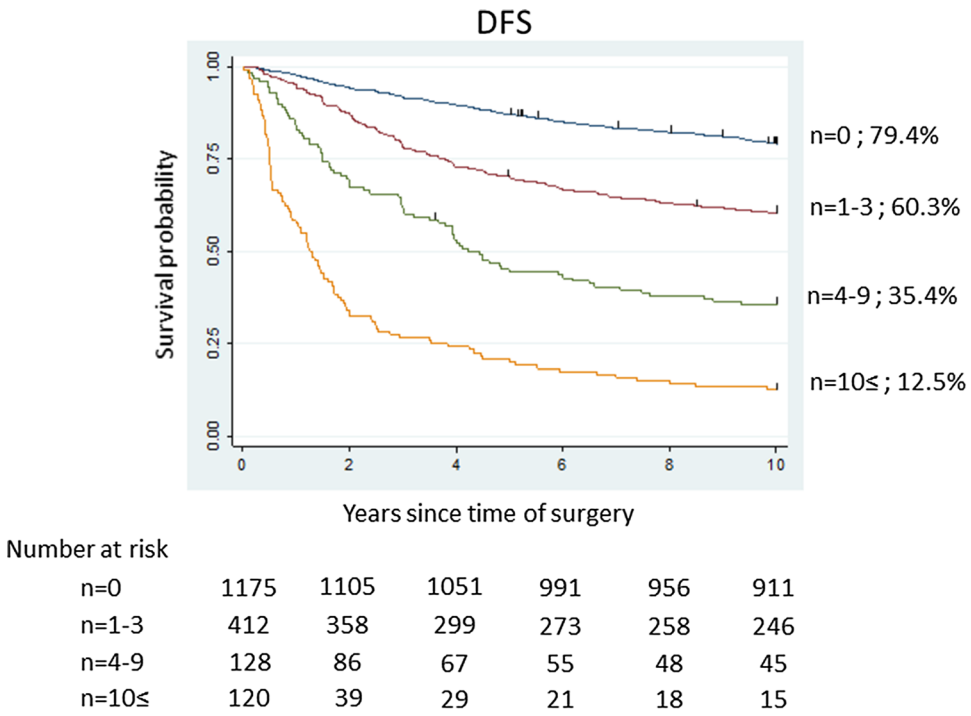

Fig. 2 The DFS according to the number of metastatic lymph nodes

Tis, 83.2% in T1, and 26.6% in T4. There were 3 deaths among the 81 patients with Tis; 1 died from breast cancer and the other 2 from other diseases. In a univariate analysis, the pathological T classification was significantly associated with the OS ($p<0.001$) (Table 3). In a multivariate analysis, the pathological T classification was not significantly associated with the OS ($p=0.084$–0.26) (Table 4). Survival curves showed that the initial stage was associated with the OS (Fig. 8). The 10-year OS rate was 97.4% in stage 0 patients, 83.1% in stage 1 patients, and 18.3% in stage IIIC patients.

Table 3 Results of a univariate analysis of the 10-year DFS and OS

Variables	Disease-free survival rate		HR	95% CI	*p* value	Overall survival rate		HR	95% CI	*p* value
	10 years (%)	95% CI				10 years (%)	95% CI			
Number of metastatic lymph nodes										
0	79.4	76.59–81.27	1.00			81.6	79.34–83.78	1.00		
1–3	60.3	55.40–64.85	2.19	1.79–2.67	< 0.001	67.3	62.59–71.66	1.98	1.59–2.46	< 0.001
4–9	35.4	27.23–43.72	4.65	3.42–5.98	< 0.001	46.4	37.60–54.83	3.92	2.98–5.15	< 0.001
≥ 10	12.5	7.35–19.09	11.44	9.06–14.44	< 0.001	18.3	12.01–25.72	9.63	7.55–12.27	< 0.001
Pathological T classification										
Tis	96.1	88.59–98.75				97.4	90.25–99.36			
T1	80.3	76.48–83.63	1.00			83.2	79.58–86.31	1.00		
T2	63.2	60.36–66.06	2.11	1.69–2.65	< 0.001	68.2	65.44–70.94	2.10	1.65–2.68	< 0.001
T3	46.3	38.24–53.97	3.82	2.84–5.13	< 0.001	52.8	44.57–60.36	3.65	2.65–5.02	< 0.001
T4	20.0	4.89–42.39	5.88	3.22–10.74	< 0.001	26.6	8.36–49.63	5.86	3.12–11.02	< 0.001
Stage										
0	96.1	88.59–98.75				97.4	90.25–99.36			
I	80.4	77.37–83.19	1.00			83.1	80.16–85.66	1.00		
IIA	73.3	68.46–77.56	1.44	1.11–1.86	0.006	76.0	71.33–80.12	1.47	1.12–1.94	0.006
IIB	63.4	58.16–68.17	2.12	1.67–2.69	< 0.001	70.4	65.38–74.88	1.92	1.47–2.49	< 0.001
IIIA	38.4	31.27–45.51	4.67	3.63–6.00	< 0.001	48.5	41.05–55.70	4.05	3.08–5.32	< 0.001
IIIB	21.4	5.02–44.79	5.78	3.13–10.69	< 0.001	28.5	8.83–52.37	5.67	2.97–10.81	< 0.001
IIIC	12.5	7.35–19.09	12.41	9.60–16.04	< 0.001	18.3	12.01–25.72	10.53	8.04–13.79	< 0.001
ER status										
Negative	58.5	50.0–65.7	1.00			61.9	54.01–69.56	1.00	1.12–1.59	
Positive	52.8	47.6–60.0	1.04	0.76–1.42	0.766	62.8	56.91–68.86	0.62	0.24–2.34	0.503

CI confidence interval, *HR* hazard ratio

Table 4 Results of a multivariate Cox regression analysis of the 10-year DFS and OS

Variables	Disease-free survival rate			Overall survival rate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Number of metastatic lymph nodes						
0	1.00			1.00		
1–3	2.11	1.44–3.11	< 0.001	1.89	1.24–2.87	0.003
4–9	3.34	2.04–5.47	< 0.001	2.64	1.52–4.58	0.001
≥ 10	9.48	5.95–15.09	< 0.001	7.46	4.58–12.14	< 0.001
Pathological T classification						
T1	1.000			1.00		
T2	2.02	1.16–3.54	0.013	1.67	0.93–3.00	0.084
T3	1.94	1.00–3.76	0.050	1.58	0.78–3.20	0.203
T4	6.78	1.50–30.57	0.013	3.22	0.41–25.12	0.263
ER status						
Negative	1.00			1.00		
Positive	1.10	0.80–1.51	0.552	0.91	0.65–1.29	0.634
Age (years)						
< 35	1.00			1.00		
35–54	0.91	0.46–1.80	0.806	0.79	0.38–1.61	0.522
≥ 55	0.77	0.34–1.71	0.525	0.78	0.33–1.84	0.586
Menopause						
Pre	1.00			1.00		
Post	1.30	0.84–2.01	0.222	1.29	0.79–2.10	0.301

CI confidence interval, *HR* hazard ratio

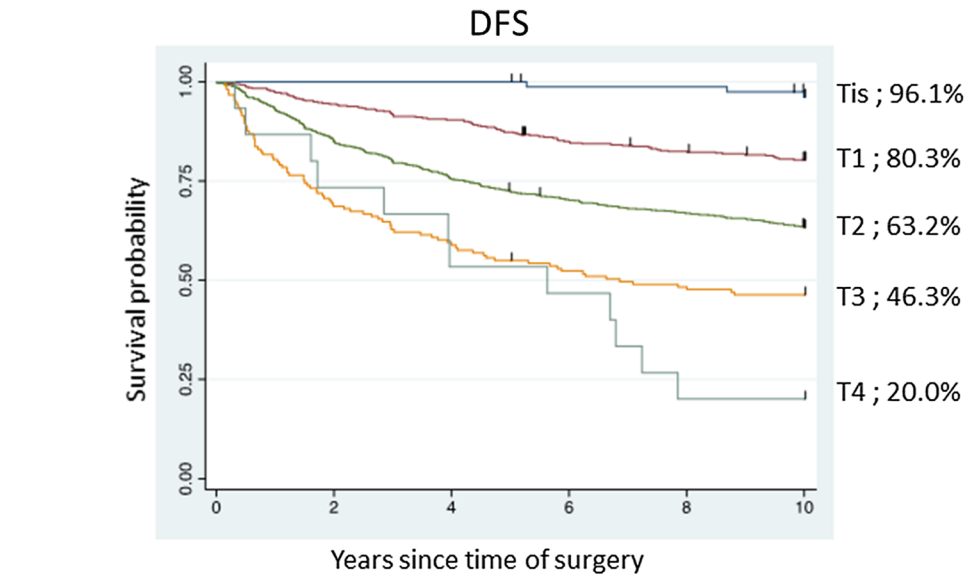

Fig. 3 The DFS according to the pT

Number at risk

Tis	81	81	81	78	78	74
T1	482	453	434	404	391	376
T2	1104	937	831	771	734	693
T3	153	105	91	79	73	70
T4	15	11	8	7	3	3

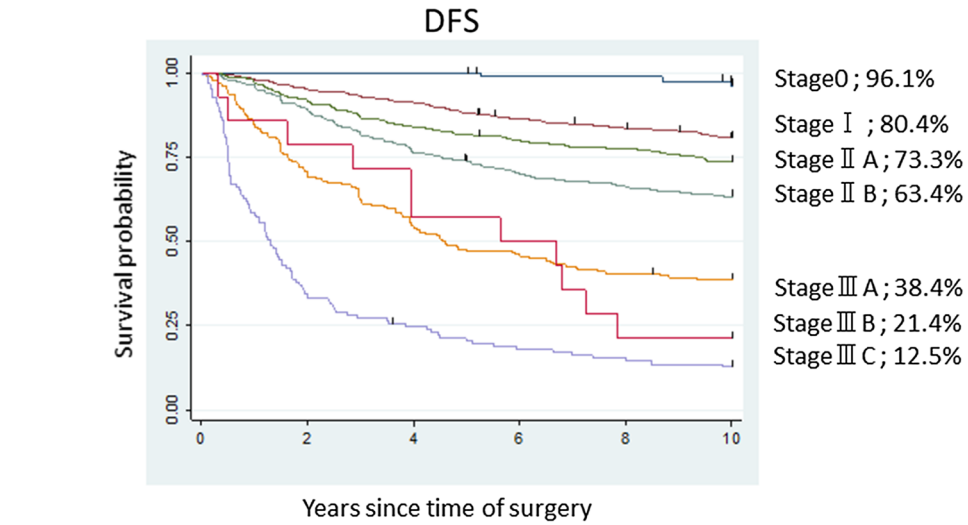

Fig. 4 The DFS according to the stage

Number at risk

Stage0	81	81	81	78	78	74
Stage Ⅰ	722	683	655	616	595	589
Stage Ⅱ A	364	334	305	290	281	265
Stage Ⅱ B	355	317	272	247	234	223
Stage Ⅲ A	178	123	96	81	71	68
Stage Ⅲ B	14	11	8	7	3	3
Stage Ⅲ C	121	39	29	21	18	15

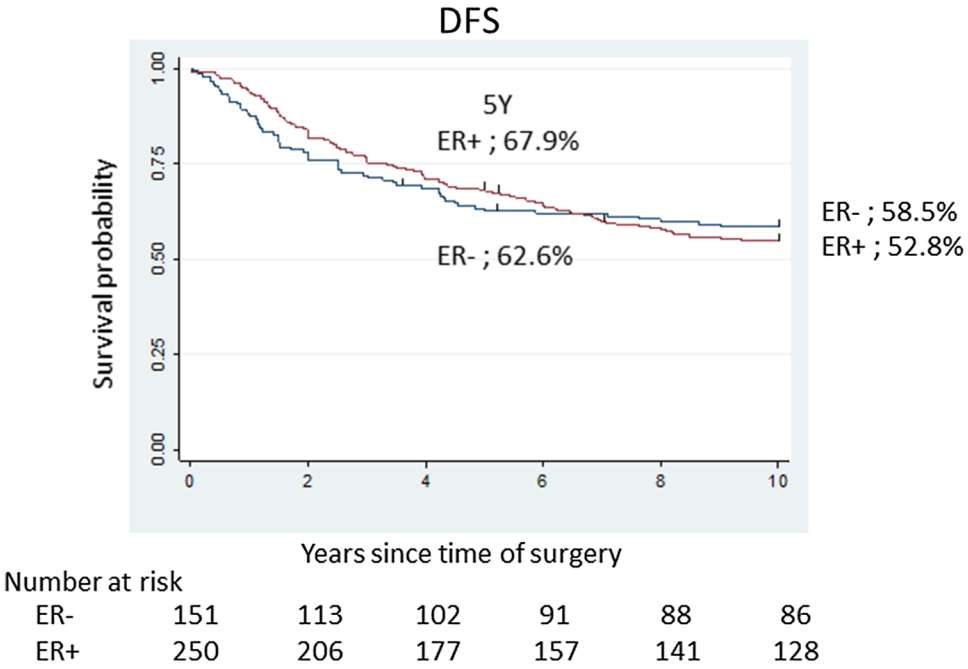

Fig. 5 The DFS according to the ER positivity (excluding patients with noninvasive cancer)

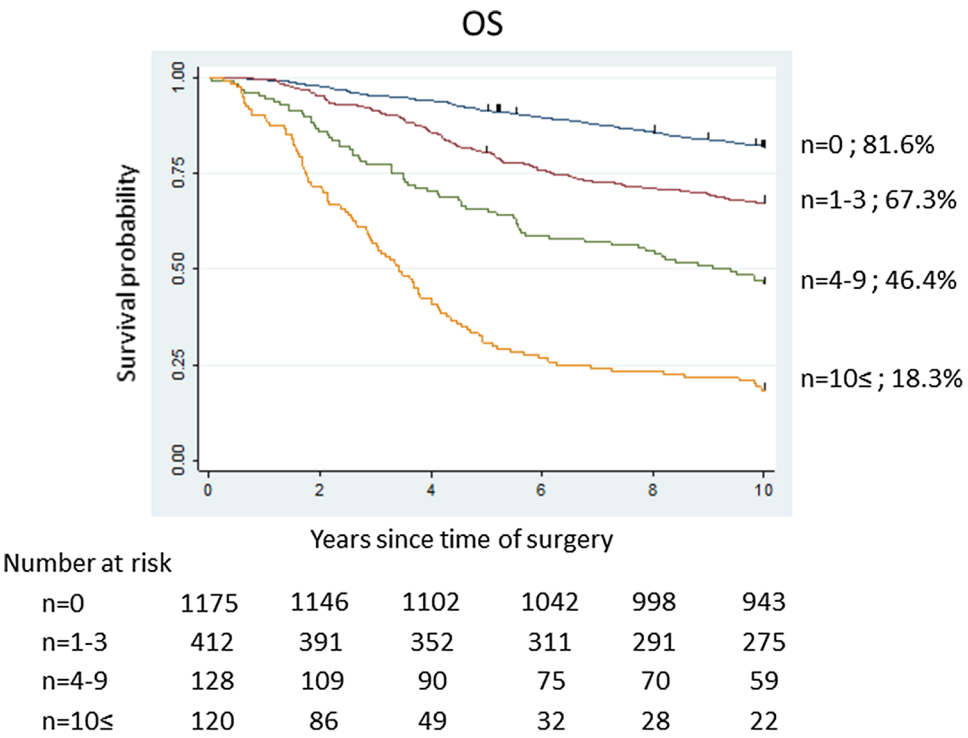

Fig. 6 The OS according to the number of metastatic lymph nodes

In a univariate analysis, the cancer stage was significantly associated with the OS ($p < 0.001$–0.006) (Table 2). With respect to the ER status, the 10-year OS was slightly better in ER-positive patients than in ER-negative ones (62.8% vs. 61.9%) (Fig. 9).

To determine the risk factors for late recurrence, we analyzed patients with late recurrence ($n = 27$) compared to those with no recurrence at 10 years ($n = 150$) (Table 5). As the number of lymph nodes increased, so did the odds ratio. The pathological T classification was not correlated with recurrence.

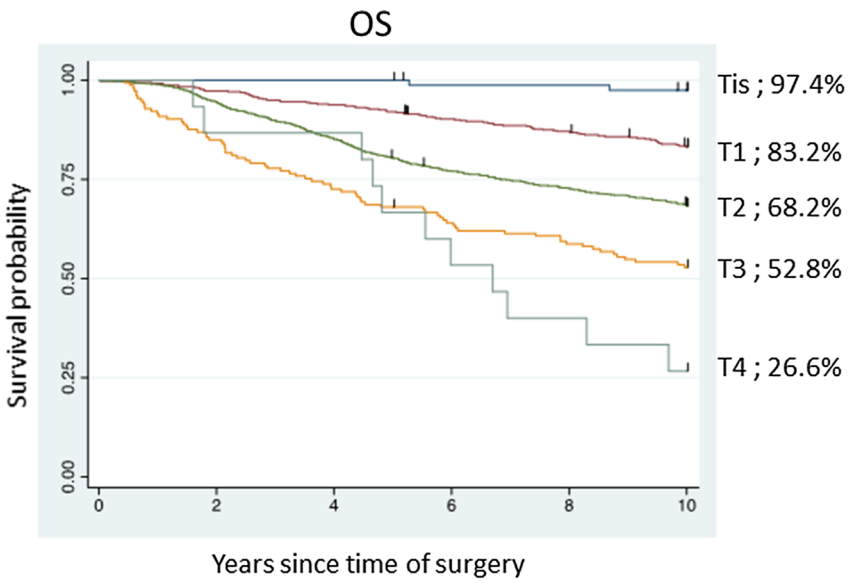

Fig. 7 The OS according to the pT

Number at risk

Tis	81	81	81	78	78	75
T1	482	467	450	429	414	391
T2	1104	1040	937	847	799	748
T3	153	130	111	97	89	80
T4	15	13	13	8	6	4

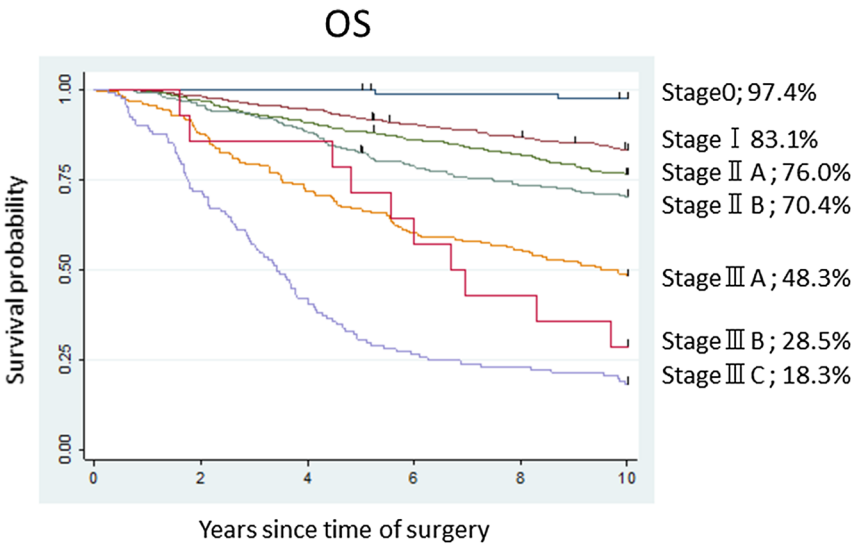

Fig. 8 The OS according to the stage

Number at risk

Stage0	81	81	81	78	78	75
Stage Ⅰ	722	706	679	645	620	589
Stage Ⅱ A	364	352	331	312	297	275
Stage Ⅱ B	355	340	314	279	260	248
Stage Ⅲ A	178	155	127	106	98	86
Stage Ⅲ B	14	12	12	8	6	4
Stage Ⅲ C	121	86	49	32	28	22

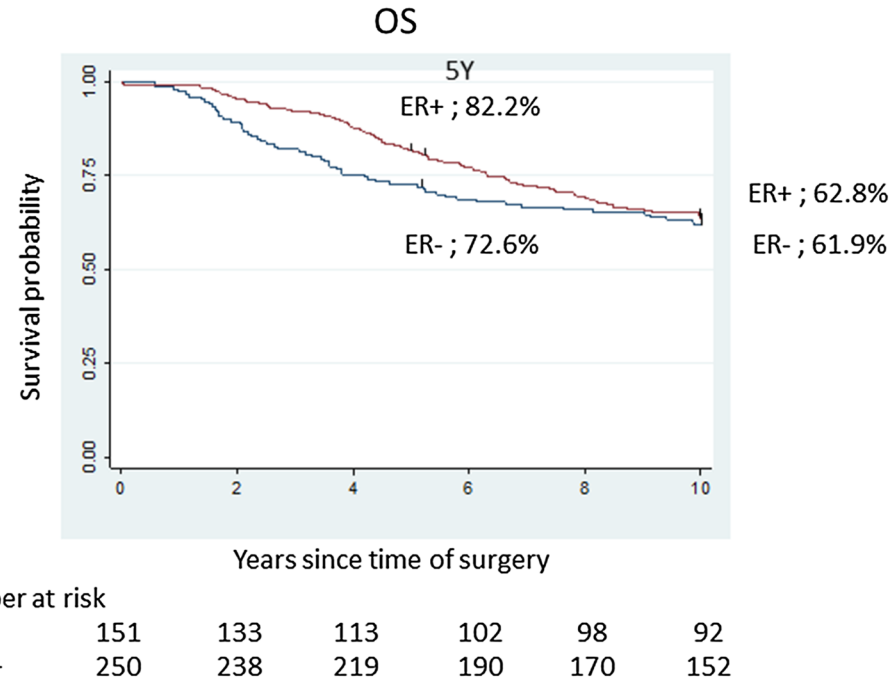

Fig. 9 The OS according to the ER positivity (excluding patients with noninvasive cancer)

Table 5 Risk factors for late recurrence

Variables	Late recurrence cases ($n=27$)	No recurrence cases ($n=150$)	Odds ratio	95% CI	p value
Number of metastatic lymph nodes (pNs)					
0	11	96	1.00		
1–3	8	42	1.66	0.62–4.46	0.308
4–9	6	9	5.82	1.65–20.57	0.002
≥10	2	1	17.45	1.30–234.76	0.003
Pathological tumor size (pT)					
T1	5	30	1.00		
T2	18	104	1.03	0.35–3.04	0.945
T3	4	13	1.84	0.42–8.20	0.413
T4	0	1	0.0		0.688

CI confidence interval

Discussion

In this study, we investigated the DFS and OS of postoperative patients without adjuvant systemic therapy due to the dearth of baseline risk data in Japan. We analyzed the survival data according to the number of metastatic lymph nodes, pathological T classification, stage, and ER status. Our findings suggest that the number of metastatic lymph nodes and stage may be important prognostic factors. While this has been previously shown in another study [9], the patients included in that study had undergone hormonal therapy. The tumor size was significantly associated with the DFS in a multivariate analysis, although it was not significantly associated with the OS. In addition, we found that the rate of recurrence was lower in patients with ER-positive tumors than in those with ER-negative tumors in the first 5 years but was higher at 10 years. This is in agreement with the findings of previous studies in patients who underwent hormonal therapy [9–11].

A study in The Netherlands investigated 93,569 patients diagnosed with primary breast cancer between 2006 and 2012 for their 15-year OS and DFS according to the number of metastatic lymph nodes and pathological T classification [3]. They found that the number of metastatic lymph nodes and pathological T classification were significantly associated with the OS. The data showed that the 15-year OS was 90% in N0, 88% in N1, 81% in N2, and 66% in N3, while the 15-year OS was 91–95% in T1a to T1b, 82% in T2, 73% in T3, and 45% in T4. An analysis of a Japanese dataset found

that the 5-year survival rate of each stage of breast cancer patients was 95.8% in stage I, 91.9% in stage II, and 77.6% in stage III [12]; however, these patients underwent adjuvant systemic therapies. The survival rate in our study was worse than these previously reported values, probably due to the lack of adequate adjuvant therapy. However, we found that 80% of stage I patients who underwent surgery with no intervention by systemic therapy did not experience recurrence for a period of 10 years. A total of 12.8% of stage IIIC patients who underwent surgery without adjuvant therapy were still alive 10 years after surgery.

Several previous studies have shown that the significance of ER as a prognostic marker varies depending on the time of observation [10, 11, 13]. Ke-Da et al. investigated 111,993 cases using the Surveillance Epidemiology and End Results (SEER) database from 1990 to 2003 [14]. They showed that, in the early stage after the diagnosis, patients with ER-positive tumors had lower relapse rates, and the breast cancer-specific mortality was lower than in those with ER-negative tumors; however, the results were the opposite in the late stage after the diagnosis.

Our study has several limitations. First, we lacked data regarding the intrinsic subtype, because patients underwent surgical resection between 1964 and 1992. Thus, our analysis could not adjust for this potential confounding factor. By examining the HER2 and Ki67 status, it would be possible to estimate the prognosis according to the intrinsic subtype (luminal A, luminal B, HER2-enriched, basal-like). In addition, the ER status of the patients included in this study was evaluated by the DCC method. Since then, immunohistochemistry (IHC) has become the standard method used worldwide, since it more accurately reflects the prognosis [15], although agreement of IHC and DCC was reported in 91% specimens [16]. Therefore, the survival curve shown here might be different if patients had been evaluated using IHC. In addition, the nuclear grade and lympho-vascular invasion are risk factors for recurrence, but at the time our patients were evaluated, those factors were not examined routinely.

Conclusion

We determined the survival rates of patients without adjuvant therapy according to the TNM classification and ER status. We evaluated the 10-year DFS and OS according to the number of metastatic lymph nodes, pathological T classification, stage, and ER status in Japanese postoperative patients. These data will prove to be important for evaluating the baseline risk for postoperative breast cancer patients based on several risk factors. Our results will facilitate treatment selection during shared decision making between doctors and patients.

Funding We report no financial support.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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