Prognostic factors for survival after first recurrence in breast cancer: A retrospective analysis of 252 recurrent cases at a single institution

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Concise title
Prognostic factors for survival after first recurrence

List of abbreviations used
ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; pN: axillary lymph node involvement; TNM: clinical stage; pTNM: pathological stage; OS: overall survival; DFI: disease-free interval.

Abstract

Introduction: Previous studies have shown that primary breast cancer patients with estrogen receptor (ER)-positive status have better outcomes in terms of both overall survival and disease-free intervals (DFI). However, 25.2% of our ER-positive patients experienced recurrence.-This study aimed to define factors potentially predicting survival after first recurrence in surgically treated patients with stage I-III breast cancer.

Methods: We retrospectively analyzed 252 females with recurrent breast cancer who had undergone surgery and been followed at Kyoto University Hospital in Japan. Age, clinical stage, pathological stage, axillary lymph node involvement, ER status at the time of diagnosis, progesterone receptor status, human epidermal growth factor receptor 2 status, operative method, adjuvant chemotherapy, adjuvant endocrine therapy, use of trastuzumab after recurrence, site of recurrence, DFI, and time of recurrence were examined for possible influences on survival after the first recurrence.

Results: Positive ER status and positive PR status at the time of diagnosis were significantly favorable factors of survival after first recurrence for patients with recurrence; $p < 0.001$ and $p = 0.021$, respectively. More than 2 sites of recurrence ($p < 0.001$) were associated with shorter survival time after the first recurrence on multivariate analysis. Survival of patients with recurrent breast cancer steadily improved from 1980-1994 to 1995-2008, significantly in ER-negative subgroups.

Conclusions: Positive ER status at the time of diagnosis is a powerful predictor for favorable survival after first recurrence. Survival time after first recurrence of breast cancer has steadily increased in recent decades. Advances in treatments and attitudes about breast cancer have contributed to this improvement in survival after first recurrence.

Introduction

Breast cancer patients follow a variety of clinical courses, depending on tumor characteristics. Some relapse a few months after operation, while others may relapse many years later. Recurrent breast cancer patients usually die from their disease, but the time from recurrence to death differs markedly among these patients.

Prognostic factors are important for estimating outcomes and determining the optimal form of treatment. When a patient is considered to be at high risk for recurrence, physicians must plan follow-up and treatments carefully. Prognostic factors related to overall survival (OS) and disease-free interval (DFI) have been extensively evaluated. In addition, we previously reported that estrogen receptor (ER)-positive patients had better OS- and DFI-related prognostic factors [1, 2].

Breast cancer treatment is usually combined with surgery, chemotherapy, endocrine therapy, molecular-targeted therapy, and/or radiation therapy. Recent progress in breast cancer treatments has benefited some patient populations. There are several reports documenting improved survival of breast cancer patients [3]. In our previous study, we described prolongation of OS over time [2]. However, 25.2% of ER-positive patients in our prior study experienced recurrence.

We retrospectively analyzed data from 252 recurrent breast cancer patients to determine factors possibly influencing outcomes and changes in the duration of survival over time after first recurrence. We emphasize that this study was based on results from a single institution. Such a single institutional study has the advantage that patient backgrounds are homogenous and follow-up methods are consistent.

Methods

Patients

This study was approved by the Kyoto University ethics committee. From 1980 to 2005, 922 female patients with stage I-III breast cancer underwent breast surgery with axillary lymph node dissection at Kyoto University Hospital. Out of 922 total patients, 252 (27.3%) breast cancer patients had recurrence before December 31, 2008. The characteristics of 252 patients of stage I-III with recurrence and 670 patients without recurrence are shown in Table 1. All patients were female, and 43.7% of the patients with recurrence were older than 55 years old and were postmenopausal. Staging of clinical stage (TNM) and pathological stage (pTNM) were determined by the UICC stage classification system. Breast-conserving surgery has been performed since 1990. As a rule, all of the patients who underwent breast-conserving surgery received radiation therapy to the conserved breast.

Most of the patients were followed at Kyoto University Hospital, and some of them were followed at Kitano Hospital, Osaka, Japan, which is an affiliate hospital of Kyoto University Hospital. More than 80% of patients had a single recurrent organ at first recurrence, and 17.5% of patients had more than 2 recurrent organs at first recurrence (Table 2). Forty percent of patients had soft-tissue recurrence, 19.4% of patients had bone metastasis, 17.5% of patients had lung or pleura metastasis, and 5.2% of patients had liver metastasis.

Pathological data

Pathological data, including the number of axillary lymph node metastasis (pN), ER status, progesterone receptor (PR) status, and human epidermal growth factor receptor 2 (HER2) status, were evaluated at Department of Pathology in Kyoto University Hospital. Method for determining ER and PR status varied during the study period. ER and PR status have been determined immunohistochemically (IHC) since 2000. Before 2000, we evaluated ER and PR status with dextran charcoal-coating method or by enzyme immunoassay (EIA). HER2 status has been evaluated since 2000.

Enzyme immunoassay

SRL Inc. (Tokyo, Japan) undertook the measurement. Briefly, 0.5 g of breast tumor tissue was placed on dry ice immediately after excision, and stored at −80°C until processing for routine biochemical measurement. Before cytosol preparation, fat, blood, and necrotic tissue were eliminated from each sample and discarded, leaving a piece of tumor tissue between 0.1 and 0.2 g. This tissue was homogenized in buffer solution, and centrifuged at 4°C for 10 minutes at 800 × g. Cytosol was obtained from the supernatant by centrifugation at 4°C for 60 minutes at 105,000 × g. One hundred microliter of cytosol was diluted with 100 μL of specimen diluent. The estrogen receptor concentrations in the diluted cytosol specimens were determined using the ER-EIA kit from Abbott Japan Co. Ltd. (Tokyo, Japan) according to the manufacturer's instructions. ER values ≥ 13 fmol/mg protein and PR values ≥ 10 fmol/mg protein were regarded as positive.

Immunohistochemistry

For IHC, we used Ventana HX BenchMark system (Ventana Medical Systems, Inc., Tucson, AZ, USA), according to the manufacturer's instructions. Briefly, for antigen retrieval, a retrieval solution (Ventana Medical Systems, Inc.) was automatically poured onto the sections, and they were heated on a slide heater to 100 °C for 60 minutes.

Endogenous peroxidase activity was quenched by immersion in 3% hydrogen peroxide for 4 minutes. Tissue sections were incubated with a primary antibody; a monoclonal antibody to ER (clone SP1, Ventana Medical Systems, Inc.), PR (clone SP1, Ventana Medical Systems, Inc.), or HER2 (clone 4B5, Ventana Medical Systems, Inc.) for 32 minutes at 42 °C. Immunoperoxidase staining was performed using I-VIEW DAB Universal Kit (Ventana Medical Systems, Inc.), and sections were counterstained with hematoxylin. ER and PR were considered to be positive if more than 10% of cells showed positivity. However, indications for endocrine therapy were considered in patients with less than 10% positive cells. HER2 status was defined as positive when IHC score was 3+ or HER2/centromere probe of chromosome (CEP) 17 ratios was more than 2.2 in fluorescent in situ hybridization.

Postsurgical therapy

Patients underwent clinical and blood examination every 3 months. Chest X-ray examination, abdominal ultrasonography, and bone scintigraphy were performed annually before 2001. After 2002, chest computed tomography replaced chest X-ray examination. Hormone receptor-positive patients usually receive endocrine therapy for at least 5 years. Tamoxifen was used for pre- and post-menopausal patients, toremifene for post-menopausal patients. Tamoxifen and toremifene has been approved since 1981 and 1995, respectively. Medroxyprogesterone acetate was used in some patients. Luteinizing hormone-releasing hormone (LHRH) analog was used for premenopausal patients after 1992. The third generation aromatase inhibitors have been administered to postmenopausal patients since 2001. For the patients with node-positive or high nuclear grades, chemotherapy was administered. Oral chemotherapy, such as tegafur (FT), carmofur (HCFU), tegafur-urasil (UFT) or doxifluridine (5′DFUR), was administered in the 1980s. In 1990s, anthracycline mono-therapy was administered. Taxane or anthracycline-containing regimen was used after 2000. Trastuzumab was added for patients with a HER2-positive tumor after 2008.

Treatment after recurrence

Treatment after recurrence varied for each patient. The goals of treatment for recurrent patients were prolonging life and maintaining quality of life. Considering patient's general condition, treatments were started based on phenotype of the recurrent tumor. For hormone receptor-positive patients, endocrine therapy was applied. Drugs were chosen among aromatase inhibitors, tamoxifen, LHRH analog, high dose toremifene, or medroxyprogesterone acetate. For triple-negative tumors, chemotherapy

was given. First-line palliative chemotherapy included an anthracycline or taxane. Second-line chemotherapy was mostly based on non-anthracycline non-taxane. For HER2-overexpressing tumors, trastuzumab combined with chemotherapy was given after 2000. For bone metastasis, bisphosphonates were used. If necessary, radiotherapy was added.

Statistical analysis

We statistically analyzed prognostic factors related to survival time from first recurrence to death. Survival curves were estimated with the Kaplan–Meier method. The univariate analysis was performed using the log-rank test and the univariate Cox regression analysis for estimating hazard ratios. The multivariate Cox regression analysis with backward elimination method was used to estimate hazard ratios and to identify independent prognostic factors. The univariate logistic regression analysis was used to investigate the independence between recurrent date (period I: 1980–1994; period II: 1995–2008) and each factor: age at primary breast surgery, TNM, pTNM, pN, ER status, PR status, HER2 status, breast surgery, adjuvant endocrine therapy, adjuvant chemotherapy, site of first recurrence, use of trastuzumab after recurrence, and DFI. All reported *p* values are two-sided, and a value below 0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Factors related to survival after first recurrence

With the univariate analysis, pTNM ($p = 0.009$), pN ($p = 0.024$), ER status ($p < 0.001$), PR status ($p = 0.005$), adjuvant chemotherapy ($p = 0.038$), the site of first recurrence ($p = 0.001$), DFI ($p < 0.001$), and recurrent date ($p < 0.001$) were related to survival after first recurrence. Meanwhile, age at the time of primary breast surgery, TNM, HER2 status, breast surgery, adjuvant endocrine therapy and use of trastuzumab after recurrence had no relationship with survival after first recurrence (Table 3).

ER status and PR status were strongly related to survival time after recurrence. The Kaplan–Meier analysis revealed that ER-positive patients showed more favorable survival rates throughout the 10 years after the first recurrence than ER-negative patients (Figure 1-A). ER positivity was strong predictor both in pre- and post-menopausal patients ($p<0.001$).

The site of first recurrence was significantly associated with survival after first recurrence. Patients with liver metastasis and metastases of more than 2 organs showed

poorer survival rates than those with single metastasis of soft tissues, lung/pleura, or bone (Figure 1-B). ER-positive patients tend to have liver, lung/pleura, or bone metastases. Otherwise, ER-negative patients tend to have shorter DFI (Table 2). There was no patient whose first recurrent site was the brain.

The patients with a longer DFI had better survival rates after first recurrence than those with a shorter DFI (Figure 1-C).

Independent prognostic factors after first recurrence

With the multivariate analysis, ER status ($p < 0.001$), the site of first recurrence ($p < 0.001$), time of first recurrence ($p < 0.001$), PR status ($p = 0.031$), and DFI ($p = 0.033$) were significant and independent factors influencing the survival after first recurrence (Table 4). In particular, the hazard ratio in the ER-positive patients was 0.351 (95% confidence interval: 0.228 to 0.540), compared with that in ER-negative patients after adjustment for the site of recurrence, time of recurrence, PR status, and DFI. Time of first recurrence was still significant on the multivariate analysis.

Chronological changes in survival after first recurrence curve

The number of patients who were recurrent in period I (1980–1994) and in period II (1995–2008) was 87 and 165 (Table 5), respectively. In period I, the percentage of patients with pathological stage I, II, and III was 6.9%, 36.8% and 56.3%, respectively. Meanwhile in period II, the percentage of patients with pathological stage I and II increased to 13.3% and 47.9%, respectively. However the percentage of patients with pathological stage III decreased to 38.8% in period II. The percentage of patients who underwent breast-conserving surgery in period I and period II was 1.1% and 43.6%, respectively. In period I, no patients received aromatase inhibitor as adjuvant endocrine therapy, and trastuzumab after recurrence. With the multivariate analysis, recurrent date was related to survival time after first recurrence (hazard ratio: 0.503, $p < 0.001$, Table 4). Survival after first recurrence was significantly improved from period I to period II ($p<0.001$, Figure 2-A). From period I to period II, the median survival time was 967 days (2.65 years) and 1831 days (5.02 years), respectively. Survival after first recurrence was improved both in the ER-positive and ER-negative subgroups (Figure 2-B and 2-C). In the ER-positive subgroup, the median survival time was 1520 days (4.16 years) and 2569 days (7.04 years) for period I and period II, respectively ($p=0.053$). In the ER-negative subgroup, the median survival time was 660 days (1.808 years) and 879 days (2.41 years) for period I and period II, respectively ($p=0.022$).

Factors contributing to chronological change of survival after first recurrence

In order to determine the factors contributing to the chronological change in survival, we performed a univariate logistic regression analysis. Pathological TNM ($p = 0.024$), breast surgery ($p < 0.001$), adjuvant chemotherapy ($p = 0.014$), and DFI ($p < 0.001$) had a significant relationship with chronological improvement in survival (Table 6). The patients in period II had an earlier stage, longer DFI, and received more breast-conserving surgery, and more intravenous adjuvant chemotherapy than the patients in period I.

Discussion

Twenty percent to 30% of early breast cancer patients experience recurrence [4]. The course of treatment for these patients is determined based on the Hortobagyi's decision tree [5]. When a patient is diagnosed with recurrent breast cancer, hormone-receptor status, DFI, age, and menopausal status are initially assessed. When the disease is hormone-responsive and non-life-threatening, the patient receives first-line endocrine therapy. Thus, ER status is the first important decision-making factor.

We previously reported that ER status was a favorable prognostic factor of OS and DFI [1, 2]. In this study, we showed that ER status and PR status at the time of the operation were independent predictors of survival after first recurrence (Table 4). Although the assessment process has changed, ER positivity remained a strong predictor throughout our study period. The 5-year survival rate after the first recurrence in ER-negative patients was 27% (95% confidence interval [CI], 17%-37%), while that in ER-positive patients was 54% (95% CI, 42%-64%). This result confirmed several reports describing ER status as the best predictor of survival after first breast cancer recurrence [6-9]. In our present study, HER2 positive status did not indicate a poor prognosis with statistical significance. This was due to the small number of patients with ascertained HER2 status, because HER2 assessment began in 2000.

With the univariate analysis, axillary lymph node status was related to survival after first recurrence ($p = 0.024$). However, based on multivariate analysis, axillary lymph node status was not an independent factor determining survival after first recurrence. There were several reports that the multivariate analysis showed axillary lymph node status to be independently associated with survival after first recurrence [6] [8] [9], while another report showed that axillary node status indicated the probability of relapse but did not influence the length of survival after relapse[7]. In this study, DFI was also an independent prognostic factor of survival after first recurrence. Clark et al [6]

and Insa et al [8] reported that DFI provided independent information for predicting patient survival after recurrence, while Koenders et al [9] observed no association between survival from the detection of first metastasis and DFI. Moreover, Howell el al [7] reported that there was no significant difference between patients with receptor-positive and receptor-negative tumors in the relapse-free interval, but survival from first relapse was longer in patients with receptor-positive tumors. One of the reasons of this difference might be due to chronological changes of adjuvant treatments.

The site of initial recurrence is an important determinant for predicting survival from the time of initial recurrence. There are several reports indicating ER-positive status to be significantly associated with a higher rate of bone metastasis [6][10][11]. In this study, 53.1% of patients with bone metastasis were ER-positive, and 34.7% of patients with bone metastasis were ER-negative (Table 2). The 5-year post-recurrent survival rate was 55% (95% CI, 39%-69%) in patients whose site of first recurrence was bone, while being only 13% (95% CI, 1%-43%) in those with the liver as first site of recurrence (figure 1B), and the multivariate analysis showed the first dominant site of metastasis to be independently associated with survival after recurrence as showed by others [6][8][9]. In our present study, more than 2 metastatic sites predicted a poor outcome. Multiple metastases mean that cancer cells have disseminated extensively. Some patients develop limited numbers and sites of metastatic disease. Oligometastasis is the term describing restricted tumor metastatic capacity, and is associated with a better prognosis [10]. Patients with oligometastases are sometimes curable following surgical treatment. Patients with more than 2 sites of organ involvement mostly deviate from this concept, and are less curable. Liver metastasis is also associated with a poor prognosis, because it also means disseminated cancer cells and leads to early mortality. Even among patients with liver metastasis, the existence of multiple metastases represents a poorer prognosis after liver resection[11].

Time of the first recurrence is one of the prognostic factors of survival after the first recurrence (Table 4). The survival curves after the first recurrence improved from 1980-1994 to 1995-2008 (Fig. 2). We previously reported that OS of primary breast cancer patients in our institute improved significantly from 1982–1989 to 1990–2003 [2]. The improvement of OS is suggested to reflect improvement in survival after the first recurrence.

On logistic regression analysis, breast surgery, and adjuvant chemotherapy were treatment-related factors contributing to improved survival over time (Table 6). In view of breast surgery, partial mastectomy was applied to relatively small size of tumor; early stage breast cancer. The remnant breast after partial mastectomy generally receives

radiation therapy. Radiation therapy had been reported to reduce breast cancer-related mortality [12]. Radiation therapy is suggested to affect the result in addition to breast surgery.

Adjuvant chemotherapy has dramatically changed in the past quarter century. Oral chemotherapy had been the mainstream in the 1980's in our institution. New drugs, such as taxane, trastuzumab-combined chemotherapy, or anthracycline containing regimen, have become available after 2000. These drugs have been demonstrated by randomized trials to improve survival. We did not identify any specific drug as contributing to improved survival over time, but we assume that advances in adjuvant chemotherapy in general have all contributed to this clear trend. As adjuvant endocrine therapy, selective estrogen receptor modulators such as tamoxifen were approved in 1981, and third generation aromatase inhibitors have been administered since 2001 in Japan. In this study, the number of patients given aromatase inhibitors as adjuvant therapy was quite small, such that their impact on improvements over time appeared to be minimal. This supports the view that adjuvant endocrine therapy did not affect chronological change.

The ways of treatment after recurrence are vary with each individual. ER-negative patients usually receive chemotherapy after recurrence. In late years, many new drugs for metastatic breast cancer have appeared, for example, capecitabine, trastuzumab, vinorelbine, or gemcitabine in addition to taxane or anthracycline. Trastuzumab has also improved survival of HER2-positive patients [13], although our study does not significantly support this. In addition to chemotherapy or molecular-targeted therapy, wide varieties of endocrine therapy are used after recurrence in many ER-positive patients. Drugs that may benefit ER-positive patients include aromatase inhibitor, tamoxifen, LHRH analog, high dose toremifene, and medroxyprogesterone acetate. We document the importance that increasing in approved drugs affects better survival after recurrence.

The survival curve showed improvement both in ER-positive and in ER-negative subgroups. Especially in ER-negative subgroup, survival after first recurrence increased significantly ($p=0.022$). Our results differ from reports by Andre [14] or Shigematsu [15]. They reported that hormone receptor-positive subgroup has a better survival improvement. In our institution, adjuvant chemotherapy has changed from oral therapy to intravenous multi-therapy. On univariate logistic analysis, adjuvant chemotherapy is one of the factors contributing to chronological survival changes. Our results indicate that survival improvement has led by the change in adjuvant chemotherapy.

Pathological TNM was a factor contributing to changes in survival over time. This prompted us to speculate that greater numbers of women undergoing breast cancer screening including mammography, and therefore seeking treatment in earlier stages of breast cancer, has resulted in better outcomes[16].

DFI was also one of the factors significantly influencing chronological change. It is reasonable to assume that DFI was prolonged because of advances in adjuvant treatments and better patient awareness of breast cancer. Prolonged DFI also impacted the observed improvement not only in survival over time but also in the survival after first recurrence. Certain factors such as the attitudes of patients and their families, or the method of follow up, may affect the ongoing improvement in survival. These results give us hope that survival time after the first recurrence will be even longer in the future.

Conclusions

The series of patients examined in this study showed ER-positive status at the time of diagnosis to be associated with increased OS, DFI, and survival time after the first recurrence of breast cancer. However, the site of recurrence, PR status at the time of diagnosis, DFI, and recurrent year were also factors predicting outcomes. Survival time after the first recurrence of breast cancer has steadily increased in recent decades significantly in ER-negative subgroups. We confirmed that advances in treatments and attitudes about breast cancer have contributed to this improvement in survival after first recurrence.

Disclosure

The authors declare that they have no competing interests.

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Figure legends

Figure 1: Kaplan–Meier estimates for survival after first recurrence according to (A) estrogen receptor (ER) status, (B) site of recurrence, and (C) disease-free interval (DFI).

Figure 2: Chronological changes in survival after first recurrence of (A) all patients, (B) ER-positive subgroup, and (C) ER-negative subgroup.

Figure 1A

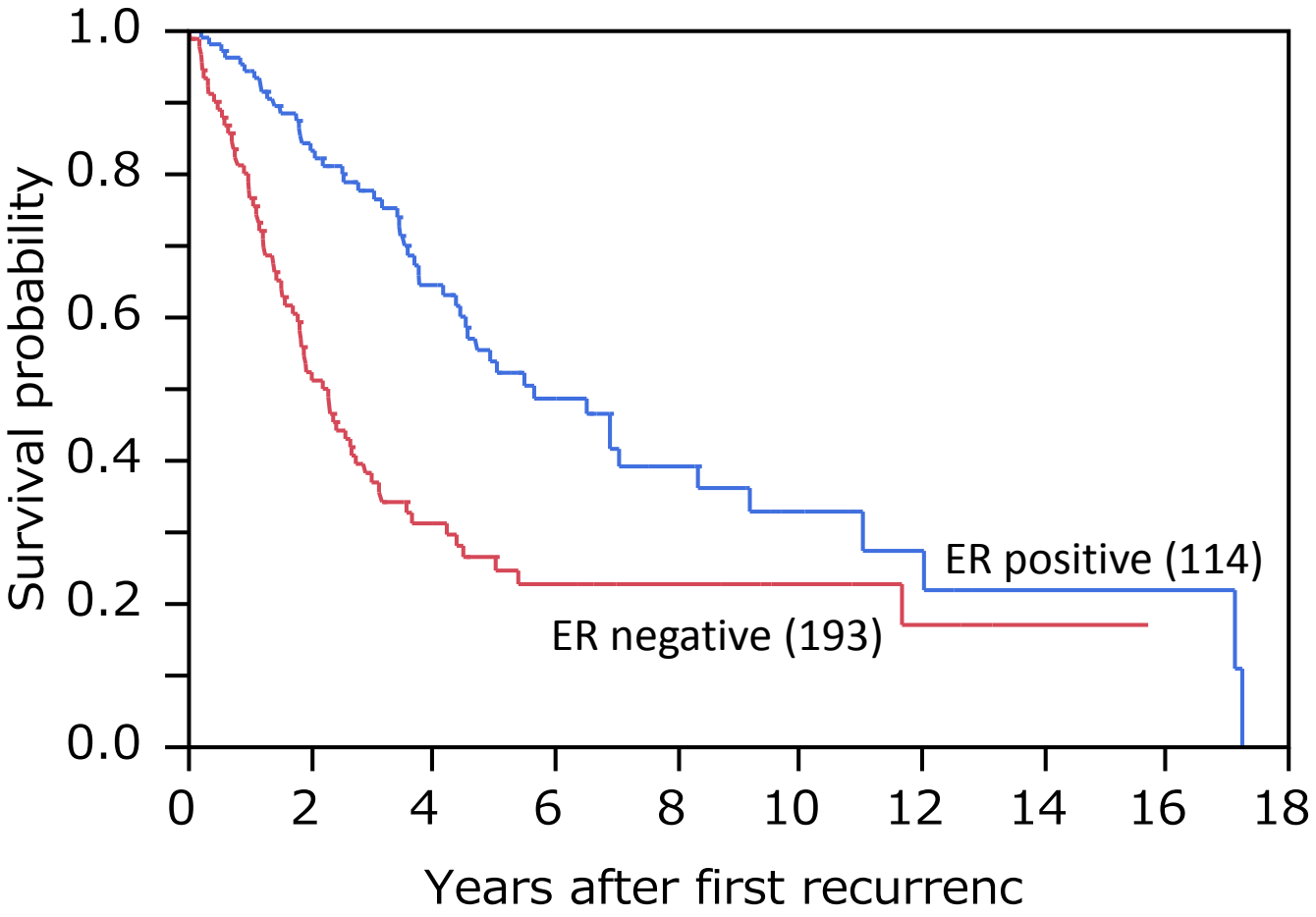

1.0
0.8
0.6
0.4
0.2
0.0
Survival probability
ER positive (114)
ER negative (193)
0
2
4
6
8
10
12
14
16
18
Years after first recurrenc

Figure 1B

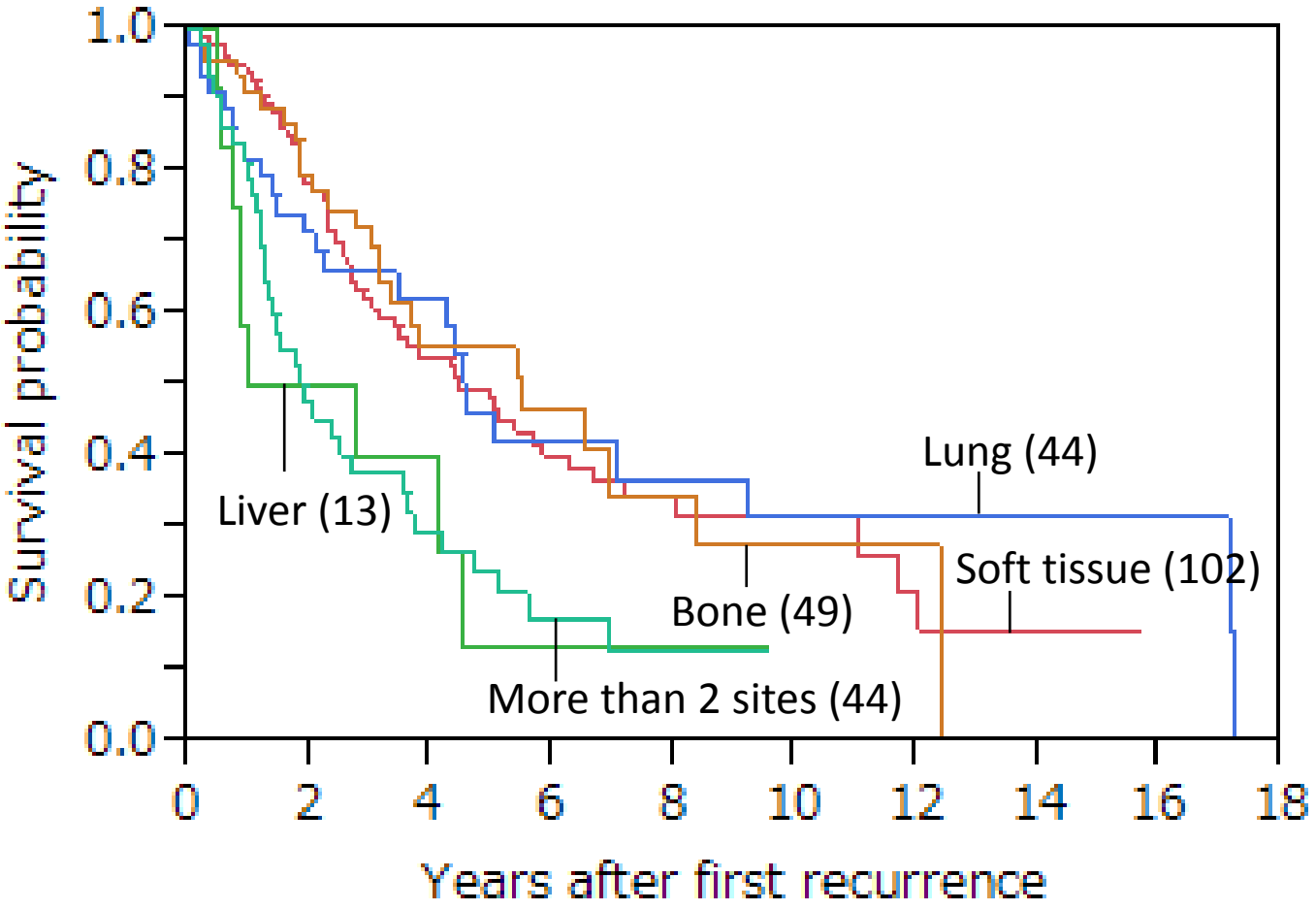

1.0
0.8
0.6
0.4
0.2
0.0
Survival probability
0
2
4
6
8
10
12
14
16
18
Years after first recurrence
Liver (13)
Lung (44)
Soft tissue (102)
Bone (49)
More than 2 sites (44)

Figure 1C

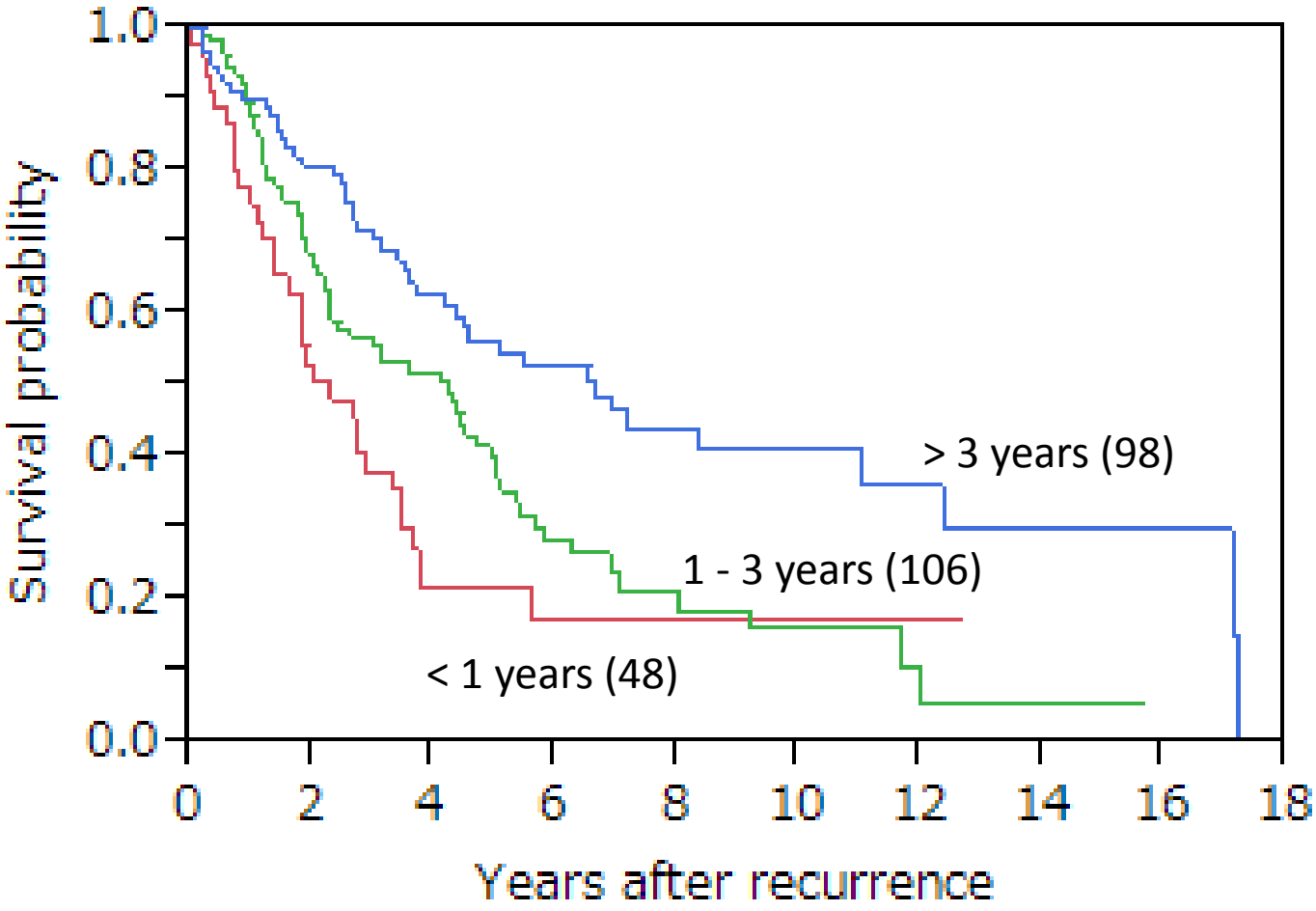

1.0
0.8
0.6
0.4
0.2
0.0
Survival probability
0
2
4
6
8
10
12
14
16
18
Years after recurrence
> 3 years (98)
1 - 3 years (106)
< 1 years (48)

Figure 2A

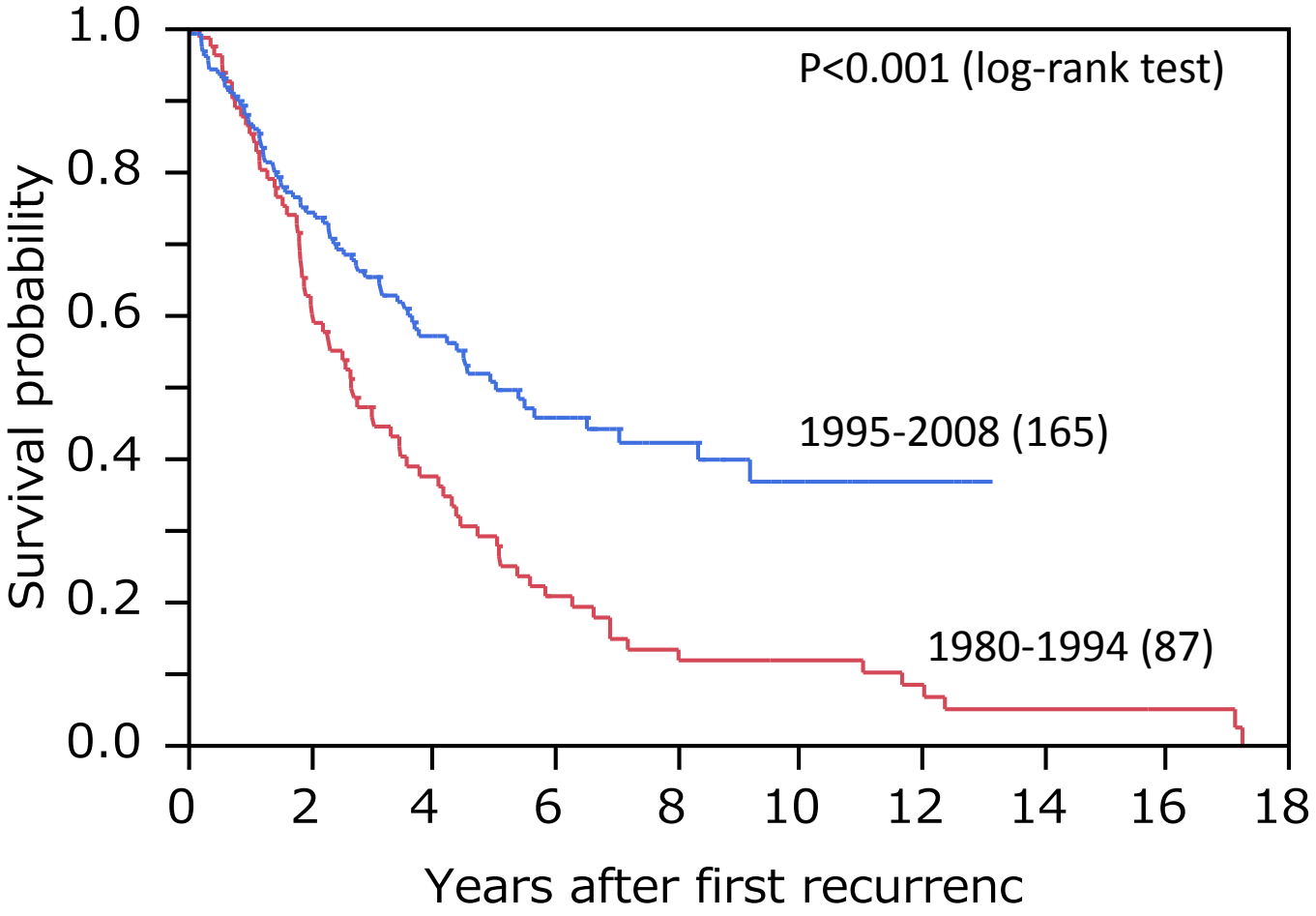

1.0
0.8
0.6
0.4
0.2
0.0
Survival probability
P<0.001 (log-rank test)
1995-2008 (165)
1980-1994 (87)
0
2
4
6
8
10
12
14
16
18
Years after first recurrenc

Figure 2B

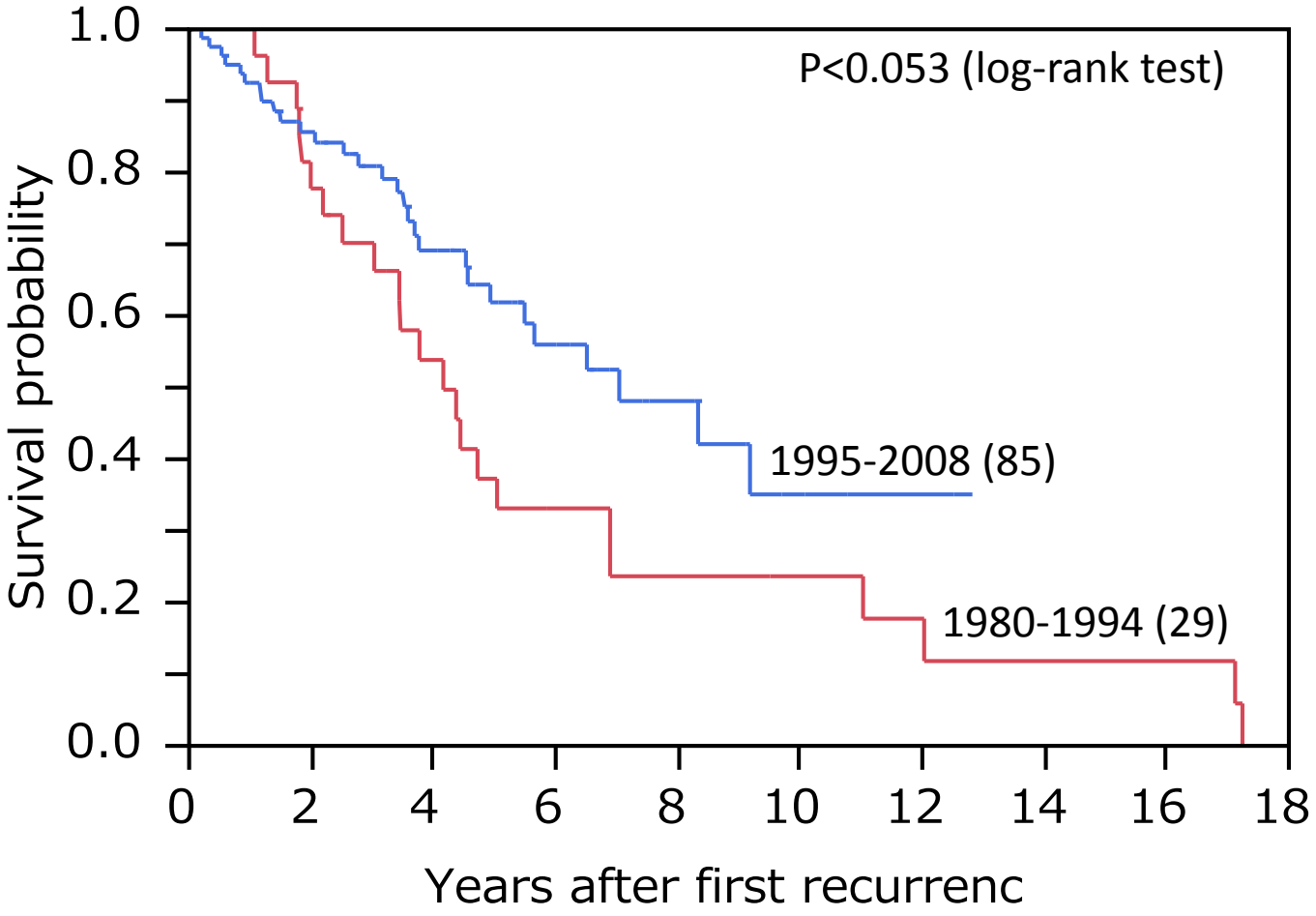
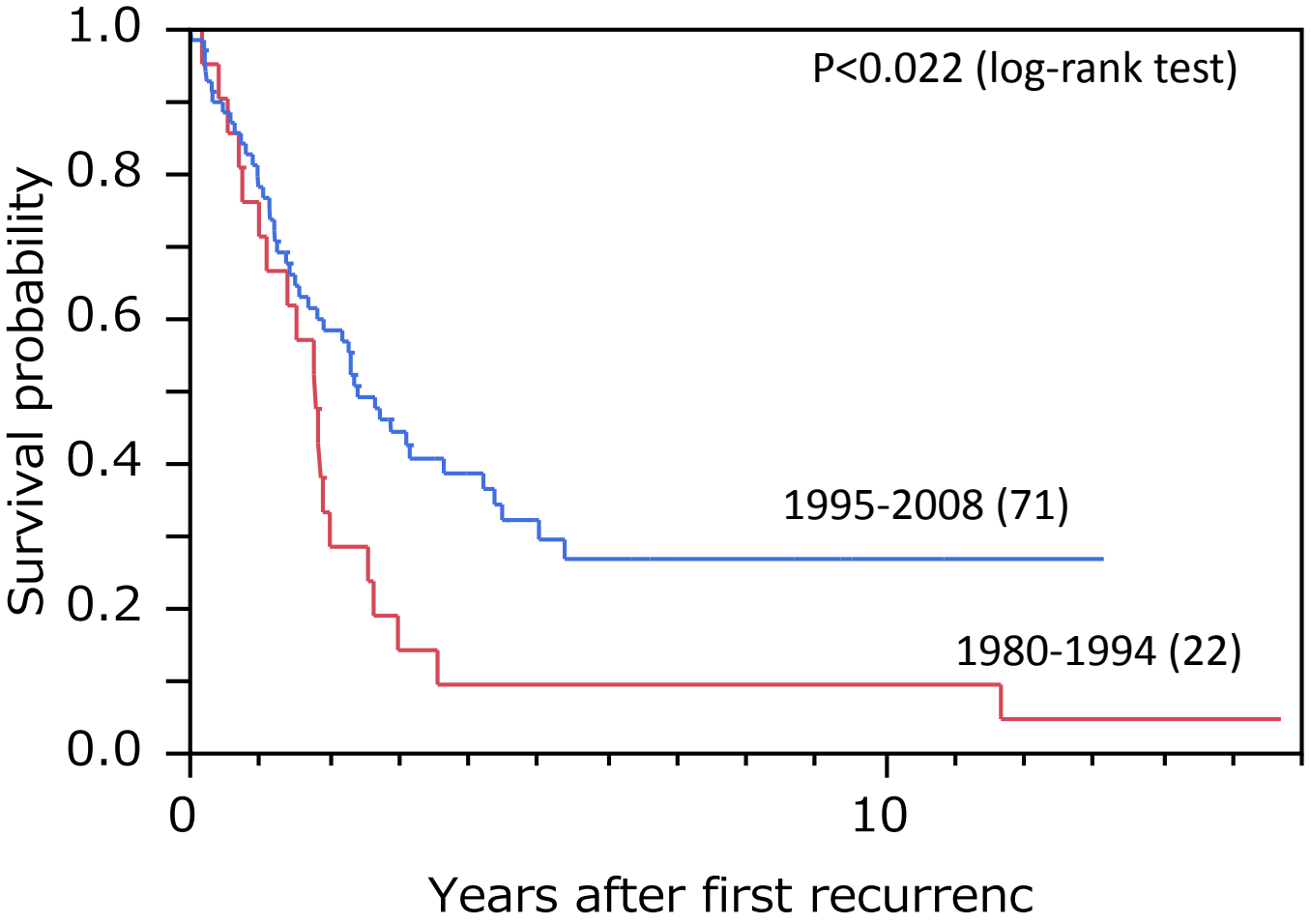

P<0.053 (log-rank test)
1995-2008 (85)
1980-1994 (29)
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
12
14
16
18
Years after first recurrenc

Figure 2C


1.0
0.8
0.6
0.4
0.2
0.0
Survival probability
P<0.022 (log-rank test)
1995-2008 (71)
1980-1994 (22)
0
10
Years after first recurrenc