

Clinical Visit for Anamnesis and Physical Examination

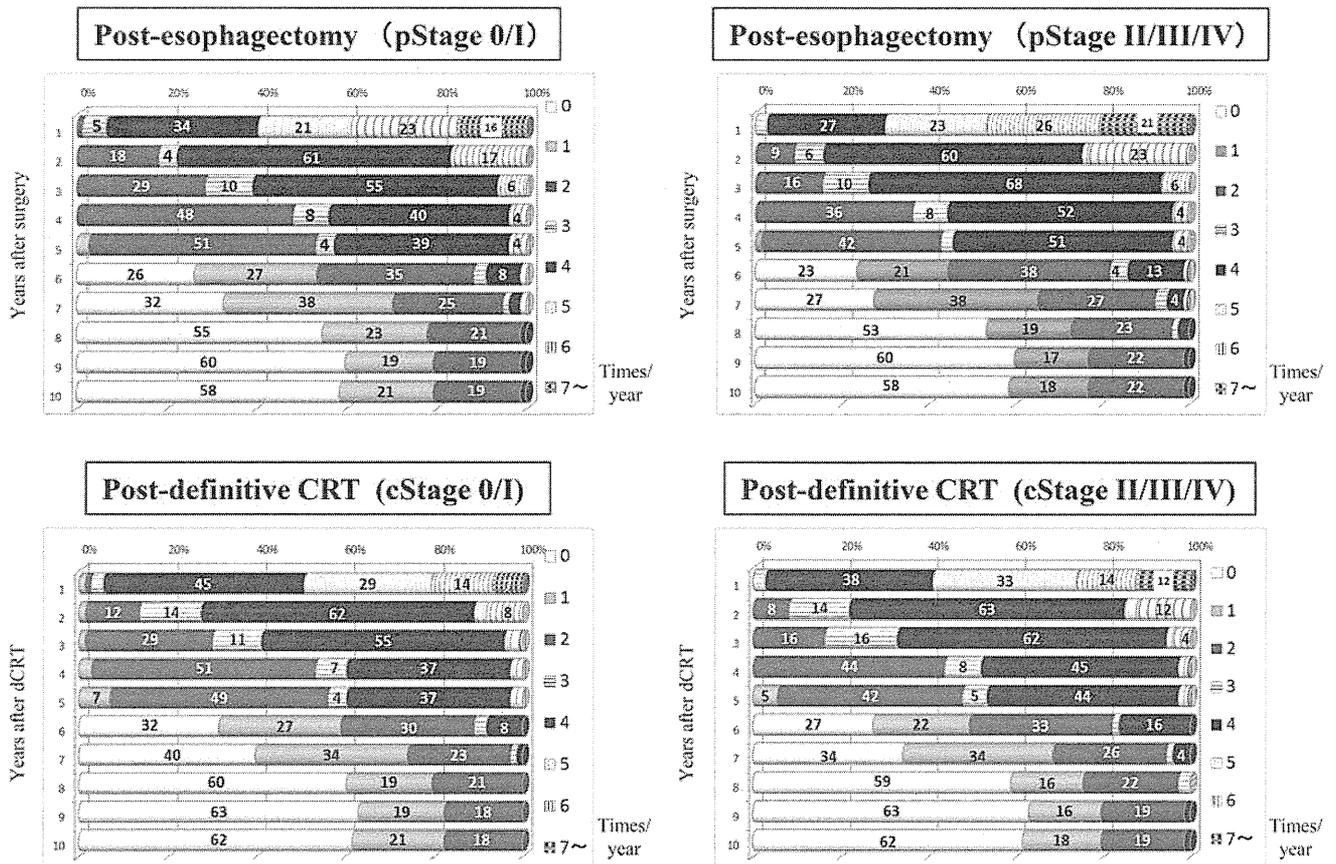


Fig. 1 The frequencies per year and duration after treatments with curative intent concerning “clinical visits for anamnesis and physical examination” after esophagectomy (pStage0/I and pStageII/III/IV)

and definitive chemoradiotherapy (cStage0/I and cStageII/III/IV) are shown separately

Upper gastrointestinal endoscopy (UGIE)

The purpose of UGIE is to check for recurrences at the anastomotic sites after esophagectomy or at the primary lesions that responded completely to dCRT, for the occurrence of multiple metachronous cancers in the remnant esophagus and the conduits, including the stomach and the colon, and for the occurrence of gastro-esophageal reflux disease and anastomotic strictures.

For post-esophagectomy patients of any pStage, UGIE was performed once or twice a year in most hospitals for 5 years and was continued until the 7th and the 10th years in more than 70 and 40 % of the hospitals, respectively. For post-dCRT patients of any cStage, UGIE was performed much more frequently than for post-esophagectomy patients, possibly because the whole esophagus is preserved. In the 1st year after

dCRT, approximately 50 % of the hospitals reported that they performed UGIE four times or more per year. UGIE was continued in nearly 100, 65 and 40 % of the hospitals until the 5th, 7th and the 10th years, respectively (Fig. 3).

Screening of metachronous multiple cancers in other organs

It is well known that esophageal cancers are frequently accompanied by metachronous cancers of other organs, especially of the H&N regions, stomach and colon [15]. The screening of H&N cancers by H&N surgeons and/or UGIE was performed once a year in only half of the hospitals for 5 years after both esophagectomy and dCRT, regardless of stage (Online Resource 9). The screening of colon cancers was performed bi-annually at approximately 20 % of the hospitals (Online Resource 10).

Cervical – Chest CT

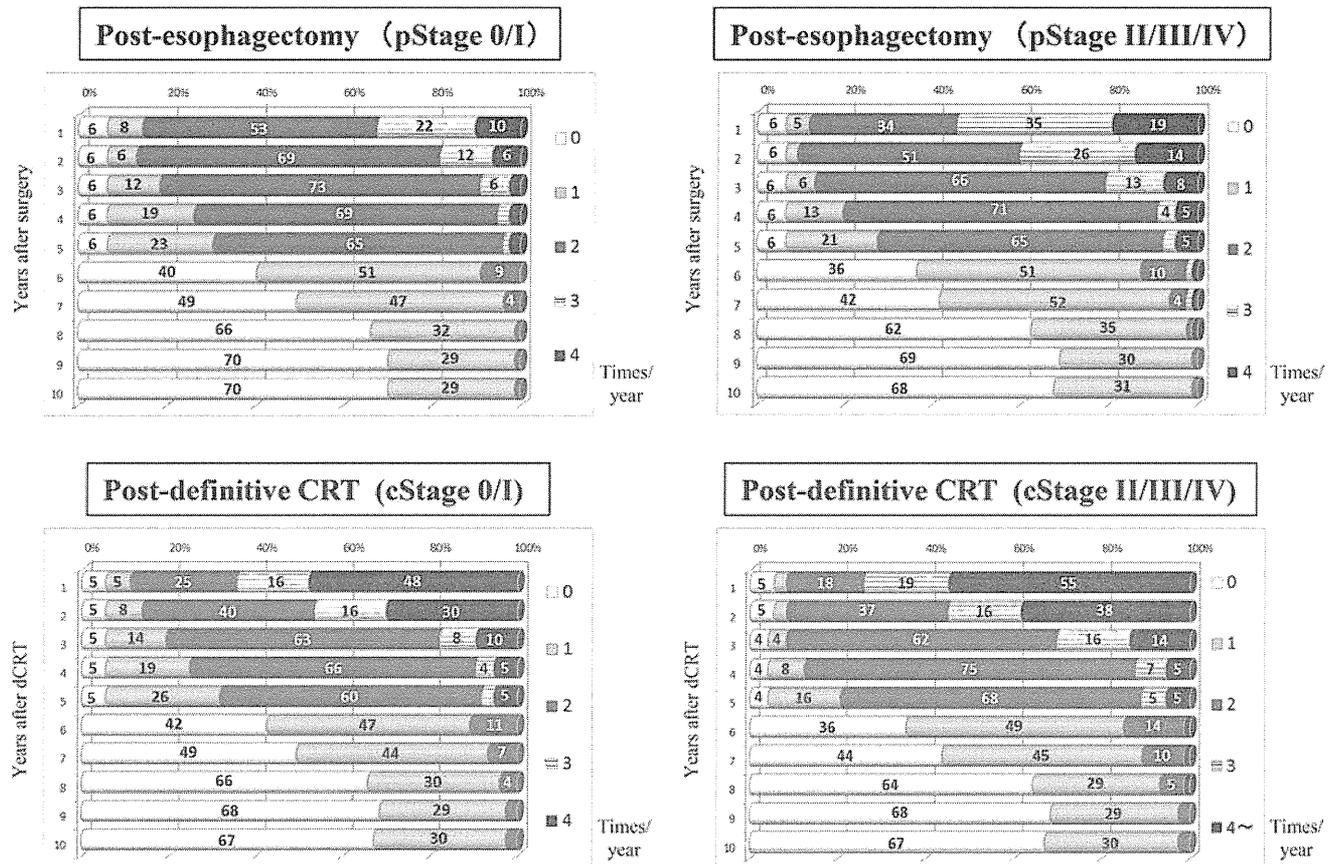


Fig. 2 The frequencies per year and duration after treatments with curative intent concerning “cervical to chest CT” after esophagectomy (pStage0/I and pStageII/III/IV) and definitive chemoradiotherapy (cStage0/I and cStageII/III/IV) are shown separately

Evaluation of post-treatment QOL

Only 7 and 6 hospitals evaluated the patient’s QOL after esophagectomy and dCRT, respectively, using validated tools such as EORTC-OES18 and FACT-E [16, 17] (data not shown).

Discussion

It is obvious that some of the patients with recurrence after a curative esophagectomy or dCRT can be cured when they are diagnosed at an early stage by re-resection, radiotherapy or chemoradiotherapy [18–24]. Thus, it is important to find recurrences of esophageal cancers after a curative esophagectomy or dCRT at the earliest stage possible for the patients to be able to undertake further curative treatments before the tumor becomes unresectable and/or their general status deteriorates. Furthermore, the early detection of recurrence might achieve better compliance to various

treatments and the opportunity to obtain a more prolonged survival and a better QOL. Abate et al. [1] showed that frequent early follow-up was appropriate after esophagectomy for adenocarcinoma and that survival after recurrence was improved by the therapies. On the other hand, there are some reports suggesting that an annual CT scan does not improve the clinical outcome after esophagectomy for esophageal cancer [6] and that intensive follow-up with routine imaging and endoscopy after surgery might not be justified for patients with gastro-esophageal cancers, especially in the light of the cost [8].

No standard, evidence-based method for follow-up observation after a curative esophagectomy or dCRT for esophageal cancer has ever been established [1, 5, 6]. In these circumstances, the follow-up protocols after esophagectomy or dCRT vary widely throughout the world and reflect institutional preferences [1, 5, 6]. At present, follow-up trends have not been investigated, even on a single-country basis. Thus, this nation-wide survey was conducted in order to clarify the present status of follow-up

Upper Gastrointestinal Endoscopy

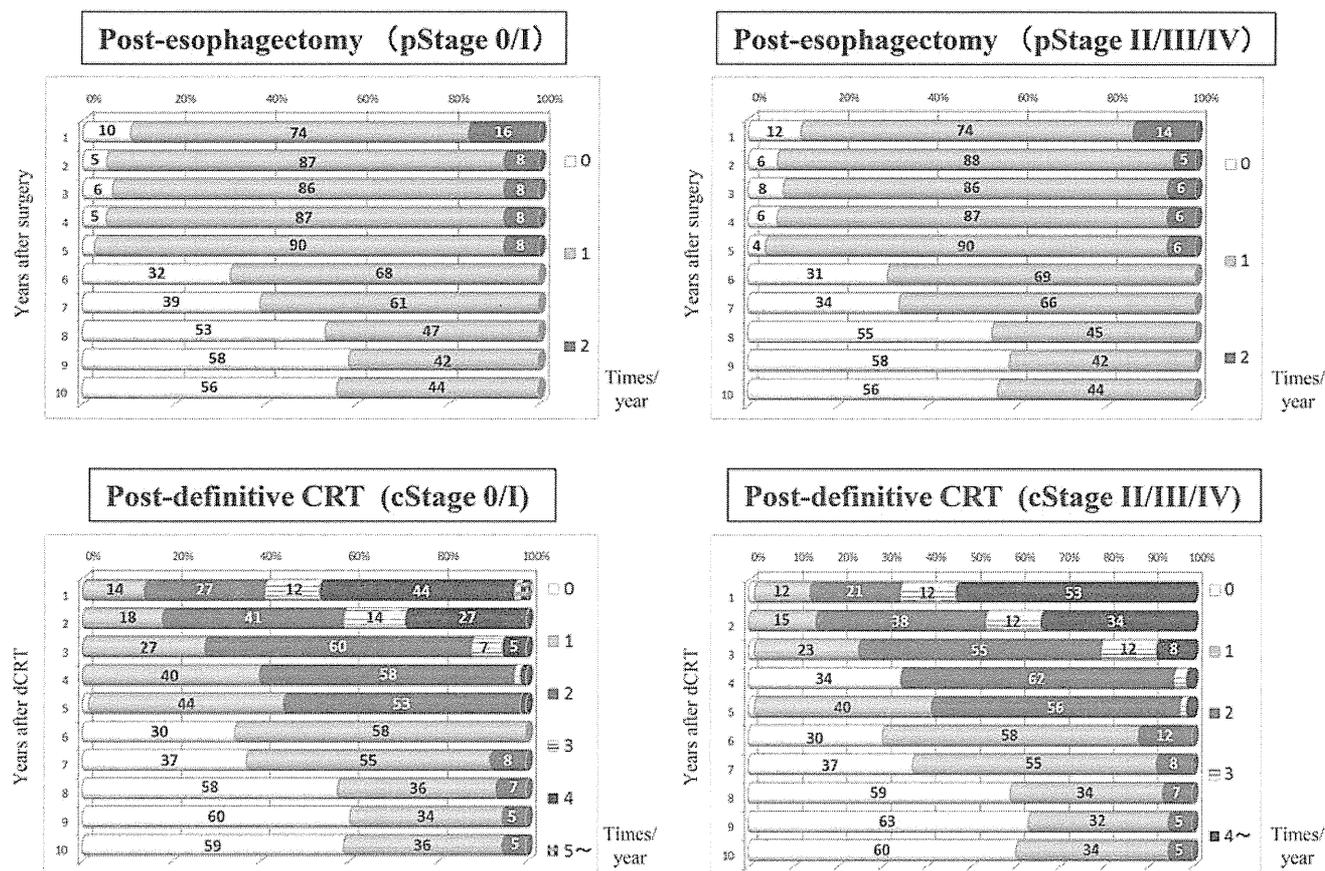


Fig. 3 The frequencies per year and duration after treatments with curative intent concerning “upper gastrointestinal endoscopy” after esophagectomy (pStage0/I and pStageII/III/IV) and definitive chemoradiotherapy (cStage0/I and cStageII/III/IV) are shown separately

protocols after esophagectomy or dCRT and, if possible, to reach a general agreement among Japanese hospitals.

With regard to the frequency and duration of follow-up, most hospitals follow their patients for 5 years after esophagectomy or dCRT, and at an especially high frequency in the first 3 years after treatment (Fig. 1). This seems to be reasonable, considering that most of the recurrences are reported to occur within 2 years after esophagectomy [5, 25, 26] and dCRT [4]. Moreover, about 70 and 40 % of the hospitals continue the follow-up until the 7th and 10th years after the treatments, respectively. This may be beneficial for checking for any changes of the patients’ QOL, the occurrence of late toxicities due to dCRT [9], and for managing the patients’ general conditions.

Almost all hospitals utilized a CT scan ranging from the cervix to the abdomen for follow-up (Fig. 2). Other imaging modalities such as FDG-PET/CT, cervical and abdominal USs, and chest and abdominal Xps were incorporated at much lower rates. UGIE was more frequently performed for post-dCRT patients than post-esophagectomy patients

(Fig. 3). This is reasonable, because locoregional recurrence after dCRT occurs in 41 % of all patients, most frequently at the site of the primary tumor in the esophagus [4]. It is also necessary to check the development of either metachronous remnant esophageal cancer or multiple cancers of the H&N region, the stomach and the colon, because Sato et al. [27] reported that a second malignancy was the major cause of death among patients without any lymph node metastasis who underwent an esophagectomy for thoracic esophageal cancer. Oki et al. [28] reported that frequent endoscopic examinations were important even several years after performing an esophagectomy, since the risk of gastric tube cancer was higher than the risk of a recurrence of esophageal cancer several years after an esophagectomy and that only an early diagnosis permitted a less invasive and appropriate approach for the treatment of gastric tube cancer.

Although it is very difficult to establish a follow-up protocol with a nation-wide consensus, we dare to propose a follow-up protocol after curative esophagectomy and

Table 1 The most common modalities and their frequencies per year at participating hospitals during follow-up protocol after treatments with curative intent of esophageal cancer patients

	Year after treatment	1st		2nd		3rd		4th		5th		6th		7th		8th		9th		10th	
		Times/year	%																		
Clinical visit																					
Post-esophagectomy	Most	4	27	4	60	4	68	4	52	4	51	2	38	1	38	0	53	0	60	0	58
	2nd most	6	26	6	23	2	16	2	36	2	42	0	23	0 or 2	27	2	23	2	22	2	22
Post-dCRT	Most	4	38	4	63	4	62	4	45	4	44	2	33	1 or 0	34	0	59	0	63	0	62
	2nd most	5	33	3	14	2 or 3	16	2	44	2	42	0	27	0 or 1	34	2	22	2	19	2	19
Tumor marker (CEA) ^a																					
Post-esophagectomy	Most	4	35	4	53	4	57	2	44	2	52	2	40	1	35	0	55	0	61	0	61
	2nd most	6	21	6	18	2	25	4	43	4	42	1	30	2	31	2	25	2	23	2	21
Post-dCRT	Most	4	38	4	56	4	52	2	45	2	44	2	38	0	41	0	63	0	67	0	67
	2nd most	5	32	3	14	2	21	4	40	4	37	0	33	1	30	2	21	2	18	2	18
CT (cervical-abdominal)																					
Post-esophagectomy	Most	3	35	2	51	2	66	2	71	2	65	1	51	1	52	0	62	0	69	0	68
	2nd most	2	34	3	26	3	13	1	13	1	21	0	36	0	42	1	35	1	30	1	31
Post-dCRT	Most	4 or more	55	4 or more	38	2	62	2	75	2	68	1	49	1	45	0	64	0	68	0	67
	2nd most	3	19	2	37	3	16	1	8	1	16	0	36	0	44	1	29	1	29	1	30
Upper GI endoscopy																					
Post-esophagectomy	Most	1	74	1	88	1	86	1	87	1	90	1	69	1	66	0	55	0	58	0	56
	2nd most	2	14	0	6	0	8	0 or 2	6	2	6	0	31	0	34	1	45	1	42	1	44
Post-dCRT	Most	4 or more	53	2	38	2	55	2	62	2	56	1	58	1	55	0	59	0	63	0	60
	2nd most	2	31	4	34	1	23	1	34	1	40	0	30	0	37	1	34	1	32	1	34
Screening of H&N cancers																					
Post-esophagectomy	Most	1 or more	51	1 or more	55	1 or more	48	1 or more	52	1 or more	53	0	57	0	62	0	79	0	81	0	81
	2nd most	0	49	0	40	0	47	0	43	0	42	1	43	1	38	1	21	1	19	1	19
Post-dCRT	Most	0	51	1 or more	59	1 or more	51	1 or 2	56	1 or 2	53	0	59	0	66	0	82	0	84	0	82
	2nd most	1 or more	32	0	41	0	49	0	44	0	47	1 or 2	41	1 or 2	34	1 or 2	18	1 or 2	16	1 or 2	18

The most and the 2nd most popular frequencies of each modality for each year are shown
dCRT definitive chemoradiotherapy, *CT* computed tomography, *GI* gastrointestinal, *H&N* head and neck

^a Tumor marker SCC-Ag is also included in the follow-up schedule by most of the hospitals

dCRT, based on the present data concerning the modalities incorporated by most of the participating hospitals and the most and the 2nd most popular frequencies of each modality for each year (Table 1). The appropriateness of this popular follow-up protocol should be verified in the future by comparing various aspects including the detection rate of recurrences and the overall survivals after treatments of recurrences between this protocol and less or more intensive ones. In addition, cost-effectiveness of each should also be considered [29]. Moreover, the patient's desire should also be taken into consideration, because Blom et al. [30] showed that two-thirds of the patients who underwent potentially curative esophagectomy for esophageal cancers preferred follow-up with routine imaging, even if screening would not provide a survival benefit.

The present study is associated with some limitations. (1) The data were only collected from 77 hospitals in Japan, which suggests the possibility that it does not represent the true status of follow-up protocols in Japan, although all of the surveyed hospitals were certified by the JES as training hospitals for a certified esophageal surgeon. (2) It is unknown whether a protocol shown here will reflect a truly favorable outcome for patients with esophageal cancer after esophagectomy or dCRT. Finally, (3) we did not consider the financial implications of costly investigations.

In conclusion, we tried to clarify the nation-wide trends in the follow-up protocol after curative esophagectomy and dCRT and attempted to propose a consensus protocol (Table 1). The suitability and efficacy of the protocol shown in the present study are not known with respect to cases of recurrent esophageal cancer. However, in spite of the above-mentioned limitations, we believe that the results of this nation-wide survey and a proposed protocol will contribute to the accumulation of larger-scale clinical data based on a fixed schedule with a consensus and to obtain evidence for making a more efficient and rational follow-up protocol to diagnose and treat recurrent esophageal cancers after curative esophagectomy and dCRT. In the future, the performance of meta-analyses using the findings of many reports on the outcome of a follow-up after a curative esophagectomy and dCRT will be necessary.

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Compliance with ethical standards

Ethical Statement This article does not contain any studies with human or animal subjects performed by any author(s).

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

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Comprehensive prognostic report of the Japanese Breast Cancer Society Registry in 2004

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Preface

In 1975, the Breast Cancer Study Group (the predecessor of the Japanese Breast Cancer Society) initiated the Breast Cancer Registry and had registered 188,265 breast cancer patients during the 29 years from 1975 to 2003. In 2004, a new registration system was implemented, which had registered a total of 207,468 patients up to 2009.

When the Personal Information Protection Law came into effect in 2004, the previous paper-based registration

system was converted to the web-based system, which includes anonymized efficacy data. At the same time, the data center was moved from the National Cancer Center to the Japan Clinical Research Support Unit (J-CRSU), a non-profit organization, and the Public Health Research Foundation.

Herein, we are pleased to report, for the first time under the new system, results on five-year prognosis of patients that were registered in 2004 (Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9; Supplementary Tables 1–9). We are deeply grateful to the medical and administrative staff as well as the patients who co-operatively participated in this study.

A total of 16,087 patients were originally registered from 317 institutions in 2004. Of these, 8585 (53.4 %) patients from 156 institutions were included in this prognostic study; we need to promote further participation in

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

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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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Comprehensive prognostic report of the Japanese Breast Cancer Society registry in 2006

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Preface

The prognostic study for the Japanese Breast Cancer Society (JBCS) registry in 2006 was finally published here (Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9, Sup. Table 1–9). The JBCS registry has been started from 1975. To 2003, for 29 years,

188,265 cases have been registered. With the cooperation of the Non-Profit Organization Japan Clinical Research Support Unit (J-CRSU) and the Public Health Research Foundation, we have moved to the new system by the web registration from 2004.

In 2006, the number of the registry for institutions was 352 and cases were 22,005. The number of institutions in this prognostic study was 134 and cases were 8788, with 39.9 %. An assessment of 5-year prognosis for cases registered in 2006 has been carried out, and here we report the results thanks to a number of efforts and cooperation. We believe that it is necessary to further promote the registry for contributions to improving breast cancer care and prognosis.

Background characteristics of the patients are summarized in Table 1. The 5-year disease-free survival (DFS) was

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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

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Abstract

Purposes We conducted a study to analyze the clinicopathological characteristics of breast cancer in Japan registered to the Japanese Breast Cancer Registry of the Japanese Breast Cancer Society (JBCS). Trends in the management of breast cancer patients in Japan were also analyzed.

Patients and methods More than 250,000 breast cancer patients were registered to the JBCS registry between 2004

and 2011. Demographic and clinicopathological factors in newly diagnosed primary breast cancer patients were registered to the JBCS through the Web-based system from affiliated institutes nationwide.

Results Two distinct peaks were observed, in patients in their late 40s and early 60s, in the population-adjusted age distribution of breast cancer patients. An increased rate of screen-detected breast cancer may contribute to an earlier detection of breast cancer and increased rate of non-invasive ductal carcinoma. The positive rate of either ER or PgR appears to have increased in recent years. The annual rates of patients treated with breast-conserving surgery

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increased until 2006, but these increases stopped in 2007 and thereafter plateaued at approximately 60 %. The annual rates of patients treated with sentinel lymph node dissection alone have steadily increased. The annual rates of patients treated with preoperative trastuzumab plus chemotherapy have also increased, as well as those treated with postoperative aromatase inhibitors. The annual rates of patients treated with postoperative anthracycline-containing regimens have decreased, whereas those treated with postoperative taxane-containing regimens have increased. The postoperative use of trastuzumab has markedly increased since 2007.

Conclusion Although this study was based on the registry database, several unique clinicopathological characteristics of breast cancer in Japan have been unveiled. Our results suggest that recent trends in the management of breast cancer patients in Japan were strongly followed by clinical evidence that originated from a number of clinical trials worldwide.

Keywords Clinicopathological characteristics · Trends in the management of breast cancer patients · Japanese Breast Cancer Society · Registry · Japan

Introduction

Breast cancer is one of the leading causes of cancer-related death in Japan and western countries. It has also been the most prevalent cancer in women in the last 20 years in Japan. The morbidity of breast cancer has been increasing for over 40 years in Japan. The main reason for this increase is considered to be the westernization of Japanese women in terms of their lifestyles. The lifetime risk for breast cancer in Japanese women was previously reported to be one in twelve in 2014 [1]. The prevention and early detection of breast cancer as well as the medical and social management of patients with breast cancer have been important medical issues in Japan. The Japanese Breast Cancer Society (JBCS) was founded in 1992 and has been a leading scientific society dealing with these issues.

In order to obtain a deeper insight into the clinicopathological characteristics of breast cancer and recent trends in the management of breast cancer patients in Japan, the JBCS started a Web-based registration system in 2004 [2]. The number of registered patients has steadily increased every year. A total of 48,133 patients were registered in 2010. According to the latest statistical analysis by the Center for Cancer Control and Information Services, National Cancer Center, Japan, a total of 68,107 breast cancer patients were estimated to be newly diagnosed in 2010 [1]. Approximately 70 % of newly diagnosed breast

cancer patients in Japan were registered to the JBCS registry in 2010.

Since ethnic differences and significant differences in the morbidity of breast cancer have been reported between Japanese women in Japan and Caucasian women in western countries, significant differences are considered to exist in breast cancer characteristics; however, these differences have not yet been elucidated in detail. A large number of Japanese breast cancer patients (more than 250,000) were registered to the JBCS registry between 2004 and 2011; therefore, we conducted this study in order to analyze the clinicopathological characteristics of breast cancer in Japan registered to the JBCS registry. Recent trends in the management of breast cancer patients in Japan were also examined because a number of new local and systemic therapies have been introduced into clinics in the last decade.

Patients and methods

Data collection

More than 50 items on the demographic and clinicopathological factors of newly diagnosed primary breast cancer patients were voluntarily registered to the Japanese Breast Cancer Registry of the JBCS through the Web-based system from affiliated institutes. The TNM classification was registered according to the *Unio Internationalis Contra Cancrum* (UICC) staging 6th edition [3]. Histological classification was registered according to the WHO classification [4].

This registry system has been conducted by the Registration Committee of the JBCS and supported by the Public Health Research Foundation (Tokyo, Japan). Annual reports on this registry have been published in Japanese and publicized through the JBCS homepage to active members of the JBCS (<http://www.jbcs.gr.jp/Member/tourokusyukei.html>).

Statistical analysis

Right and left breast tumors in patients with synchronous or asynchronous bilateral breast cancer were respectively treated as two different breast tumors in this registration system. The age-adjusted prevalence of primary breast cancer per 100,000 women was calculated based on the population database in each year provided from the Ministry of Health, Labour and Welfare, Japan. Statistical analyses were performed using SAS software (SAS Institute Japan Ltd., Tokyo, Japan) and Microsoft Excel software (Microsoft Japan, Tokyo, Japan).

Results and discussion

Breast cancer patients registered to the Breast Cancer Registry of the JBCS between 2004 and 2011

The annual number of breast cancer patients registered and that of affiliated institutes markedly increased between 2004 and 2011 (Supplementary Figure 1A and 1B). In the first year (2004) of the Web system, a total of 14,805 breast cancer patients were registered from 387 affiliated institutes nationwide in Japan. In the last year (2011), a total of 48,481 patients were registered from 845 affiliated institutes nationwide in Japan.

Gender

The annual rate of male breast cancer patients was between 0.38 and 0.49 % of all breast cancer patients registered in these eight years. According to reviews on male breast cancer [5], breast cancer is a rare disease in men, accounting for nearly 1 % of all breast cancer cases in western countries. The rate of male breast cancer patients appears to be lower than in western countries.

Only female breast cancer patients were analyzed in the following data analyses.

Bilateral breast cancer

The annual rates of synchronous bilateral breast cancer gradually increased from 3.5 % in 2004 to 4.8 % in 2011, while those of asynchronous bilateral breast cancer were 2.8–3.2 % in these years. An increase in the sensitivity of breast imaging modalities such as magnetic resonance imaging to detect early breast cancer may have led to increases in the rate of synchronous bilateral breast cancer.

According to a large cohort study ($n = 6550$) in Sweden, the rate of synchronous bilateral breast cancer was 1.5 % and that of asynchronous bilateral breast cancer was 3.8 % [6]. Another cohort study ($n = 1465$) reported that the rate of synchronous bilateral breast cancer was 3.0 % and that of asynchronous bilateral breast cancer was 7.1 % [7]. The rate of synchronous bilateral breast cancer appears to be slightly higher in Japan than in western countries.

Family history

The annual rates of breast cancer patients with a family history of breast cancer gradually increased from 8.0 % in 2004 to 9.7 % in 2011. A positive family history in this registry included not only breast cancer cases in first-degree relatives, but also those in second- or third-degree relatives. According to the Utah Population Database

survey ($n = 3864$), the rate of patients with a family history of first-degree relatives was 5.7 % [8]. Difficulties have been associated with comparing the rates of family history between breast cancer patients in Japan and those in western countries.

Menopausal status

The annual rates of premenopausal and postmenopausal breast cancer patients were 33.2–35.7 % and 61.3–63.8 % in these 8 years, respectively, while those with an unknown menopausal status including post-hysterectomy patients were 2.6–3.5 % in these years. Menopause was not strictly defined in this registry. According to data from the surveillance, epidemiology, end results (SEER) Program between 2007 and 2011 in the United States, the rates of newly diagnosed breast cancer patients less and more than or equal to 55 years old were 33.1 and 66.9 %, respectively [9]. The rate of premenopausal breast cancer patients appears to be slightly higher in Japan than in western countries.

Age

Two distinct peaks were observed, in patients in their late 40s and early 60s, in the population-adjusted age distribution of breast cancer patients in Japan (Fig. 1).

According to the SEER database between 2007 and 2011, there was only one peak, at the early 60s, in the age distribution of newly diagnosed breast cancer patients in the USA [9]. In contrast, there was one peak, in patients in their 40s, in this age distribution in South Korea [10]. These findings indicate that there are two mixed peaks in Japan: in patients in their 40s, similar to East Asian women, and those in their early 60s, similar to western women.

Body mass index (BMI)

The annual rates of obese breast cancer patients (BMI >25) were 22.4–23.4 % between 2004 and 2011. The distribution of BMI in breast cancer patients did not change between 2004 and 2011.

Based on data from one of the largest clinical trials in western countries, the Arimidex, Tamoxifen Alone, or in Combination study [11], BMI over 25 was observed in 56.8 % of the enrolled postmenopausal patients. In addition, based on data from the large breast cancer database of the University of Texas MD Anderson Cancer Center ($n = 6342$), BMI over 25 was observed in 60 % of the registered premenopausal and postmenopausal patients [12]. The rate of obese breast cancer patients appears to be markedly lower in Japan than in western countries.

Fig. 1 Population-adjusted age distribution of breast cancer patients between 2004 and 2011 in Japan

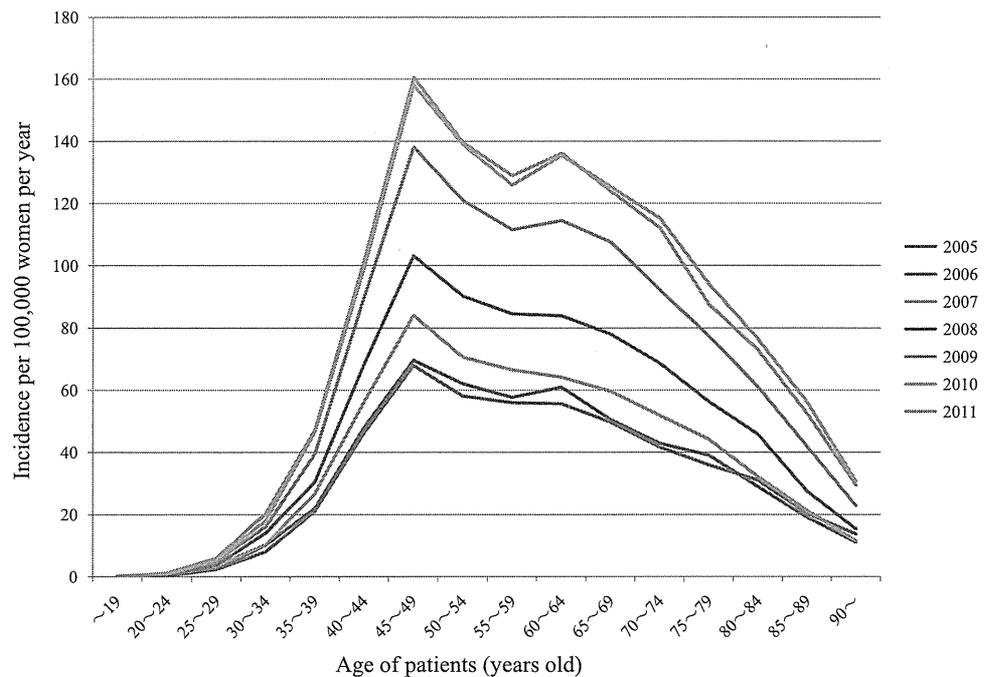
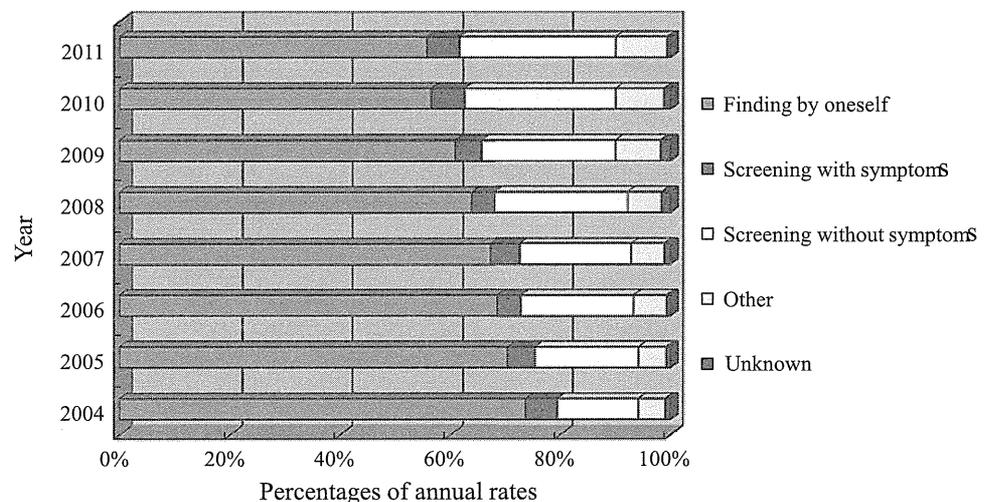


Fig. 2 Percentages of annual rates of breast cancer patients stratified by breast cancer detection methods between 2004 and 2011 in Japan



Detection by breast cancer screening

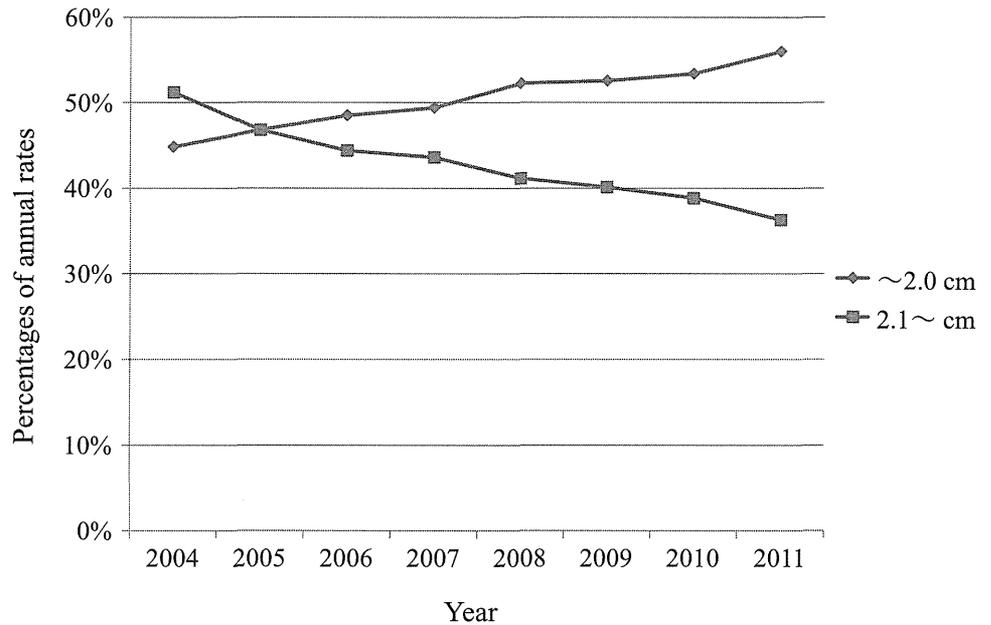
The annual rates of breast cancer patients without any symptoms and detected by breast cancer screening steadily increased from 14.9 % in 2004 to 28.6 % in 2011 (Fig. 2). These marked changes have been attributed to an increase in the annual rates of Japanese women receiving breast cancer screening, in particular, mammographic screening. According to statistical data provided from the Ministry of Health, Labour and Welfare in Japan, the annual rates of women receiving breast cancer screening in Japan increased from 24.7 % in 2007 to 30.6 % in

2011 [13]. These findings indicate that the earlier detection of primary breast cancer may be mainly caused by an increase in the rate of women receiving breast cancer screening in Japan.

Clinical tumor size

The annual rates of patients with tumors larger than 2.0 cm in size steadily decreased from 51.2 % in 2004 to 36.3 % in 2011 (Fig. 3). These marked changes also appear to have been due to an increase in the annual rates of Japanese women receiving breast cancer screening.

Fig. 3 Percentages of annual rates of breast cancer patients with tumors more than 2 cm in clinical size or less than or equal to 2 cm in clinical size between 2004 and 2011 in Japan



Skin changes, chest wall fixation, and inflammatory breast cancer

The annual rates of patients with tumors with skin changes were 3.6–4.4 % in these eight years, while those of patients with breast tumors fixed to chest wall were 0.5–1.2 %. The annual rates of patients with inflammatory breast cancer decreased from 1.2 % in 2004 to 0.3 % in 2011.

TNM stage

The annual rates of patients with Tis and T1 breast tumors increased from 7.4 and 37.3 % in 2004 to 11.2 and 45.3 % in 2011, respectively, whereas those with T2, T3, and T4 breast tumors decreased from 38.4, 5.0, and 5.9 % in 2004 to 27.5, 2.8, and 3.9 % in 2011, respectively (Supplementary Figure 2).

The annual rates of patients with N0 increased from 77.0 % in 2004 to 82.3 % in 2011. In addition, the annual rates of patients with M0 increased from 95.6 % in 2004 to 97.0 % in 2011.

The annual rates of patients with stage 0 and I breast cancer increased from 7.0 and 33.1 % in 2004 to 10.8 and 41.5 % in 2011, respectively (Supplementary Figure 3).

Pathological findings

1. Infiltrating tumor size

The annual rates of patients with breast tumors equal to or less than 2 cm in pathologically infiltrating tumor size increased from 53.6 % in 2004 to 63.0 % in 2011, whereas

those with breast tumors 2.1–5.0 cm and over 5.0 cm in pathologically infiltrating tumor size decreased from 36.3 and 6.9 % in 2004 to 26.6 and 4.9 % in 2011, respectively (Supplementary Figure 4).

2. Nodal status

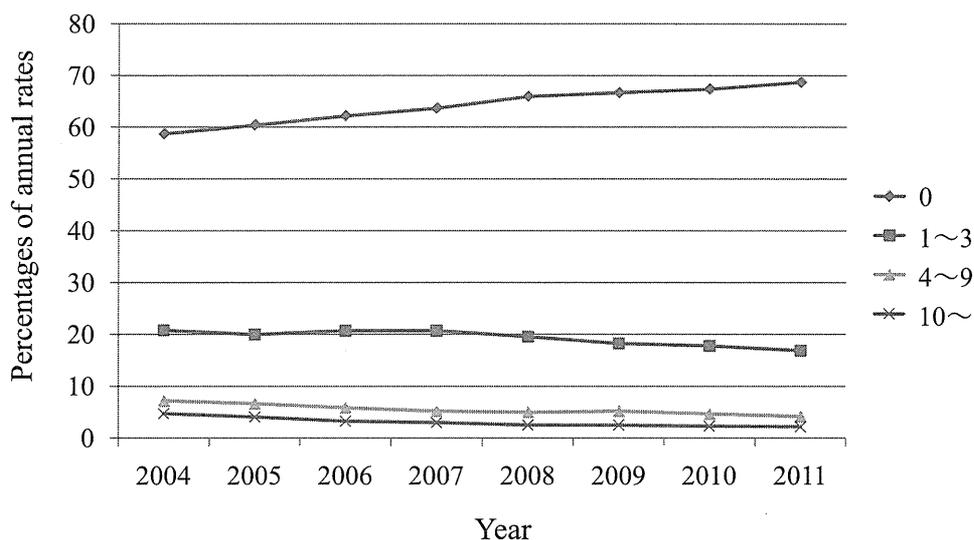
The annual rates of patients with no lymph node metastasis increased from 58.7 % in 2004 to 68.7 % in 2011, while those with 1–3, 4–9, and more than or equal to 10 metastatic lymph nodes decreased from 20.8, 7.2, and 4.7 % in 2004 to 16.9, 4.2, and 2.2 % in 2011, respectively (Fig. 4).

According to analyses based on the SEER database (2001–2008) and a cohort study in Belgium (2000–2009), the rates of node-negative breast cancer patients were 65.4 and 62.0 %, respectively [14, 15]. No significant difference was observed in the rate of node-negative breast cancer patients between patients in Japan and those in western countries.

3. Histological classification

The annual rates of patients with non-invasive ductal carcinoma increased from 8.2 % in 2004 to 14.3 % in 2011. These results indicated that this increase was mainly due to an increase in the rate of breast cancer patients detected by mammographic screening. According to a large cohort study in the USA [16], the rate of non-invasive ductal carcinoma has markedly increased for the last 20 years in parallel with increases in the rate of breast cancer patients detected by mammographic screening, and was approximately 20 % in 2003.

Fig. 4 Percentages of annual rates of breast cancer patients stratified by the number of metastatic lymph nodes between 2004 and 2011 in Japan



In contrast, the annual rates of patients with invasive ductal carcinoma decreased from 79.8 % in 2004 to 74.0 % in 2011, while those with non-invasive lobular carcinoma, special types, and others did not significantly change in those years.

The annual rates of patients with invasive lobular carcinoma slightly increased from 3.1 % in 2004 to 3.7 % in 2011. Previous studies reported that the rate of invasive lobular carcinoma had increased and was 5–15 % in western countries [17, 18].

4. Estrogen receptor (ER) and progesterone receptor (PgR) status

The annual rates of patients with ER-positive breast tumors increased from 71.8 % in 2004 to 79.7 % in 2011, whereas those with ER-negative breast tumors decreased from 24.5 % in 2004 to 17.5 % in 2011, respectively.

It should be noted that not only the cutoff level of ER positivity, but also test procedures for ER immunostaining have not yet been standardized in Japan or other countries. Therefore, it is difficult to conclude the trend in the rate of ER positivity in Japan.

The annual rates of patients with PgR-positive breast tumors increased from 58.8 % in 2004 to 69.5 % in 2011, whereas those with PgR-negative breast tumors decreased from 37.2 % in 2004 to 27.7 % in 2011, respectively. Because of its similar background to ER positivity, it is difficult to conclude the trend in the rate of PgR positivity in Japan.

The annual rates of patients with ER-positive and PgR-positive breast tumors increased from 58.9 % in 2004 to 70.8 % in 2011, whereas those with ER-positive and PgR-negative, ER-negative and PgR-positive, and ER-negative and PgR-negative breast tumors have decreased from 15.5,

2.4, and 23.2 % in 2004 to 11.2, 0.7, and 17.2 % in 2011, respectively.

According to our previous cohort study, either the ER-positive rate or PgR-positive rate of breast tumors was higher in patients in their 40s than in those over 50 [19, 20]. To clarify this finding, we analyzed both ER-positive and PgR-positive rates stratified by age in breast cancer patients registered in 2011. As expected, the ER-positive rate was approximately 90 % in patients in their 40s and approximately 80 % in those over 50, and the PgR-positive rate was approximately 85 % in patients in their 40s and less than 70 % in those over 50 (Supplementary Figure 5).

5. HER2 status

The annual rates of patients with HER2-positive and HER2-negative breast tumors were 12.3–15.5 and 67.4–77.7 %, respectively. No significant changes were observed between 2004 and 2011. The annual rates of patients with HER2-unknown breast tumors steadily decreased from 20.2 % in 2004 to 7.7 % in 2011.

According to an analysis of the California Cancer Registry database (2006–2008), HER2 positivity rates were 13 % for white women, 17 % for black women, 18 % for Hispanic women, and 20 % for Asian women, respectively [21]. Since not only the cutoff level of HER2 positivity, but also test procedures for HER2 immunostaining and HER2 gene amplification have not yet been standardized in Japan or other countries, it is difficult to compare HER2 positivity rates among different countries.

Local therapies

1. Surgical procedures for breast tumors

The annual rates of patients treated with breast-conserving surgery increased from 50.1 % in 2004 to 58.6 % in 2011. However, these increases stopped in 2007 and thereafter plateaued at 59 %. The annual rates of patients treated with modified radical mastectomy steadily decreased from 42.5 % in 2004 to 26.9 % in 2011, while those with standard or extended radical mastectomy were 0.3–0.6 % and did not significantly change in those years. The annual rates of patients treated with simple mastectomy increased from 5.6 % in 2004 to 13.0 % in 2011, and this was attributed to an increased rate of patients receiving simultaneous breast reconstruction in recent years (Fig. 5).

Medical care systems and socio-economic backgrounds strongly influenced the choice of modalities of local therapy for breast cancer among different countries. The rate of breast-conserving surgery was previously reported to be 50–60 % in western countries and 10–30 % in China and India [22, 23].

2. Surgical procedures for axillary lymph nodes

The annual rates of patients treated with sentinel lymph node biopsy alone steadily increased from 18.3 % in 2004 to 59.0 % in 2011, whereas those treated with axillary lymph node dissection steadily decreased from 69.6 % in 2004 to 31.7 % in 2011 (Fig. 6).

Sentinel lymph node biopsy was approved for practical use by the Ministry of Health, Labour and Welfare, Japan in 2010. This approval clearly increased the rate of sentinel lymph node biopsy alone in Japan, and the rate of 59 % in 2011 was almost equal to that in western countries [24].

3. Postoperative radiotherapy

Stage IV breast cancer patients were excluded to simplify this analysis, and patients treated with two major breast surgical procedures, breast-conserving surgery and modified radical mastectomy, were selected as study subjects.

The annual rates of patients treated with breast-conserving surgery followed by postoperative radiotherapy steadily increased from 72.0 % in 2004 to 80.0 % in 2011, while those treated with modified radical mastectomy followed by postoperative radiotherapy also increased from 8.6 % in 2004 to 14.6 % in 2011 (Supplementary Figure 6).

According to an analysis on the SEER database for patients with invasive breast cancer in Detroit and Los Angeles (2005–2007), postoperative radiotherapy was performed if indicated in 80.0–95.4 % of patients treated with breast-conserving surgery and in 47.5–77.6 % of patients treated with mastectomy [25]. These findings suggest that postoperative radiotherapy was more frequently performed in the USA than in Japan.

Systemic therapies

1. Preoperative systemic therapies

The annual rates of patients treated with preoperative systemic therapies increased from 9.6 % in 2004 to 14.2 % in 2008, but decreased from 14.0 % in 2009 to 9.3 % in 2011. Preoperative chemotherapies were more common

Fig. 5 Percentages of annual rates of breast cancer patients according to surgical procedures for breast tumors between 2004 and 2011 in Japan

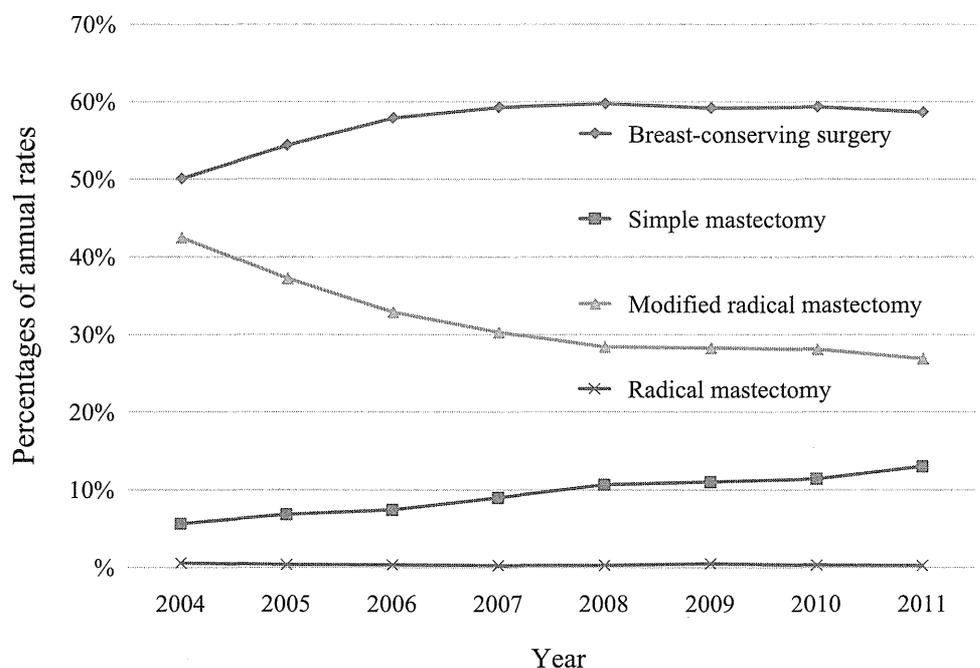
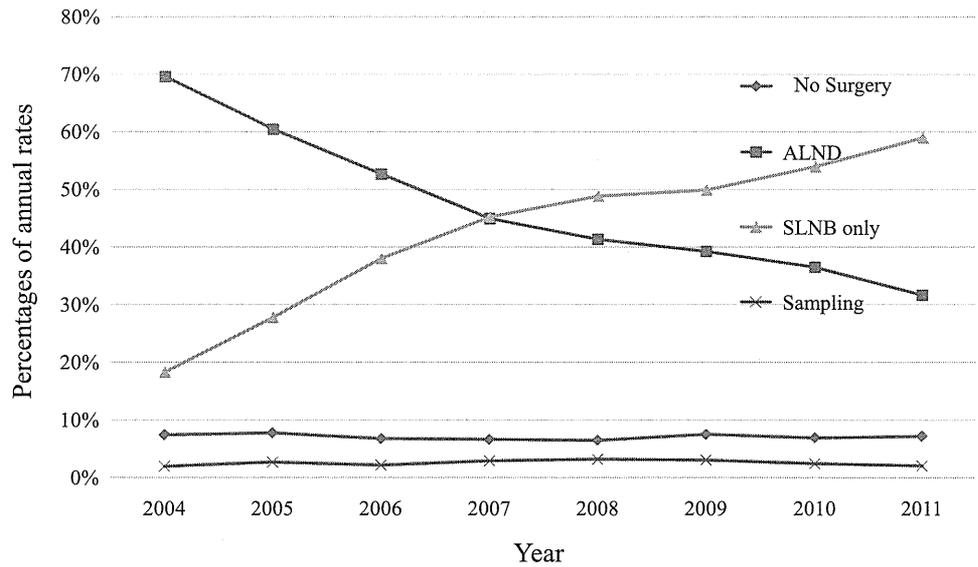


Fig. 6 Percentages of annual rates of breast cancer patients according to surgical procedures for axillary lymph nodes between 2004 and 2011 in Japan. *ALND* axillary lymph node dissection, *SLNB* sentinel lymph node biopsy



than preoperative endocrine therapies. However, the annual rates of patients treated with preoperative endocrine therapies in all patients treated with preoperative systemic therapies slightly increased from 15.8 % in 2004 to 20.6 % in 2011 (Supplementary Figure 7).

Anthracycline- and taxane-containing regimens were frequently used as preoperative chemotherapies between 2004 and 2011. Approximately 70 % of patients treated with preoperative systemic therapies received both regimens. Aromatase inhibitors were the most frequently used as preoperative endocrine therapeutic agents. The annual rates of patients treated with preoperative trastuzumab plus chemotherapy increased from 5.8 % in 2004 to 20.5 % in 2011.

2. Postoperative systemic therapies

The annual rates of patients treated with postoperative systemic therapies were 85.9–90.6 % between 2004 and 2011. No significant changes were observed in these rates during that time. Postoperative endocrine therapies were more common than postoperative chemotherapies. The annual rates of patients treated with postoperative chemotherapies in all patients treated with postoperative systemic therapies gradually decreased from 40.0 % in 2004 to 33.7 % in 2011 (Fig. 7).

Aromatase inhibitors and tamoxifen were the most commonly used as postoperative endocrine therapeutic agents. The annual rates of patients treated with postoperative aromatase inhibitors in all patients treated with postoperative systemic therapies increased from 39.5 % in 2004 to 49.2 % in 2011, whereas those treated with postoperative tamoxifen slightly decreased from 38.3 % in 2004 to 32.8 % in 2011.

Anthracycline- and taxane-containing regimens were commonly used as postoperative chemotherapies between 2004 and 2011. The annual rates of patients treated with postoperative anthracycline-containing regimens in all patients treated with postoperative systemic therapies gradually decreased from 35.7 % in 2004 to 20.6 % in 2011, whereas those treated with postoperative taxane-containing regimens steadily increased from 14.7 % in 2004 to 22.4 % in 2011 (Supplementary Figure 8).

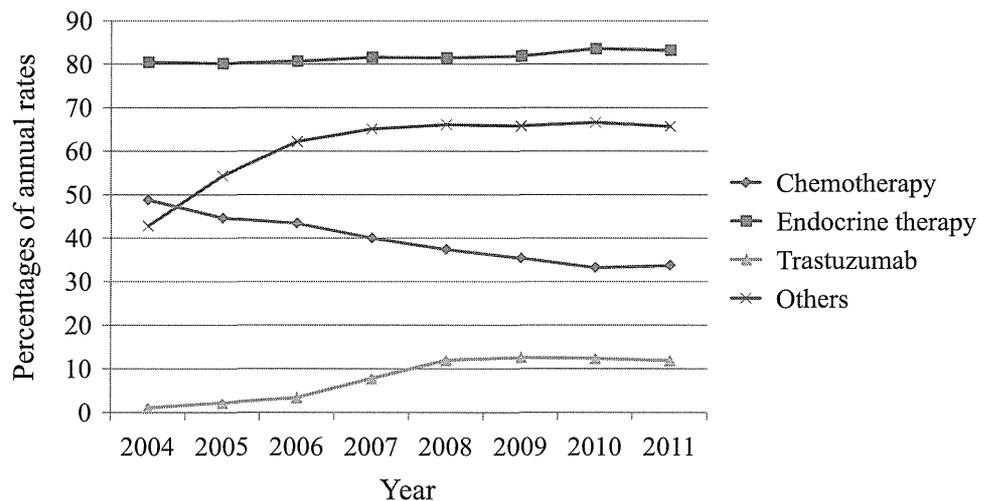
The postoperative use of trastuzumab markedly increased since 2007 because its postoperative application was approved by the Ministry of Health, Labour and Welfare, Japan in 2007. The annual rates of patients treated with postoperative trastuzumab in all patients treated with postoperative systemic therapies were 0.1–2.5 % between 2004 and 2006, and significantly increased to 7.7–12.5 % between 2007 and 2011.

Conclusions

The results of the present study, which was based on the data of the Web-based registry for newly diagnosed breast cancer patients between 2004 and 2011 in Japan, revealed a number of interesting findings with regard to breast cancer characteristics and recent trends in the management of breast cancer patients in Japan as follows:

1. Two distinct peaks were observed, in patients in their late 40s and early 60s, in the population-adjusted age distribution of breast cancer patients.
2. The rate of obese breast cancer patients was markedly lower in Japan than in western countries.

Fig. 7 Percentages of annual rates of breast cancer patients treated with postoperative chemotherapy, endocrine therapy, trastuzumab therapy, or others (most of them were postoperative radiotherapies) in all patients treated with postoperative systemic therapies between 2004 and 2011 in Japan



- Although the morbidity of breast cancer continues to increase in Japan, the higher rate of screen-detected breast cancer may contribute to the earlier detection of breast cancer and an increased rate of non-invasive ductal carcinoma.
- Although there are some confounding factors influencing the positivity of ER or PgR in breast cancer, the positive rate of either ER or PgR appears to have increased in recent years.
- The annual rates of patients treated with breast-conserving surgery increased until 2006, but these increases stopped in 2007 and thereafter plateaued at approximately 60%. The annual rates of patients treated with modified radical mastectomy steadily decreased between 2004 and 2011, while those treated with simple mastectomy increased in these years.
- The annual rates of patients treated with sentinel lymph node biopsy alone steadily increased between 2004 and 2011.
- The annual rates of patients treated with breast-conserving surgery followed by postoperative radiotherapy and with modified radical mastectomy followed by postoperative radiotherapy have increased in recent years.
- The annual rates of patients treated with preoperative endocrine therapies have increased in recent years.
- The annual rates of patients treated with preoperative trastuzumab plus chemotherapy have increased in recent years.
- The annual rates of patients treated with postoperative aromatase inhibitors have increased, whereas those treated with postoperative tamoxifen have decreased in recent years.
- The annual rates of patients treated with postoperative anthracycline-containing regimens have decreased,

whereas those treated with postoperative taxane-containing regimens have increased in recent years.

- The postoperative use of trastuzumab has markedly increased since 2007.

Although this study was based on the registry database and several categories in the data registration, such as family history and the positivity of ER and PgR, were not strictly defined, several unique clinicopathological characteristics of breast cancer in Japan have been unveiled. In addition, our results suggested that recent trends in the management of breast cancer patients in Japan were strongly followed by clinical evidence that originated from a number of clinical trials worldwide.

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Conflict of Interest J. Kurebayashi and S. Saji received research funding from Eisai Co. and Chugai Pharmaceutical Co., Ltd, respectively. The other authors declare that they have no competing interests.

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JUA Cancer Registration Statistics**Oncological outcomes of the prostate cancer patients registered in 2004: Report from the Cancer Registration Committee of the JUA**

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Objectives: In 2001, the Cancer Registration Committee of the Japanese Urological Association initiated a data collection of prostate cancer patients into a computer-based database. The aim of the present study is to report the clinical and pathological characteristics and outcomes of prostate cancer patients diagnosed in 2004 in Japan.

Methods: Overall, 11 385 patients from 239 institutions were registered into the database. After excluding 1105 patients because of insufficient data, duplication or insufficient follow up, 10 280 patients were eligible for the analysis. Most of them (10 198, 99.2%) were Japanese and 1195 (11.6%) had metastatic disease at the time of diagnosis. The mean and median follow up was 53.2 months and 61.5 months, respectively.

Results: The 5-year overall and prostate cancer-specific survival rate was 89.7% and 94.8%, respectively. The 5-year prostate cancer-specific survival rate of M0 and M1 disease was 98.4% and 61.1%, respectively. For 8424 cases of organ-confined or regional disease, Japanese urologists used as the initial treatment hormone ablation therapy alone (3360, 39.9%), radical prostatectomy (3140, 38.1%), radiation therapy (1530, 18.2%) and watchful waiting (394, 4.7%) including active surveillance or palliative observation.

Conclusions: This is the first large population report of survival data in Japanese prostate cancer patients. In Japan, the disease population, survival period with metastatic disease and ratio of patients having hormone ablation therapy differ from those in Western countries.

Key words: epidemiology, Japanese, prostate neoplasm, registration, survival.

Introduction

In the 1990s, prostate-specific antigen (PSA) testing became widespread in Japan, as in the USA and Europe. The incidence of prostate cancer in Japan also appears to be rising. There is no doubt that PSA screening contributes to earlier diagnosis of prostate cancer. Whether earlier detection of the prostate cancer in Japanese men helps reduce prostate cancer-specific mortality is unknown as a result of the lack of detailed information about Japanese prostate cancer patients.

In 2001, the Japanese Urological Association (JUA) initiated a study to estimate the etiology, diagnosis, initial treatment, pathological findings and final outcomes of prostate cancer using computer-based registration of prostate

cancer patients from institutions all over Japan. In 2005, we published the initial report on the registered 4529 prostate cancer patients diagnosed in 2000¹ and the estimated etiology, diagnosis and initial planned treatment were analyzed. In 2010, detailed information including the main treatment modality used, adjuvant therapies used and survival of prostate cancer patients diagnosed in 2004 was collected to assess the current situation of prostate cancer in Japan.

Methods**Patients and treatments**

In 2010, data on patients diagnosed with prostate cancer in 2004 were collected, along with 5-year survival data and radical prostatectomy pathology results. Incidental cancer found within specimens removed during radical cystoprostatectomy for bladder cancer and transitional cell carcinoma of the prostate concomitant with bladder cancer were excluded from this registry. In all, 11 385 patients were

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