資料38

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ORIGINAL ARTICLE

Impact of centralization in primary retroperitoneal sarcoma treatment: analysis using hospital-based cancer registry data in Japan

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Abstract

Background To elucidate the clinicopathological features, hospital-based care volume and prognoses associated with primary retroperitoneal sarcoma (PRS).

Methods Clinical data on PRS cases, diagnosed from 2008 to 2009 (cohort A) and from 2012 to 2015 (cohort B), were obtained from the national hospital-based cancer registry in Japan. Since data on survival, 5 years after PRS diagnosis, were available only for cohort A, patient prognoses were analyzed in this group alone.

Results The numbers of participating hospitals were 154 in cohort A and 537 in cohort B. In total, 380 and 2011 patients with PRS were identified in cohorts A and B, respectively. The incidence of PRS among all the registered urogenital malignancies was 0.52% (2391/462,866). Liposarcoma was the most commonly observed PRS subtype (55.8%), followed by leiomyosarcoma (19.0%). In cohort A, the 5-year overall survival (OS) was 40.4%. The 5-year OS associated with stage I ($n=107$), stages II and III ($n=61$), and stage IV ($n=59$) disease were 59%, 39%, and 6%, respectively. Only two institutions treated over ten patients per year in each cohort. When institutions were divided by hospital care volume (8 hospitals with $\geq=3$ cases and 149 with <3 cases/year), there were any statistic differences in the OS.

Conclusions We presented the distribution and prognoses associated with PRS using a real-world large cohort database. Centralization for PRS management was not established in Japan, while the prognosis did not significantly depend on the treatment volume of hospitals.

Keywords Soft tissue sarcoma · Registries · Urology

Introduction

Soft tissue sarcomas (STSs) are rare and heterogeneous tumors that originate from mesenchymal tissue. They represent < 1% of all new malignancies, and comprise > 50 histological subtypes, with various age distributions, occurrence sites, clinical and biological behaviors, and prognoses [1]. In the field of urology, there are two distinct entities: primary retroperitoneal sarcoma (PRS) and genitourinary sarcoma. PRSs account for 12% of STSs [2], followed by genitourinary sarcomas (approximately 2% of all STSs) [3].

While several population-based studies have focused on STSs [2, 4, 5], few have focused in detail on PRS. Additionally, several retrospective studies have been conducted in single tertiary referral institutions [6, 7]; however, those were limited by their relatively small sample sizes or were subject to selection bias for the more complicated cases. Therefore, there is a paucity of large-scale data on the clinical features and treatment outcomes of PRS in real-world settings, especially in Japan.

It is agreed upon that the management of STSs should be centralized to high-volume hospitals [8–11]. To this end, a comprehensive referral guideline for patients with STSs, originating in the extremities or trunk, has been proposed

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[12]. In Japan, in 2017, the National Cancer Center Japan published a list of 53 institutes with expertise in the treatment of STS of the extremities or trunk to facilitate management centralization [13]. However, to the best of our knowledge, no referral guidelines exist for patients with PRS, and the efficiency of management centralization for PRS is not well studied [9, 10, 14, 15].

The present study aimed to clarify the clinical characteristics and prognoses of recently diagnosed cases of PRS based on the records of patients from the hospital-based cancer registry (HBCR), which archives newly diagnosed cancer cases in designated cancer-care hospitals (DCCHs) and other prefecture-recommended hospitals [13, 16, 17]. Using this database, we also analyzed real-world PRS care volume data in Japan.

Patients and methods

Data source

Since 2007, the HBCR has been collecting data from DCCHs assigned by the Ministry of Health, Labor, and Welfare. In addition, as increasing the number of designating community cancer hospitals which prefectural governments have been approved, the number of hospitals submitting their data to the HBCR has increased. The HBCR database was recently found to comprise data on approximately 67% of all new cancer cases in Japan [13, 16, 17]. To clarify the clinical characteristics of recently diagnosed cases of PRS, we collected HBCR data from two cohorts. Cohort A comprised 65,121 patients diagnosed between January 2008 and December 2009, and cohort B included 397,745 patients treated between January 2012 and December 2015. The datasets of cohort A and B were registered from 154 and 537 institutions, respectively, making for 541 institutions (most institutions were registered in both cohorts). For the analysis of the clinicopathological features and hospital care volume associated with PRS, we used data from both cohorts A and B. Cohort A data were employed for the analysis of survival, as cohort B data did not include survival information. In contrast, cohort A included information on survival 5 years after diagnosis. In this cohort, data were obtained from hospitals with > 90% follow-up (F/U) rate for all cancer patients. We could not calculate the median F/U period of these patients, because data on the exact F/U period for some of the patients were not available in this database.

Trained cancer registrars at registered hospitals report data on each cancer case based on standardized rules and criteria, for submission to the HBCR. The data were entered by trained practitioners who took the tumor registrar training programs coordinated by the National Cancer Center in Japan. We extracted the cases who started their first-course treatment at the hospital to avoid duplicate counting. These include data on demographics and cancer characteristics, including topology and morphology codes of the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3), and the TNM Classification as well as initial treatments. The 6th edition of the TNM Classification was used in cohort A, and the 7th edition in cohort B. The details of histology are shown in supplemental table 1.

Data extraction

To realize the status of urological STS, we extracted eligible cases according to the availability of data on patient age, sex, histology of sarcoma, registered institution, site, treatment, stage, and prognosis. We performed abstraction with the following criteria: malignancies (1) that were diagnosed during the registry periods and started to receive initial treatment at the hospital; (2) in which the registered site was the peritoneum/retroperitoneum (C48); and (3) that had a histologically confirmed tumor classified with the ICD-O-3 histology codes relating to intermediate and malignant categories (880–885, 889–893, 896, 898, 899, 904, 912–915, 918, 923–926, 936, 947, 958), according to the World Health Organization's classification of STS.

Data analysis

We evaluated the distributions of patient age, sex, stage, histology, treatment, and institutions. To evaluate the centralization of management, we divided the participating hospitals into two groups, according to the care volume, setting a cut-off value of three cases per year. We analyzed all data using Microsoft Excel and JMP 10 software. A Chi-square test was used to compare categorical variables with the level of significance set at a two-sided p value < 0.05. We estimated the overall survival (OS) rate by the Kaplan–Meier method.

Ethical considerations

This study, including all its protocols and data processing methods, was approved by the Tsukuba University Hospital Ethical Board (approval number: H29-267).

Results

Patients' background and clinical data

As shown in Fig. 1, after extraction of initial treatment patients, 380 (0.58%) and 2011 (0.51%) PRS cases were identified from cohort A and B, respectively. Table 1 shows the patients' background and clinical data. In terms of age and sex, there were no significant differences between the

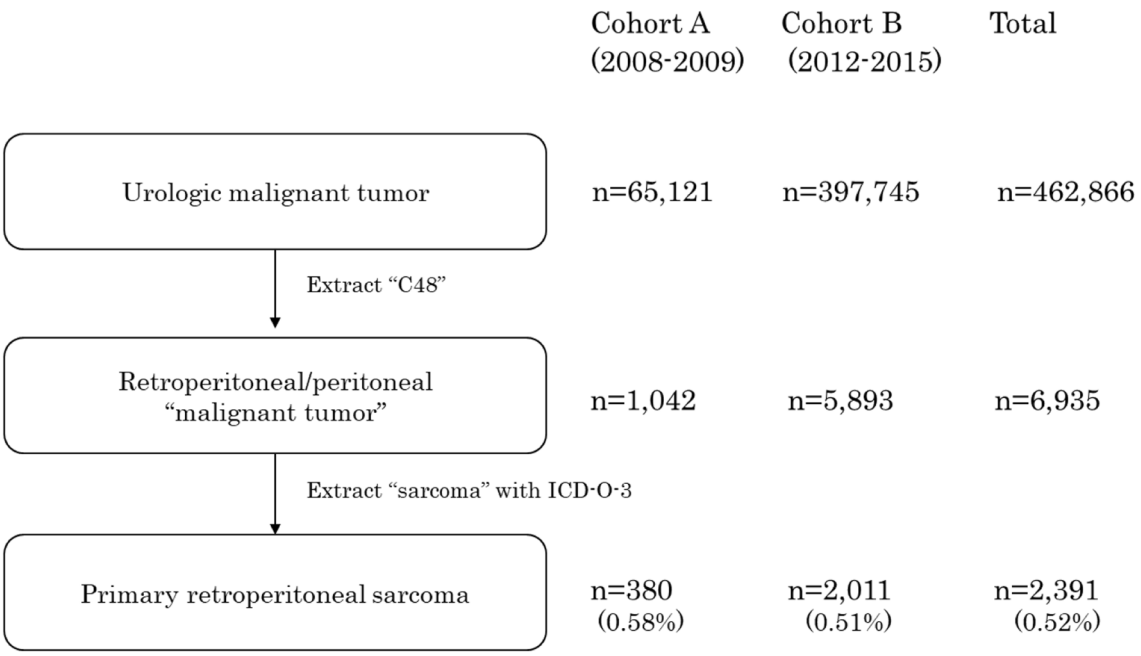

Fig. 1 Schema of the data extraction methods used. The whole HBCR dataset was filtered by ICD-O-3 location and histological codes. *ICD* International Classification of Disease, *HBCR* hospital-based cancer registry

two cohorts. The most commonly observed histology was liposarcoma (adipocytic tumor), followed by leiomyosarcoma. Most of the histological subtypes did not show any differences between the two cohorts. The distribution of clinical stage showed the same trend in both cohorts. The proportions of patients treated with surgery and chemotherapy did not differ across both cohorts. However, the proportion of patients treated with radiotherapy in cohort A tended to be higher than that in cohort B ($p = 0.056$).

Centralization of sarcoma patients' management

Figure 2 shows the care volume at each institution. We assigned the number of cases per year to the vertical axis, and the total number of institutions to the horizontal axis. Only two institutions treated over ten patients per year in both cohorts. These two institutions were located in Tokyo. The numbers of hospitals that treated over five cases per year were almost the same, at 4 (2.6%) in cohort A and 14 (2.6%) in cohort B. The numbers of small-volume hospitals with fewer than three cases per year were 149 (95.0%) and 500 (92.4%) in cohorts A and B, respectively.

Prognosis of primary retroperitoneal sarcoma patients

We analyzed the OS of PRS patients in cohort A. Overall, the 5-year OS was 40.4 [95% confidence interval (CI) 34.1–47.0]%. Stratified by clinical stage, the 5-year OS values of the stage I, stage II and III, and stage IV cases were 58.9 (95% CI 49.3–67.7)%, 38.4 (95% CI 26.9–51.4)%, and 6.0 (95% CI 1.9–16.9)%, respectively (Fig. 3). When limited to liposarcoma patients, the 5-year OS associated with stage I disease was 63.8 (95% CI 51.9–74.2)%, which tended to be higher than that of the stage I non-liposarcoma patients [50.0 (95% CI 34.6–65.4)%]. However, the difference was not statistically significant ($p = 0.098$).

Differences in treatment outcomes by hospital volume

Table 2 shows the distribution of the clinical factors and treatment modalities in cohorts A and B. These were compared between hospitals treating three or more cases per year and < 3 cases per year in both cohorts. The distribution of age, sex, and disease stages did not differ between the hospitals divided by care volume. However, in cohort B, the proportion of patients treated with radiation therapy was significantly higher in hospitals with ≥ = 3 cases per year compared to that in hospitals with < 3 cases per year (9.1–6.2%, respectively, $p = 0.019$). Additionally, the proportion of patients treated with chemotherapy tended to be higher in the former group than the latter group in cohort A (30.8–22.8%, respectively, $p = 0.132$) and this tendency became significant in cohort B (25.9–17.5%, respectively, $p < 0.001$). Consequently, in cohort B, the proportion of patients treated with multimodal treatment

Table 1 Patients' background and clinical data

	Total	Cohort A (2008–2009)	Cohort B (2012–2015)	*p*
	n %	*n* %	*n* %	
Number of patients	2391 (100)	380 (100)	2011 (100)	
Age (year)				n.s
Median	65	63	65	
Range	0–97	1–88	0–97	
Gender				n.s
Male	1174 (49.1)	186 (49.0)	988 (49.1)	
Female	1217 (50.9)	194 (51.0)	1023 (50.9)	
Histology				
Adipocytic tumor (liposarcoma)	1333 (55.8)	176 (46.3)	1157 (57.5)	n.s
Fibroblastic/myofibroblastic tumor	72 (3.0)	18 (2.6)	54 (2.7)	n.s
So-called fibrohistiocytic tumor	72 (3.0)	16 (4.2)	56 (2.8)	n.s
Smooth muscle tumor (leiomyosarcoma)	454 (19.0)	73 (19.2)	381 (18.9)	n.s
Skeletal muscle tumor (rhabdomyosarcoma)	45 (1.9)	11 (2.9)	34 (1.7)	n.s
Tumors of uncertain differentiation	82 (3.4)	28 (7.4)	54 (2.7)	0.055
Sarcoma (unclassified)	333 (13.9)	58 (15.3)	275 (13.6)	n.s
Clinical stage				n.s
I	883 (37.4)	107 (28.2)	776 (38.6)	
II and III	454 (19.2)	61 (16.0)	393 (19.5)	
IV	280 (11.9)	59 (15.5)	221 (11.0)	
Unknown	774 (32.8)	153 (40.3)	621 (30.9)	
Treatment				
Surgery				n.s
Yes	1803 (75.4)	287 (75.5)	1516 (75.4)	
No	588 (24.6)	93 (24.5)	495 (24.6)	
Radiation therapy				0.056
Yes	152 (6.4)	38 (10.0)	114 (5.7)	
No	2209 (93.6)	342 (90.0)	1867 (92.8)	
Chemotherapy				n.s
Yes	504 (21.1)	94 (24.7)	410 (20.4)	
No	1887 (78.9)	286 (75.2)	1601 (79.6)	
Multimodal treatment				n.s
Yes	311 (13.0)	63 (16.5)	248 (12.3)	
No	2080 (86.9)	317 (83.5)	1763 (87.7)	

was higher in hospitals with $\geq = 3$ cases per year than those with a smaller care volume (14.5–11.2%, respectively, $p = 0.036$).

Figure 4 shows the survival values of patients in cohort A. As shown in Fig. 4a, the survival in stage I disease tended to be better in patients treated in hospitals with $\geq = 3$ cases per year than that of those in hospitals with < 3 cases per year (5-year OS, 69.2–55.5%, respectively), but the difference was not statistically different ($p = 0.38$). There was no significant difference in the survival values associated with stages II and III, and stage IV disease according to hospital care volume (Fig. 4b, c).

Discussion

We presented data on the distribution and prognoses associated with PRS using a real-world large cohort database. The use of the large HBCR database, which includes 2391 patients in 6 years, enabled us to obtain comprehensive information regarding rare malignancies. Our findings show that centralization for PRS management was not well established in Japan, while the prognosis did not depend on the treatment volume of hospitals.

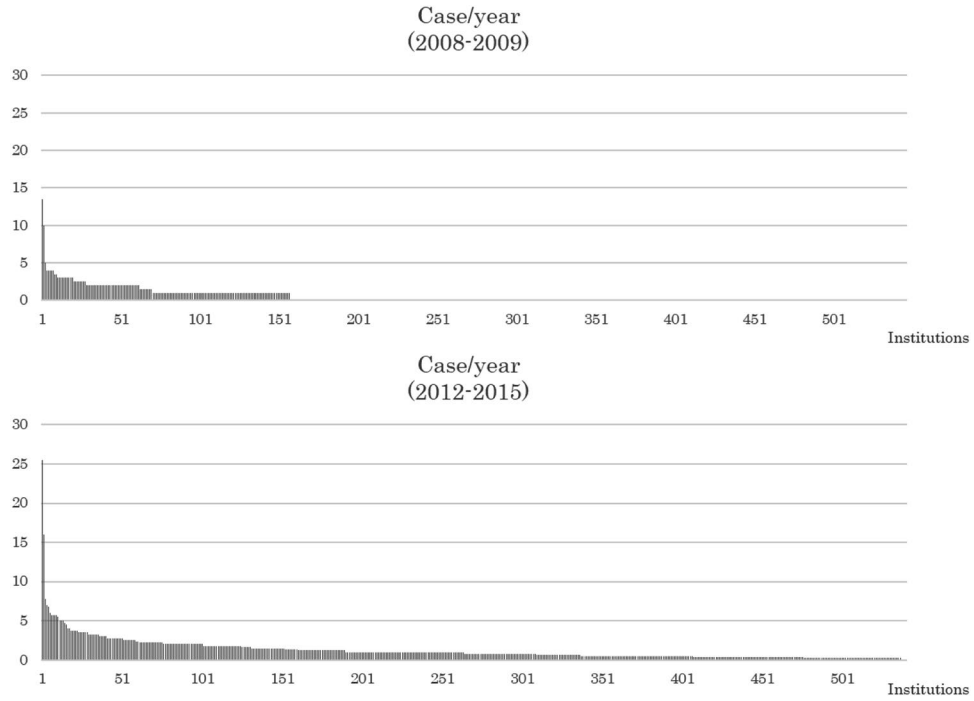

Fig. 2 Bar graphs of the care volume distribution per institution. **a** Data in 2 years from 2008 to 2009. **b** Data in 4 years from 2012 to 2015

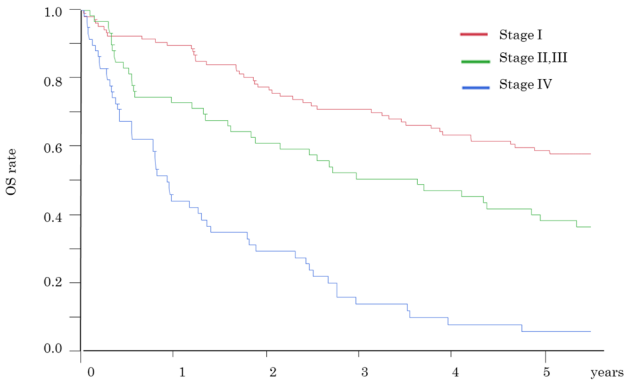

Fig. 3 Overall survival curves of primary retroperitoneal sarcoma patients stratified by clinical stage (I, II and III, IV). OS, overall survival

The National Institute for Health and Clinical Excellence guidance recommends that multidisciplinary teams for sarcoma manage at least 100 new patients with STS per year [18]. Hoekstra et al. reported that five sarcoma research centers across 96 hospitals managed around 40% of all STS patients in the Netherlands [10]. Gutierrez et al. analyzed the Florida Cancer Data System and reported that 7 high-volume centers among 256 hospitals managed one-third of all STS patients [15], and the average number of patients per year across the 7 centers ranged from 5 to 24. However, in Japan, as presented in the present study, only two of all the registered institutions were primarily managed as large centers and treated 220 patients with PRS (9.3%) over a 6-year period. Due to the presence of a well-structured health-care environment, sarcoma patients tend to visit the nearest district general hospital and may not wish to venture far from their hometown because they could access minimum health service near their hometown. Our data could not clearly show statistic differences in the prognosis between high volume centers and others. The degree of hospital centralization should be discussed: whether it would improve the prognoses of PRS patients in Japanese well-established health-care circumstances.

Optimal PRS treatment is complex and multimodal in nature, including high-quality surgery, high-technology radiotherapy, and chemotherapy, with accurate radiological and pathological diagnoses. Sarcoma treatment centers are thought to have extended multidisciplinary teams at an appropriate geographical level (regional, national and supranational) [19]. For PRS, no established cutoff value separates high- and low-volume hospitals. Recently, Keung et al. reported that PRS patients treated at high-volume hospitals, defined as those with $\geq$10 cases per year, had significantly higher 5-year OS values than those treated at low-volume hospitals [20]. The present study showed that the prognoses of stage I patients treated in hospitals with $\geq = 3$ cases per year were slightly better than that of those in hospitals with < 3 cases per year in cohort A. Although the treatment choices were not substantially different, the proportion of patients treated with chemotherapy was higher in the larger care volume group. Additionally, in cohort B, the proportion of patients receiving multimodal treatment was higher in hospitals with $\geq = 3$ cases per year than hospitals with a

Table 2 Distribution of the clinical factors and treatment modalities in cohorts A and B

	Cohort A (2008–2009)			Cohort B (2012–2015)		
	≥ = 3 cases/year	< 3 cases/year	*p*	≥ = 3 cases/year	< 3 cases/year	*p*
No. of institutes	8	149		41	500	
No. of patients	91	289		683	1328	
Age (year)						
Median	60	64		64	66.5	
Range	1–80	1–88		0–88	1–97	
Gender			n.s			n.s
Male	49 (53.9)	137 (47.4)		353 (51.7)	635 (47.8)	
Female	42 (46.1)	152 (52.6)		330 (48.3)	693 (52.2)	
Clinical stage						
I	26 (28.6)	81 (28.0)		245 (35.9)	531 (40.0)	
II and III	17 (18.7)	44 (15.2)		180 (26.3)	203 (15.3)	
IV	19 (20.9)	40 (13.8)		81 (11.9)	140 (10.5)	
Unknown	29 (31.8)	124 (43.0)		177 (25.9)	444 (33.4)	
Treatment						
Surgery			0.017			0..084
Yes	60 (65.9)	227 (78.6)		499 (73.1)	1017 (76.6)	
No	31 (34.1)	62 (21.4)		184 (26.9)	311 (23.4)	
Radiation therapy			0.258			0.019
Yes	12 (13.2)	26 (9.0)		62 (9.1)	82 (6.2)	
No	79 (86.8)	263 (91.0)		621 (90.9)	1246 (93.8)	
Chemotherapy			0.132			< 0.001
Yes	28 (30.8)	66 (22.8)		177 (25.9)	233 (17.5)	
No	63 (69.2)	223 (77.2)		506 (74.1)	1095 (82.5)	
Multimodal treatment			0.354			0.036
Yes	18 (19.8)	45 (15.6)		99 (14.5)	149 (11.2)	
No	73 (80.2)	244 (83.4)		584 (85.5)	1179 (88.8)	

n.s not significant

smaller care volume (14.5–11.2%, respectively, $p = 0.036$). At present, the survival data of patients in cohort B are not available because when HBCR offer reference and confirmation with checking their certificate on residence to refer each municipality to confirm survival data 5 years after registry. Therefore, it is not clear whether multimodal treatment can contribute to improved outcomes.

The present study clearly showed that many Japanese physicians, surgeons, and pathologists have lesser experience in the diagnosis and treatment of PRS than their counterparts in Western countries. This trend was observed both in cohorts A (2008–2009) and B (2012–2015). The proportions of small-volume hospitals with < 3 cases per year were 149 (95.0%) and 500 (92.4%) in cohorts A and B, respectively. As the prognoses of Japanese sarcoma patients were comparable to centralized Western countries, it is unclear whether more effort should be directed toward the achievement of centralization. If there is a hospital near PRS patients which serves multimodal therapy, they may be able to receive acceptable medical care without long distance travel. However, more centralization would be required when progress of the treatment outcome for PRS is achieved by advanced technology or medicine available only in highly selected hospitals, such as genomic medicine.

The present study has several limitations associated with the availability of data in the HBCR. First, detailed information regarding individual patients' clinical conditions was not available. Second, the registry only contains information that was provided and registered at the registering facilities. However, the data have high reliability, because HBCR data were entered by trained practitioners who took tumor registrar training programs, which have been held to renew and keep the practitioners' knowledge at a latest state and to update their qualifications. Additional data from other hospitals may be required to gain a more accurate national profile of STS. Despite these limitations, the present study reveals important information regarding rare PRS-related malignancies in Japan.

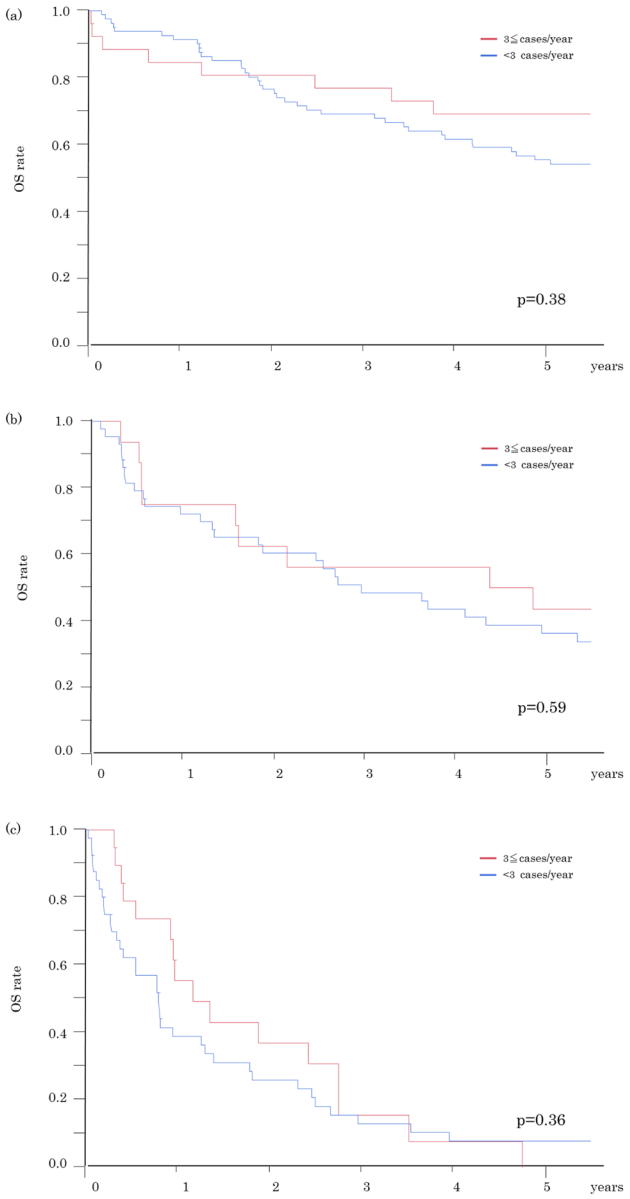

Fig. 4 Overall survival curves. **a** Stage I patients stratified into two groups by hospital care volume with a cutoff value of three cases per year. **b** Stages II and III patients same as (**a**). **c** Stage IV patients same as (**a**). *n.s* not significant, *OS* overall survival

Conclusions

In this study, we presented detailed data on the distribution patterns, prognoses, and centralization of care volume associated with PRS using HBCR data. Centralization for PRS management was not established in Japan, while the prognosis did not significantly depend on the treatment volume of hospitals. PRS management in Japan could be feasible without mature hospital centralization. As the health-care system in Japan is developing, the nation-wide database will provide more detailed analyses in the future.

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Compliance with ethical standards

Conflict of interest statement No author has any conflict of interest.

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