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Surgical volume threshold to improve 3-year survival in designated cancer care hospitals in 2004-2012 in Japan

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Abstract

In Japan, cancer care hospitals designated by the national government have a surgical volume requirement of 400 annually, which is not necessarily defined based on patient outcomes. This study aimed to estimate surgical volume thresholds that ensure optimal 3-year survival for three periods. In total, 186 965 patients who had undergone surgery for solid cancers in 66 designated cancer care hospitals in Osaka between 2004 and 2012 were examined using data from a population-based cancer registry. These hospitals were categorized by the annual surgical volume of each 50 surgeries (eg, 0-49, 50-99, and so on). Using multivariable Cox proportional hazard regression, we estimated the adjusted 3-year survival probability per surgical volume category for 2004-2006, 2007-2009, and 2010-2012. Using the joinpoint regression model that computes inflection points in a linear relationship, we estimated the points at which the trend of the association between surgical volume and survival probability changes, defining them as surgical volume thresholds. The adjusted 3-year survival ranges were 71.7%-90.0%, 68.2%-90.0%, and 79.2%-90.3% in 2004-2006, 2007-2009, and 2010-2012, respectively. The surgical volume thresholds were identified at 100-149 in 2004-2006 and 2007-2009 and 200-249 in 2010-2012. The extents of change in the adjusted 3-year survival probability per increase of 50 surgical volumes were +4.00%, +6.88%, and +1.79% points until the threshold and +0.41%, +0.30%, and +0.11% points after the threshold in 2004-2006, 2007-2009, and 2010-2012, respectively. The existing surgical volume requirements met our estimated thresholds. Surgical volume thresholds based on the association with patient survival may be used as a reference to validate the surgical volume requirement.

KEYWORDS
cancer care facilities, quality of healthcare, surgical procedures, surgical volume, survival rate

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1 | INTRODUCTION

Cancer-related deaths have increased worldwide in the last decade from 7.62 million in 2007 to 9.56 million in 2017, which accounted for 17% of all-cause deaths in 2017.[1] In Japan, 374 000 people died of cancer in 2018, accounting for 27% of all-cause deaths.[2] Reduction in cancer prevalence and mortality is the primary goal of the third-term comprehensive 10-year cancer control strategy in the country.[3] Standardization and centralization of cancer care through designated cancer care hospitals (DCCHs) have been promoted.[4]

Concentrating patients to the most experienced hospitals or care providers, so-called "centralization," is a well-known strategy to improve patient outcomes.[5] This concept originated from the established evidence that patients treated in high-volume hospitals show lower morbidity or mortality compared with those treated in low-volume hospitals.[6-8] The capability to practice high-volume surgeries may indicate that these hospitals have more specialized surgeons and resources, are equipped with well-served care units,[9] or may host several low-risk patients,[10,11] which may explain the mechanism of the volume-outcome relationship.

As a part of the centralization policy, numerous European and North American countries have developed minimal surgical volume requirements or standards based on expert suggestions and available evidence.[12,13] Minimal surgical volumes are generally defined as the number of surgical procedures per year. Whether procedures or diseases are to be centralized is defined according to the clinical rarity and complexity of the procedures or medical costs.[13] In the United States, for example, minimum hospital- and surgeon-volume standards for esophageal, lung, pancreatic, and rectal cancers are used in the "Leapfrog" healthcare organizations' hospital survey to evaluate hospital performance across the country.[14] However, no global standard has been established to date for surgical volume because decision-making for surgical volume standards is often affected by evidence, regulation, or healthcare systems available in local settings.[12]

In Japan, the designation of DCCHs started in 2006 with the aim of providing high-quality treatment and care to cancer patients across the country.[15] The surgical volume requirement is applied to examine the qualifications of DCCH candidates or monitor the annual performance of operational DCCHs. The two types of DCCHs are national and prefectural DCCHs, which are designated by the national government[16] and by the prefectural governments, respectively.[17] The national DCCHs are required to meet higher standards in infrastructure, resources, and practice than prefectural DCCHs. For example, the surgical volume requirements for national DCCHs are 400 surgeries annually for overall cancers.[16] This volume requirement was defined based on the mean surgical volume of the national DCCHs with 900-1200 newly admitted cancer patients per year.[18] For prefectural DCCHs, for example, the surgical volume requirements in Osaka prefecture are 200 surgeries annually for overall cancers.[19] This volume requirement was defined based on the opinions from local experts and administrators. Thus, whether the existing requirement may serve to ensure optimal patient outcomes in DCCHs remains unclear. To answer this question, various studies have determined surgical volume thresholds for specific cancers or procedures based on the association between surgical volume and patient mortality or complications.[20-23] However, to the best of our knowledge, no previous studies have determined the surgical volume threshold for overall solid cancers based on the association with patient survival in Japan and globally.

Therefore, this study aimed to estimate surgical volume thresholds for solid cancers based on the association with adjusted 3-year survival probability and compare them with the existing requirement. The second objective was to examine changes in surgical volume thresholds over three periods because DCCH designation started in 2006, which might have affected the surgical volume or patient survival afterwards.

2 | MATERIAL AND METHODS

2.1 | Study design, setting, and data source

This retrospective observational study was conducted in Osaka Prefecture (Osaka), Japan. Osaka is the second smallest prefecture, with the third largest population of 8.9 million in 2010.[24] We used the data obtained from the population-based Osaka Cancer Registry, which has been in operation since 1962.[25] Data from the registry have been presented in *Cancer Incidence in Five Continents*, volumes III to XI because they meet the quality of the international standard.[26] The registry records all new cancer cases recognized by reports from medical facilities or the death certificate database. Follow-up for vital status of the cancer patients is routinely performed using death certificates. Furthermore, these patients were followed up using official resident registries to verify vital status at 3, 5, and 10 years from diagnosis.[27] The registry collects patient information including sex, age, date of diagnosis and death, cancer site, pathological diagnosis, cancer stage, circumstances of cancer detection, the reception of surgery, chemotherapy, and/or radiotherapy, and the medical facility code where patients had the first contact and received diagnosis and primary treatment. The registry does not collect information on patients' socioeconomic characteristics, comorbidity history, functional ability, the content of follow-up treatment and care after the initial treatment, or causes of death.

2.2 | Study sample

The study sample comprised patients who were diagnosed with cancers in 2004-2012. Their cancers were categorized as C00-C96 in the International Classification of Diseases, 10th edition (ICD-10), except for lymphoma (C81-C85 and C96), multiple myeloma (C88-C90), and leukemia (C91-C95). The patients lived in Osaka at the time of diagnosis and underwent open surgery, endoscopic surgery, or endoscopic resection that were defined as surgery in the surgical volume requirement. They were treated at the 66 operational

DCCHs for adult cancer as of 2020 (17 national DCCHs and 49 prefectural DCCHs).[28] As mentioned earlier, the designation of DCCHs started in 2006, and the number of DCCHs gradually increased to 66 by 2020. Among all hospitals which performed surgery for solid cancers, we targeted the 66 DCCHs because these DCCHs covered 85% of surgeries for solid cancers in Osaka.[29] Furthermore, our previous studies demonstrated lower survival probability of patients treated in very low-volume hospitals[30] or non-DCCHs[29] than in high-volume or DCCHs, which suggested the importance of centralization of patients to DCCHs as mentioned in the Basic Plan to Promote Cancer Control programs.[4] Furthermore, we observed changes in surgical volume and patient survival among these 66 hospitals before and after the designation.

We included patients who met the abovementioned criteria (n = 197 364) to calculate the average annual surgical volume per hospital. To estimate the 3-year survival probability, we limited the patient age criterion to 15-84 years because patients aged <15 years are usually diagnosed with childhood cancer, and their treatment protocol and response to treatment may differ from those for adult patients.[31] Patients aged >85 years were excluded because they often have multiple chronic conditions, cognitive impairment, and vulnerability to complications,[32] which would affect the survival probability. Thus, we excluded those who were out of the age criterion (n = 7825), whose vital status at 3-year from the diagnosis was not confirmed (n = 2574), who had a survival period of 0 days (n = 174), and who had missing information on sex (n = 1) or cancer stage (n = 3). Finally, the remaining 186 965 samples were included in the survival analysis.

2.3 | Outcome variable: 3-year survival from diagnosis

The outcome of this study was 3-year survival from the date of cancer diagnosis. In contrast to clinical studies that generally define the date of surgery as the entry point of the survival period, we determined the date of diagnosis as the entry point because the data on the date of surgery were unavailable in the cancer registry. Death was described as an event occurring any time within 3 years after diagnosis.

2.4 | Independent variable: surgical volume

Surgical volume was defined as the annual average number of surgeries (ie, open surgery, endoscopic surgery, or endoscopic resection) that a hospital performed for solid cancers in a 3-year period (ie, 2004-2006, 2007-2009, and 2010-2012). We included endoscopic resection in the counting surgical volume, following the current DCCH standard. We generated a categorical variable of surgical volume by dividing at an increase of 50 surgical volumes (ie, 0-49, 50-99, 100-149, ..., and 1150-1199). Furthermore, we created surgical volume categories for the abovementioned three periods

to assess changes before and after 2006 when the designation of DCCHs started.

2.5 | Adjustment variables

We considered the following as adjustment variables in the statistical models for estimating hazard ratios and 3-year survival probability: sex (men and women), age group (15-39, 40-49, 50-59, 60-69, 70-79, and 80-84), cancer site (oral cavity and pharynx [ICD-10: C00-C14], digestive tracts [ICD-10: C15-C21], liver, biliary tract, and pancreas [ICD-10: C22-C25], respiratory and other intrathoracic organs [ICD-10: C30-34, C37-38], bone, skin, mesothelium, and soft tissue [ICD-10: C40-41, C43-C47, C49], breast [C50], female genital organs [ICD-10: C51-C58], male genital organs [ICD-10: C60-C63], urinary organs [ICD-10: C64-C68], eye, brain, central nervous system, thyroid, and other endocrine glands [ICD-10: C69, C70-C75], other and unspecified sites), circumstances of cancer detection (screen detected, non-screen detected, unknown), stage of cancer (localized, regional, adjacent, distant, and unknown), extent of remaining tumor after surgery (not remained, remained, and unknown), the receipt of chemotherapy (received, not received, and unknown), receipt of radiotherapy (received, not received, and unknown), residential area according to the eight divisions of prefectural medical administration (areas A-H), and the year of diagnosis (2004-2012).

2.6 | Statistical analysis

We first calculated the frequency and percentage of the basic characteristics of patients for the three periods (ie, 2004-2006, 2007-2009, and 2010-2012). Moreover, we calculated the numbers and percentages of hospitals and patients per surgical volume category for the three periods. We then estimated the hazard ratios (HRs) and 95% confidence intervals (CIs) of the surgical volume category using a multivariable Cox proportional hazard regression model, controlling for the abovementioned adjustment variables. Furthermore, we adjusted for potential cluster correlations within patients treated in the same hospital using robust estimators of variance. Based on the multivariable Cox proportional hazard regression model, we calculated the adjusted 3-year survival probability per surgical volume category, which was estimated based on the mean value of each independent variable for the overall estimated sample.[33] Finally, we identified the surgical volume thresholds using the joinpoint regression model.[34] The details of the model have been described elsewhere.[35] Briefly, the joinpoint regression model was initially developed to compute a change in trend over consecutive segments of time and identify inflection points at which a significant increase or decrease in the trend occurs, based on the best-fitting model. Additionally, the model was used to calculate the slope of the trend. It has been widely used to analyze changing trends in cancer incidence, mortality, and survival rates.[36-38] We used this model to analyze the changing trends in survival probability per increase in

surgical volume. We defined the surgical volume threshold as the surgical volume category at which the joinpoint model identifies the change in the trend of the association between surgical volume and adjusted 3-year survival probability. According to previous studies, the trend of the association between surgical volume and patient outcome is positive until it reaches a certain surgical volume, then plateaus or declines.[13,39,40] Furthermore, we calculated the slope of the association between surgical volume and adjusted 3-year survival probability below and above the threshold. The value of the slope indicates the percentage change in the adjusted 3-year survival probability per an increase of 50 surgeries. As a sensitivity analysis, we estimated surgical volume thresholds for adjusted 1-year survival probability (Figure S1, Supporting Information) and compared with those for adjusted 3-year survival probability. Statistical significance was set at $P < .05$. Stata statistical software package version 15.1 (Stata Corp) and joinpoint regression program software version 4.8.0.1 (National Cancer Institute) were used for the analysis.

2.7 | Ethical considerations

This study was approved by the Institutional Review Board of the Osaka International Cancer Institute (approval number, 18-0018) before conducting the study. Informed consent was not required because personally identifiable information was removed from the dataset before use. The dataset was obtained from the Osaka Cancer Registry and independently processed in accordance with the Act on Promotion of Cancer Registries.

3 | RESULTS

3.1 | Basic characteristics of the study sample

Table 1 shows the basic characteristics of the patients included in the survival analysis. The number of patients increased from 49 200 in 2004-2006 to 62 779 in 2007-2009 and 74 986 in 2010-2012. The proportion of patients aged ≥70 years increased from 36.7% in 2004-2006 to 43.4% in 2010-2012. The proportion of patients with localized stage at diagnosis slightly increased from 55.0% to 60.8%, and the proportion of those who underwent tumor resection in all parts increased from 75.6% to 82.3% in the same period. Nearly 30% of the patients received chemotherapy and 10% received radiation therapy.

3.2 | Distributions of hospitals and patients per surgical volume category

Table 2 shows the distribution of hospitals and patients according to surgical volume category. The median of the average annual surgical volume in a 3-year period was 214.0 (interquartile range [IQR] 90.0-387.1) in 2004-2006, 264.7 (IQR 119.5-474.8) in 2007-2009,

and 305.7 (IQR 200.7-513.3) in 2010-2012. The number of hospitals with surgical volumes less than 200 was 31 (47.0%), 26 (39.4%), and 16 (24.4%) in 2004-2006, 2007-2009, and 2010-12, respectively. The number of patients treated in hospitals with surgical volumes less than 200 was 7769 (15.8%), 7031 (11.3%), and 4162 (5.6%) in 2004-2006, 2007-2009, and 2010-2012, respectively.

3.3 | Adjusted 3-year mortality hazards by surgical volume

Table 3 shows the adjusted HRs of surgical volume category; the highest volume category was used as a reference group. In 2004-2006, all surgical volume categories showed significantly higher HRs than the highest volume category. In 2007-2009, the surgical volume categories with significantly higher HRs were 0-599 (ie, between 0-49 and 550-599), 650-699, and 1050-1099, whereas the category with significantly lower HR was 1100-1149. In 2010-2012, the surgical volume categories with significantly higher HRs were 0-349 (ie, between 0-49 and 300-349), 500-549, 700-749, and 1000-1049. Moreover, Table 3 shows the adjusted 3-year survival probability. The absolute difference in the adjusted 3-year survival probabilities between surgical volume categories with the lowest and highest survival probabilities changed over the three periods. The differences were 18.3% points (ranging between 71.7% and 90.0%) in 2004-2006, 21.8% points (ranging between 68.2% and 90.0%) in 2007-2009, and 11.1% points (ranging between 79.2% and 90.3%) in 2010-2012.

3.4 | Surgical volume thresholds based on the associations with the adjusted 3-year survival probability

Figure 1 presents the plots of the adjusted 3-year survival probability per an increase of 50 surgical volumes estimated by the multivariable Cox proportional hazard model and the plots of the adjusted 3-year survival probability predicted by the joinpoint regression model. The points at which the joinpoint model identified the changing trend in the association between surgical volume and adjusted 3-year survival probability were in the surgical volume categories of 100-149 in 2004-2006 and 2007-2009 and 200-249 in 2010-2012. The percentage changes in the adjusted 3-year survival probability per an increase of 50 surgical volumes below the threshold were +4.00%, +6.88%, and +1.79% points in 2004-2006, 2007-2009, and 2010-2012, respectively. The percentage changes above the thresholds were +0.41%, +0.30%, and +0.11% points in 2004-2006, 2007-2009, and 2010-2012, respectively.

In the sensitivity analysis, the estimated surgical volume thresholds for 1-year adjusted survival probability were 100-149, 250-299, and 350-399 in 2004-2006, 2007-2009, 2010-2012, respectively (Figure S1). The percentage changes in the adjusted 1-year survival probability per an increase of 50 surgical volumes

TABLE 1 Basic characteristics of patients included in the analysis

	2004-2006	2007-2009	2010-2012
	n (%)	*n* (%)	*n* (%)
Total	49 200 (26.3)	62 779 (33.6)	74 986 (40.1)
Sex			
Women	23 067 (46.9)	28 978 (46.2)	34 510 (46.0)
Men	26 133 (53.1)	33 801 (53.8)	40 476 (54.0)
Age			
15-39	1882 (3.8)	2130 (3.4)	2436 (3.3)
40-49	3645 (7.4)	4469 (7.1)	5570 (7.4)
50-59	9870 (20.1)	10 687 (17.0)	9689 (12.9)
60-69	15 769 (32.1)	20 555 (32.7)	24 775 (33.0)
70-79	14 860 (30.2)	20 085 (32.0)	25 872 (34.5)
80-84	3174 (6.5)	4853 (7.7)	6644 (8.9)
Cancer site			
Oral cavity and pharynx	1187 (2.4)	1577 (2.5)	1681 (2.2)
Digestive tracts	22 690 (46.1)	27 950 (45.0)	33 017 (44.0)
Liver, biliary tract, pancreas	3091 (6.3)	4325 (6.9)	5056 (6.7)
Respiratory and intrathoracic organs	4383 (8.9)	5514 (8.8)	6884 (9.2)
Bone, skin, mesothelial and soft tissue	999 (2.0)	1696 (2.7)	2253 (3.0)
Breast	6920 (14.1)	8359 (13.3)	9779 (13.0)
Female genital organs	3139 (6.4)	3656 (5.8)	4661 (6.2)
Male genital organs	1740 (3.5)	2678 (4.3)	3679 (4.9)
Urinary organs	3574 (7.3)	4774 (7.6)	5538 (7.4)
Eye, brain, central nervous system, thyroid and endocrine glands	1275 (2.6)	2011 (3.2)	2150 (2.9)
Other and unspecified sites	202 (0.4)	239 (0.4)	288 (0.4)
Circumstances of cancer detection			
Screening	6589 (13.4)	10 177 (16.2)	12 172 (16.2)
Not screening	7914 (16.1)	14 971 (23.9)	19 709 (26.3)
Unknown	34 697 (70.5)	37 631 (59.9)	43 105 (57.5)
Cancer stage			
Localized	27 035 (55.0)	35 477 (56.5)	45 607 (60.8)
Regional	8427 (17.1)	9158 (14.6)	10 134 (13.5)
Adjacent	7521 (15.3)	10 391 (16.6)	12 102 (16.1)
Distant	4794 (9.7)	5622 (9.0)	6032 (8.0)
Unknown	1423 (2.9)	2131 (3.4)	1111 (1.5)
Extent of remaining tumor after surgery			
Not remained	37 184 (75.6)	47 512 (75.7)	61 720 (82.3)
Remained	8534 (17.4)	10 570 (16.8)	9679 (12.9)
Unknown	3482 (7.1)	4697 (7.5)	3587 (4.8)
Chemotherapy			
Received	13 580 (27.6)	18 463 (29.4)	22 250 (29.7)
Not received	31 559 (64.1)	43 059 (68.6)	52 633 (70.2)
Unknown	4061 (8.3)	1257 (2.0)	103 (0.1)
	2004-2006	2007-2009	2010-2012
	n (%)	*n* (%)	*n* (%)
Radiation therapy			
Received	4778 (9.7)	5986 (9.5)	6812 (9.1)
Not received	39 737 (80.8)	55 429 (88.3)	68 037 (90.7)

(Continues)

TABLE 1 (Continued)

	2004-2006	2007-2009	2010-2012
	n (%)	*n* (%)	*n* (%)
Unknown	4685 (9.5)	1364 (2.2)	137 (0.2)
Residential area			
Area A	15 753 (32.0)	18 440 (29.4)	23 007 (30.7)
Area B	6324 (12.9)	7626 (12.2)	8868 (11.8)
Area C	3777 (7.7)	5263 (8.4)	6131 (8.2)
Area D	5553 (11.3)	7192 (11.5)	8350 (11.1)
Area E	4617 (9.4)	6432 (10.3)	7578 (10.1)
Area F	3509 (7.1)	4582 (7.3)	5142 (6.9)
Area G	5114 (10.4)	6531 (10.4)	7541 (10.1)
Area H	4553 (9.3)	6713 (10.7)	8369 (11.2)
Year of diagnosis in the 3 y			
First year (2004, 2007, 2010)	14 315 (29.1)	20 932 (33.3)	23 627 (31.5)
Middle year (2005, 2008, 2011)	16 307 (33.1)	20 320 (32.4)	25 092 (33.5)
Last year (2006, 2009, 2012)	18 578 (37.8)	21 527 (34.3)	26 267 (35.0)

below the threshold were +1.48%, +0.72%, and +0.29% points in 2004-2006, 2007-2009, and 2010-2012, respectively. The percentage changes above the thresholds were +0.15%, +0.07%, and +0.02% points in 2004-2006, 2007-2009, and 2010-2012, respectively.

4 | DISCUSSION

This study identified surgical volume thresholds for solid cancers based on the association with the adjusted 3-year survival probability of patients treated in 66 DCCHs by using data from a population-based cancer registry in Osaka, Japan. First, the surgical volume thresholds where the trend of the association between surgical volume and the adjusted 3-year survival probability changed were identified for the surgical volume categories of 100-149 in 2004-2006 and 2007-2009 and 200-249 in 2010-2012. Thus, the existing surgical volume requirement for national DCCH (ie, performing 400 surgeries per year) was higher than the estimated surgical volume thresholds of the three periods. Second, the estimated surgical volume threshold changed from 100-149 in 2004-2009 to 200-249 in 2010-2012, with increased median surgical volume and improved 3-year survival probability among the 66 DCCHs. These trends were consistently observed in the surgical volume thresholds of the adjusted 1-year survival probability for the three periods.

The existing surgical volume requirement for the national DCCH (ie, 400 surgical volumes per year) was sufficiently higher than the estimated thresholds. This indicates that DCCHs that meet the existing requirement may be able to achieve a patient survival rate as high as the other high-volume DCCHs. Meanwhile, the existing requirement for prefectural DCCHs (ie, 200 surgical volumes per year) was higher than the estimated threshold in 2004-2009, and it

became nearly equal to the estimated threshold in 2010-2012. This change was probably due to an improvement in the survival probability across the DCCHs during the three periods, which subsequently narrowed the gap in the survival probability across high-volume and low-volume DCCHs in 2010-2012. This finding implies that surgical volume and patient survival are expected to change in the future. It suggests regular review of surgical volume requirement for DCCHs. In the review process, the surgical volume threshold estimated by the association with patient outcomes, such as survival probability, can be used as an evidence-based reference. To date, the existing surgical volume requirement in Japan targets the total number of surgeries for all cancer sites. By contrast, several countries define the surgical volume standard for a specific cancer or procedure, probably because the frequency and complexity of surgeries[13] and the associations between surgical volume and patient outcome vary by cancer site.[30] Although our finding of surgical volume thresholds for overall solid cancers could not be compared with those in other settings, cancer site-specific surgical volume thresholds in Japan are worth investigating in our future study.

The estimated surgical volume thresholds changed during the three periods from 100-149 in 2004-2006 and 2007-2009 to 200-249 in 2010-2012. This shift may be explained by the changes in surgical volume and patient survival probability among the 66 DCCHs during the study period. We observed a decrease in the number of low-volume DCCHs. For example, the proportion of hospitals with surgical volumes <200 accounted for 47.0% in 2004-2006, which declined to 24.2% in 2010-2012. Furthermore, we found that the 3-year survival probability improved particularly in DCCHs with surgical volumes <150. These changes may have resulted in narrowing the gap in survival probability between low- and high-volume DCCHs during the period, from 18% points in 2004-2006 to only 11% points in 2010-2012. Correspondingly, the highest volume DCCHs showed significantly lower mortality hazards than the rest of

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TABLE 2 Distribution of hospitals and patients by surgical volume category

Surgical volume[a]	2004-2006		2007-2009		2010-2012	
	Hospital	Patient	Hospital	Patient	Hospital	Patient
Median[b] (IQR)	214.0 (90.0-387.1)		264.7 (119.5-474.8)		305.7 (200.7-513.3)	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
0-49	9 (13.6)	773 (1.6)	6 (9.1)	360 (0.6)	4 (6.1)	240 (0.3)
50-99	10 (15.2)	2073 (4.2)	8 (12.1)	1618 (2.6)	5 (7.6)	1024 (1.4)
100-149	9 (13.6)	3425 (7.0)	7 (10.6)	2491 (4.0)	4 (6.1)	1423 (1.9)
150-199	3 (4.6)	1498 (3.0)	5 (7.6)	2562 (4.1)	3 (4.6)	1475 (2.0)
200-249	7 (10.6)	4497 (9.1)	4 (6.1)	2409 (3.8)	10 (15.2)	6366 (8.5)
250-299	5 (7.6)	3990 (8.1)	9 (13.6)	6642 (10.6)	6 (9.1)	4771 (6.4)
300-349	4 (6.1)	3638 (7.4)	7 (10.6)	6376 (10.2)	8 (12.1)	7375 (9.8)
350-399	4 (6.1)	4315 (8.8)	3 (4.6)	3263 (5.2)	4 (6.1)	4084 (5.5)
400-449	3 (4.6)	3592 (7.3)			3 (4.6)	3624 (4.8)
450-499	3 (4.6)	4132 (8.4)	1 (1.5)	1298 (2.1)	2 (3.0)	2668 (3.6)
500-549	3 (4.6)	4067 (8.3)	2 (3.0)	3011 (4.8)	3 (4.6)	4432 (5.9)
550-599	1 (1.5)	1721 (3.5)	2 (3.0)	3324 (5.3)	1 (1.5)	1710 (2.3)
600-649	2 (3.0)	3508 (7.1)	2 (3.0)	3567 (5.7)		
650-699			3 (4.6)	5754 (9.2)		
700-749					1 (1.5)	2117 (2.8)
750-799	2 (3.0)	4506 (9.2)			4 (6.1)	8688 (11.6)
800-849						
850-899			3 (4.6)	7595 (12.1)		
900-949			1 (1.5)	2655 (4.2)	1 (1.5)	2674 (3.6)
950-999					1 (1.5)	2732 (3.6)
1000-1049					1 (1.5)	2906 (3.9)
1050-1099			1 (1.5)	3118 (5.0)	1 (1.5)	3066 (4.1)
1100-1149			1 (1.5)	3295 (5.3)		
1150-1199	1 (1.5)	3465 (7.0)	1 (1.5)	3441 (5.5)	4 (6.1)	13 611 (18.2)

IQR, interquartile range.

[a]Surgical volume was defined as the annual average number of surgeries (ie, open surgery, endoscopic surgery, or endoscopic resection) that a hospital performed for solid cancers in a 3-y period (ie, 2004-2006, 2007-2009, and 2010-2012).

[b]Median of the annual average number of surgeries in a 3-y period among the 66 designated cancer care hospitals.

the lower-volume DCCHs in 2004-2006. In 2010-2012, 17 DCCHs showed comparable mortality hazard to the highest volume DCCHs. These positive changes may have been attributed to the effect of the third-term comprehensive 10-year strategy for cancer control (2004-2013) that promoted the development of DCCHs and equal delivery of high-quality cancer medical services through DCCHs.[41] Although this study showed that the survival probability of patients treated in DCCHs has improved during the study period, approximately 14% of cancer patients still underwent surgery in non-DCCHs in 2010-2012. Moreover, the surgical volume and survival probability of non-DCCHs were significantly lower than those of national or prefectural DCCHs.[29] Through the cancer control strategy, further centralization of patients from non-DCCHs to DCCHs is expected to

be promoted in the future. Therefore, monitoring changes in surgical volume and patient survival and regularly evaluating the optimal surgical volume requirement are crucial.

Additionally, we found that the association between surgical volume and 3-year survival probability showed a similar trend across the three periods (Figure 1). The extent of change in the 3-year survival probability per an increase of 50 surgical volumes was larger below the estimated surgical volume thresholds, compared with that above the thresholds. This trend has been previously reported.[13] This indicates that the effect of surgical volume on patient survival is larger until the threshold is reached and suggests that efforts to improve patient survival should be made in hospitals with surgical volumes lower than the threshold.

TABLE 3 Adjusted hazard ratios and adjusted 3-y survival probability by survival volume category

	2004-2006		2007-2009		2010-2012	
	aHR (95%CI)	Survival[a]	aHR (95%CI)	Survival[a]	aHR (95%CI)	Survival[a]
0-49	3.16 (2.62-3.79)	71.7	2.87 (2.21-3.71)	68.2	1.92 (1.14-3.21)	79.2
50-99	2.92 (2.50-3.41)	73.5	2.12 (1.68-2.67)	75.4	1.87 (1.54-2.27)	79.6
100-149	2.20 (2.01-2.42)	79.3	1.61 (1.39-1.87)	80.7	1.58 (1.35-1.85)	82.5
150-199	2.14 (1.72-2.66)	79.8	1.64 (1.42-1.89)	80.4	1.42 (1.08-1.87)	84.1
200-249	1.98 (1.64-2.39)	81.2	1.41 (1.07-1.85)	82.9	1.32 (1.11-1.57)	85.1
250-299	1.88 (1.57-2.25)	82.0	1.35 (1.14-1.61)	83.5	1.25 (1.02-1.55)	85.8
300-349	1.98 (1.82-2.15)	81.2	1.26 (1.11-1.42)	84.6	1.25 (1.04-1.50)	85.9
350-399	1.88 (1.74-2.03)	82.1	1.27 (1.08-1.49)	84.4	1.17 (0.98-1.41)	86.7
400-449	2.08 (1.80-2.41)	80.3			1.08 (0.83-1.39)	87.7
450-499	1.92 (1.45-2.53)	81.7	1.31 (1.18-1.44)	84.0	1.18 (0.92-1.52)	86.6
500-549	2.16 (1.98-2.35)	79.7	1.16 (1.05-1.29)	85.6	1.22 (1.04-1.42)	86.2
550-599	1.84 (1.70-2.00)	82.4	1.30 (1.09-1.55)	84.0	1.13 (0.97-1.30)	87.2
600-649	1.84 (1.45-2.34)	82.4	1.03 (0.90-1.18)	87.1		
650-699			1.21 (1.02-1.44)	85.1		
700-749					1.50 (1.29-1.74)	83.3
750-799	1.82 (1.67-1.99)	82.5			1.09 (0.91-1.29)	87.6
800-849						
850-899			1.17 (0.99-1.38)	85.6		
900-949			1.01 (0.91-1.13)	87.4	0.84 (0.70-1.00)	90.3
950-999					1.02 (0.86-1.21)	88.3
1000-1049					1.28 (1.10-1.48)	85.6
1050-1099			1.19 (1.04-1.37)	85.3	1.16 (0.96-1.39)	86.8
1100-1149			0.79 (0.71-0.89)	90.0		
1150-1199	Reference	90.0	Reference	87.5	Reference	88.5

aHR, adjusted hazard ratios; CI, confidence interval.

[a]Survival means the adjusted 3-y survival probability estimated by multivariable Cox proportional hazard model with adjustment for sex, age, cancer site, circumstances of cancer detection, cancer stage, the extent of remained tumor, the reception chemotherapy, the reception of radiation therapy, residential area, and the year of diagnosis.
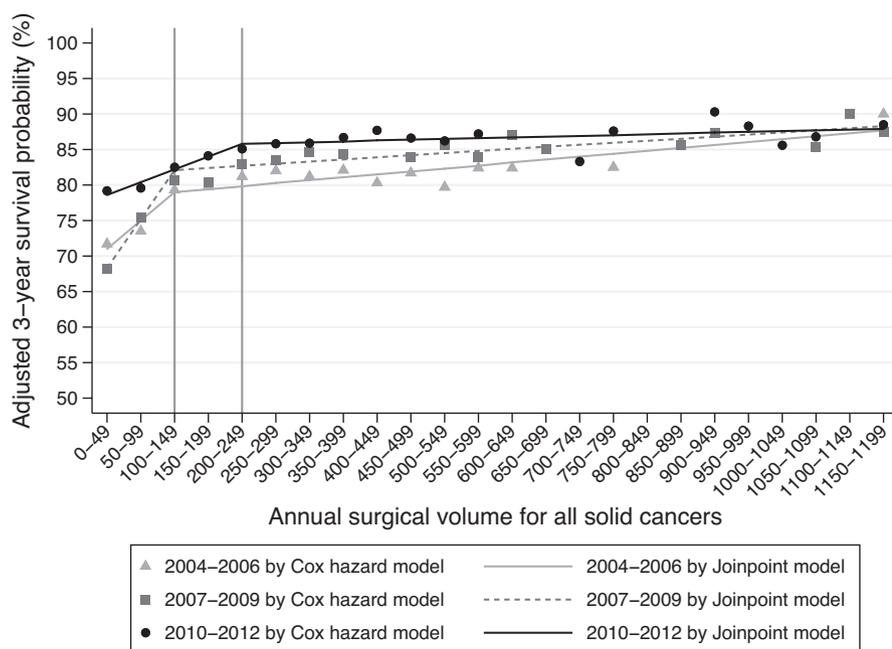

FIGURE 1 Estimated surgical volume thresholds based on the association between surgical volume and adjusted 3-y survival probability. Note: We plotted the adjusted 3-y survival probability per annual surgical volumes in 2004-2006, 2007-2009, and 2010-2012 estimated by a multivariable Cox proportional hazard model. Based on the association between surgical volume and adjusted 3-y survival probability, we described the linear relationship and identified the surgical volume thresholds (the gray vertical lines) for 2004-2006, 2007-2009, and 2010-2012 using the joinpoint regression model

This study had several limitations. First, the hazard ratios and survival probability were potentially biased because we could not control potential confounders, such as patients' socioeconomic characteristics, pre-existing comorbidity, performance status, time from diagnosis to surgery, and treatment for the cancer or any other diseases that a patient received after the surgery, and hospital characteristics, including surgeon volume, resources, and infrastructure. Second, we could not calculate cancer-specific mortality because of the absence of information on the cause of death in the database. Finally, the generalizability of the study findings was limited because the cancer burden and health system would vary by setting, which affects the estimation of surgical volume threshold. Despite these limitations, this study showed one potential method to define evidence-based surgical volume standards to ensure optimal patient survival in DCCHs in Japan.

In conclusion, the surgical volume thresholds based on the association with the adjusted 3-year survival probability were 100-149 in 2004-2006 and 2007-2009 and 200-249 in 2010-2012, with increased surgical volume and improved survival probability, particularly in low-volume DCCHs during these periods. The existing surgical volume requirement for the national DCCH met our estimated threshold. The surgical volume requirement should be regularly reviewed, and surgical volume threshold based on the association with patient survival may be used as an evidence-based reference.

DISCLOSURE

The authors have no conflict of interest.

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