Gastric Cancer (2017) 20:508–516
DOI 10.1007/s10120-016-0636-y

ORIGINAL ARTICLE

Institutional variation in short- and long-term outcomes after surgery for gastric or esophagogastric junction adenocarcinoma: correlative study of two randomized phase III trials (JCOG9501 and JCOG9502)

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Received: 26 June 2016 / Accepted: 17 August 2016 / Published online: 27 August 2016

Abstract

Background A critical issue in multicenter randomized trials focusing on surgical techniques is quality control, as the quality of the surgery usually varies widely if the procedure employed is complicated. Few studies have evaluated interinstitutional variation in randomized trials in order to check not only the generalizability of the results but also the reliability of the study group itself.

Methods Two randomized phase III trials (JCOG9501 and JCOG9502) were conducted that compared standard and experimental surgery for gastric and esophagogastric junction adenocarcinomas. Mixed effects models were used to examine short- and long-term outcome data for 521 patients from 23 hospitals in JCOG9501 and 157 patients from 21 hospitals in JCOG9502.

Results In both trials, some variation was observed in the number of dissected lymph nodes, the operative time, and the volume of blood lost. Estimated 5-year overall survival after standard surgery differed among hospitals (JCOG9501, 58.0–75.1 %; JCOG9502, 49.1–58.7 %), while there was little variation in the hazard ratio for overall survival (OS) for experimental versus standard surgery (JCOG9501, 1.05–1.48; JCOG9502, 1.44–1.48). Higher hospital gastrectomy volume was significantly correlated with a lower proportion of postoperative complications in JCOG9501 ($\rho = -0.524$, $P = 0.010$) and reduced blood loss in JCOG9502 ($\rho = -0.442$, $P = 0.045$). OS was not correlated with hospital or surgeon volume.

Conclusions There was some degree of interinstitutional variation in outcomes after standard surgery, but there was little variation in the hazard ratio for OS for experimental surgery, indicating that the final conclusions of the two randomized phase III trials can be generalized to their respective target populations.

Keywords Gastric cancer · Institutional variation · Heterogeneity · Generalizability · Hospital volume · Surgeon volume

Introduction

Surgery is still the main treatment for solid tumors in which local control is required to cure the disease. In the last few decades, more and more multicenter randomized controlled trials focusing on surgical techniques with or without appropriate systemic therapy have been reported [1–5]. Variation in the quality of surgery has long been a major issue when conducting surgical trials [6]. The average number of surgeries performed at an institution (hospital volume) and by an individual surgeon (surgeon volume) are factors that may affect outcomes. Patients who undergo surgery at high-volume hospitals have lower rates of postoperative mortality than those treated at low-volume

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hospitals [7–9]. However, retrospective studies of large cohorts that were performed to evaluate the quality of surgical treatment in multicenter randomized controlled trials are scarce. Few reports have assessed the surgical variation among institutions participating in randomized phase III trials in order to check not only the generalizability of the results of each study but also the reliability of the study group itself.

In the 1990s and 2000s, two randomized phase III trials comparing standard and experimental surgery for gastric or esophagogastric junction adenocarcinomas, JCOG9501 and JCOG9502, were conducted by the Japan Clinical Oncology Group (JCOG). There were strict criteria for the participation of institutions and surgeons in these trials; the credentialing of surgeons was implemented by assessing operative reports, and their performance was monitored through data collection (performance was reported to be correlated to the short-term outcomes after esophagogastric surgery in a recent systematic review [10]). Neither trial could demonstrate a survival benefit of experimental surgery [11–14]. The international statistical guideline ICH-E9 recommends that, in phase III trials, the variation in the treatment effects should be explored in order to evaluate the generalizability of the conclusions [15]. We have already succeeded in confirming the generalizability of the conclusions of a positive phase III trial in the field of chemotherapy for metastatic gastric cancer using mixed effects models [16]. Applying the same method, we evaluated interinstitutional variation in standard and experimental surgery in JCOG9501 and JCOG9502 after adjusting for various background factors that could affect outcomes in order to check not only the generalizability of the results but also the reliability of the JCOG study group itself.

Methods

JCOG9501 phase III trial

JCOG9501 was a multicenter, prospective, randomized phase III trial evaluating the survival benefit of the addition of paraaortic node dissection (PAND) to standard gastrectomy with D2 lymphadenectomy [11, 12]. Eligibility criteria included histologically confirmed adenocarcinoma of the stomach, 75 years of age or younger, clinical T2b–4 disease, no gross metastases to paraaortic nodes, and negative cytology by peritoneal lavage. The primary endpoint was overall survival. Between July 1995 and April 2001, 523 patients from 24 hospitals were randomized to standard D2 lymphadenectomy (263 patients) or experimental D2 lymphadenectomy plus PAND (260 patients). In the standard D2 group, gastrectomy with D2 lymphadenectomy was carried out according to the first English edition of the Japanese Classification of Gastric Carcinoma (12th Japanese version) [17]. In the experimental D2 plus PAND group, the paraaortic lymph nodes were also dissected. The spleen was removed when total gastrectomy was performed. The reconstruction method was not prespecified. Adjuvant therapy was not allowed. This study was approved by the JCOG protocol review committee and the institutional review boards of all participating hospitals, and was registered with ClinicalTrials.gov (no. NCT00149279).

JCOG9502 phase III trial

JCOG9502 was a multicenter, prospective, randomized phase III trial evaluating the survival benefit of the left thoracoabdominal (LTA) approach compared to the abdominal transhiatal (TH) approach [13, 14]. Eligibility criteria consisted of histologically confirmed adenocarcinoma of the gastric cardia or body with esophageal invasion of 3 cm or less, 75 years of age or younger, clinical T2–4 disease, no distant metastases, and no lymph nodes larger than 1 cm in the hepatoduodenal ligament or the paraaortic field. The primary endpoint was overall survival. Between July 1995 and December 2003, 167 patients from 27 hospitals were randomized to the standard TH approach (82 patients) or the experimental LTA approach (85 patients). In the standard TH group, total gastrectomy with D2 and additional dissection of the left upper paraaortic nodes were performed. The lower mediastinum was accessed through the esophageal hiatus, which was extended by a longitudinal incision in the medial part of the diaphragm. In the experimental LTA group, a long oblique incision over the seventh intercostal space was extended to the right abdomen. In the abdominal cavity, the same procedure was carried out, and thorough mediastinal lymph node dissection below the inferior pulmonary vein was performed. The reconstruction method was not prespecified. Adjuvant therapy was not allowed. This study was approved by the JCOG protocol review committee and the institutional review boards of all participating hospitals, and was registered with ClinicalTrials.gov (no. NCT00149266).

Outcomes in this study

Among the 24 participating hospitals in the JCOG9501 trial and 27 hospitals in the JCOG9502 trial, hospitals with fewer than 3 patients for the entire duration of the trial were excluded from the analysis. Patients who were randomized into the standard D2 group in the JCOG9501 trial and the standard TH group in the JCOG9502 trial were analyzed to evaluate the interinstitutional variation in outcomes after standard surgery. Short-term outcomes included the number of dissected lymph nodes, operative

time, intraoperative blood loss volume, and proportion of patients with postoperative complications such as anastomotic leakage, pancreatic fistula, intra-abdominal abscess, pyothorax, pneumonia, and mediastinitis. The long-term outcome was the OS from the date of randomization to the date of death from any cause. We also examined the correlation between the variation in each outcome and hospital volume (number of gastrectomy procedures each year during the accrual period) or surgeon volume (number of gastrectomies per surgeon each year during the accrual period).

Statistical analysis

Mixed effects models were used to evaluate interinstitutional variation. The variation in the number of dissected lymph nodes, operative time, and blood loss volume among institutions was estimated using linear mixed effects models, and a mixed effects logistic regression model was used for the proportion of patients with postoperative complications. In these models, the institutional effect was considered to be random, while the effects of other baseline factors (treatment group, age, sex, body mass index, type of gastrectomy, Borrmann macroscopic type, location of the primary tumor, tumor size, histological type, pathological T stage, and pathological N stage) were considered to be fixed. We used mixed effects proportional hazards models with the Weibull baseline hazard to investigate baseline risks (i.e., the deviation of each hospital from the overall baseline risk that was not explained by other prognostic factors) and treatment effects (i.e., the deviation of each hospital from the overall treatment effect that was not explained by other prognostic factors) in OS among hospitals. Treatment effects were considered to be random effects and the effects of other baseline factors were considered to be fixed.

To evaluate the baseline risk, the predicted OS for each hospital was translated into a 5-year OS to facilitate the interpretation of our results. To investigate the reason for the observed interinstitutional variation, Spearman's correlation coefficients were calculated for associations between the estimated outcomes and hospital or surgeon volume. All statistical analyses were performed with the SAS software (versions 9.1 and 9.2) and the WinBUGS software (version 1.4.2).

Results

A patient flow diagram for the two trials is shown in Fig. 1. In total, 521 patients from 23 hospitals in the JCOG9501 trial and 157 patients from 21 hospitals in the JCOG9502 trial were included in the analysis. There were 258 patients randomized to the experimental D2 plus PAND group in the JCOG9501 trial and 81 patients randomized to the experimental LTA group in the JCOG9502 trial who were included in the analysis of the effect of the experimental surgery treatment. Characteristics of the patients included in this study are shown in Table 1.

Table 2 shows the estimated short-term outcomes for standard surgery after adjusting for ten background factors. The largest difference between the maximum and minimum number of dissected lymph nodes at a particular hospital was 49 in the JCOG9501 trial and 36 in the JCOG9502 trial. Some variation in both operative time and blood loss volume was also observed in both trials. On the other hand, the interinstitutional variation in the proportion of patients with postoperative complications was relatively small in both trials (JCOG9501, 8.9 %; JCOG9502, 8.6 %).

Figure 2 shows the estimated OS for standard surgery in each hospital after adjusting for ten background factors. Some variation in the 5-year OS was observed in both the JCOG9501 trial (mean, 69.2 %; range, 58.0–75.1 %) and the JCOG9502 trial (mean, 52.3 %; range, 49.1–58.7 %).

Figure 3 shows the estimated HRs for OS for experimental versus standard surgery in each hospital. Although some degree of variation in the effect of the experimental surgical treatment occurred in the JCOG9501 trial, the HR for experimental versus standard surgery exceeded 1.00 in every hospital (range, 1.05–1.48). In the JCOG9502 trial, there was little variation in the HR for OS for experimental versus standard surgery (range, 1.44–1.48).

The median hospital and surgeon volumes in the JCOG9501 trial were 130 (range, 40–438) and 62 (range, 13–280), while those in the JCOG9502 trial were 139 (range, 44–511) and 68 (range, 15–179), respectively. Correlations between estimated outcomes for standard surgery and hospital or surgeon volume are shown in Table 3. For gastrectomy, higher hospital volume was significantly correlated with a lower proportion of patients with postoperative complications ($\rho = -0.524$, $P = 0.010$) in the JCOG9501 trial and a smaller blood loss volume ($\rho = -0.442$, $P = 0.045$) in the JCOG9502 trial. There was a trend towards a correlation of higher surgeon volume with a higher number of dissected lymph nodes in both trials, but it was not statistically significant. We also found a trend towards a correlation between blood loss volume and hospital or surgeon volume in the JCOG9501 trial. On the other hand, there was no correlation between OS and hospital or surgeon volume. We additionally evaluated the correlation between OS and the above short-term outcomes (the number of dissected lymph nodes, operative time, blood loss volume, and proportion of patients with postoperative complications), but we could not find any trend in either trial (data not shown).

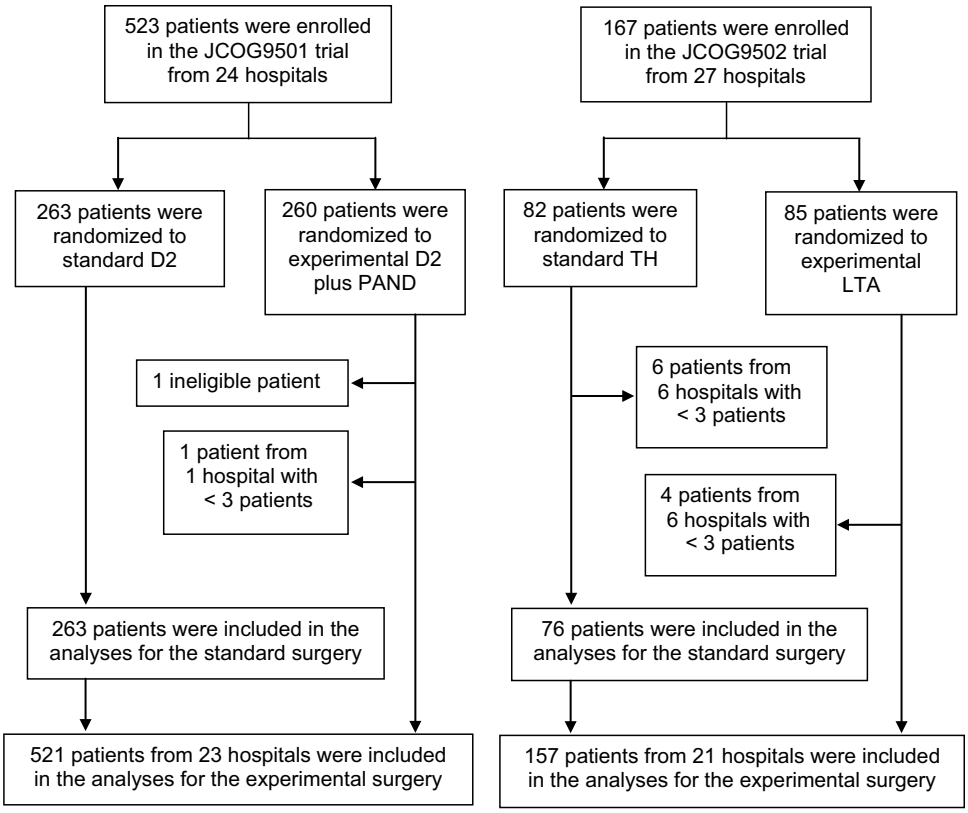

Fig. 1 Patient flow diagram for the two trials. *PAND* paraaortic node dissection, *TH* transhiatal, *LTA* left thoracoabdominal

Discussion

JCOG9501 and JCOG9502 are landmark phase III trials in the field of gastric and esophagogastric junction adenocarcinoma surgery [11–14]. The results of these two trials are reflected in the Japanese Gastric Cancer Association (JGCA) guidelines as well as the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines [18–20]. However, this correlative study of the two trials indicated that there was some degree of interinstitutional variation in short- and long-term outcomes after standard surgery in these phase III trials. JCOG included only "expert" Japanese hospitals, and there were strict inclusion criteria for both trials, i.e., only institutions that performed at least 50–80 gastrectomies each year were considered. A recent systematic review analyzing the quality of surgery within randomized controlled trials for the treatment of gastric and esophagogastric junction adenocarcinoma concluded that credentialing of surgeons was one of the most important methods of reducing the variation in short-term outcomes [10]. In the JCOG9501 and JCOG9502 trials, only surgeons who had performed more than 100 gastrectomies were allowed to participate. Nevertheless, differences in estimated 5-year OS rates between the highest and lowest hospitals were as high as 10–17 % in both trials. Since this interinstitutional variation in standard surgery results could affect the primary endpoint, OS, we also evaluated the interinstitutional variation in treatment effects for experimental surgery (D2 plus PAND in JCOG9501 and LTA in JCOG9502). However, the variation in the HR for OS for experimental surgery compared to standard surgery was small in both trials, indicating that the final results of JCOG9501 and JCOG9502 could be generalized to their respective target populations.

The association between hospital volume and short- or long-term outcomes after gastric cancer surgery has been discussed in previous reports. A strong correlation between hospital volume and short-term outcomes was observed in three studies from the United States, one from Taiwan, and one from Japan [21–25], while two other studies from the United States and the Netherlands, respectively, did not show a positive relationship between higher hospital volume and lower in-hospital mortality [26, 27]. Regarding long-term outcomes, a study from the United States showed a positive relationship between hospital volume and long-term survival [28], while a Dutch study showed that high hospital volume was associated with long-term survival after esophagectomy, but not gastrectomy [27]. Thus, the association between hospital volume and short- or long-term outcomes after gastric cancer surgery has remained controversial. One of the reasons for this might be an insufficient number of gastrectomies, even in "high-volume" hospitals, in these studies. Indeed, the minimum number of

Table 1 Characteristics of the patients in the two trials

	JCOG9501		JCOG9502	
	Standard D2 ($n = 263$)	Experimental D2 plus PAND ($n = 258$)	Standard TH ($n = 76$)	Experimental LTA ($n = 81$)
Age (years)				
Median (range)	60 (25–75)	61 (27–75)	60.5 (36–75)	63 (38–75)
Sex				
Male	176	182	66	60
Female	87	76	10	21
Body mass index (kg/m^2)[a]				
Median (range)	23.8 (15.4–31.0)	22.1 (13.8–30.5)	21.8 (14.6–29.1)	22.2 (15.0–32.0)
Type of gastrectomy[b]				
Total	102	96	73	78
Distal or proximal	161	162	3	2
Borrmann macroscopic type				
0, 1, 2	94	111	35	35
3, 4, 5	169	147	41	46
Location (only JCOG9501)				
Upper, middle	210	212		
Lower	53	46		
Location (only JCOG9502)[b]				
Siewert type II			49	41
Siewert type III or non-EGJ tumor			27	39
Tumor size (cm)[b]				
Median (range)	5.5 (2.0–17.0)	5.5 (2.0–15.2)	6.4 (2.5–19.0)	7.0 (2.0–18.0)
Histological type[b]				
Differentiated	97	106	38	42
Undifferentiated	166	152	38	38
pT stage (UICC TNM classification, 6th edition)[b]				
T1–2	134	145	32	40
T3–4	129	113	44	40
pN stage (UICC TNM classification, 6th edition)[b]				
N0	79	95	13	14
N1–3	184	163	63	66

pT and pN stage were gauged according to the 6th edition of the International Union Against Cancer (UICC) TNM classification

PAND paraaortic node dissection, *TH* transhiatal, *LTA* left thoracoabdominal, *EGJ* esophagogastric junction

[a] Data not available for three patients in the LTA group

[b] Data not available for one patient in the LTA group

gastrectomies per year needed to qualify as a high-volume hospital in Western studies has been only 16–21 [26–28]. Another reason is probably incomplete adjustment for various background factors, because most previous studies have been based on national registries, which include patient characteristics such as age, sex, performance status, comorbidities, body mass index, tumor stage, surgical procedure, and perioperative treatment. Large variations in patient characteristics led to potential biases that made it difficult to evaluate interinstitutional variations in surgery. In our study, we used the data from two landmark phase III trials involving patients with homogeneous baseline characteristics and treatment histories, and adjusted for ten background factors that could affect outcomes. We found a positive relationship between higher hospital volume and both lower morbidity in JCOG9501 and reduced blood loss in

Table 2 Interinstitutional heterogeneity in short-term outcomes for standard surgery

	Standard D2 in the JCOG9501 ($n = 263$) Median (range)	Standard TH in the JCOG9502 ($n = 76$) Median (range)
Number of dissected lymph nodes	56 (40–89)	66 (51–87)
Operative time (min)	229 (144–442)	293 (238–483)
Blood loss volume (mL)	564 (180–871)	836 (397–1197)
Proportion of patients with postoperative complications (%)	21.2 (16.3–25.2)	31.4 (28.2–36.8)

TH transhiatal

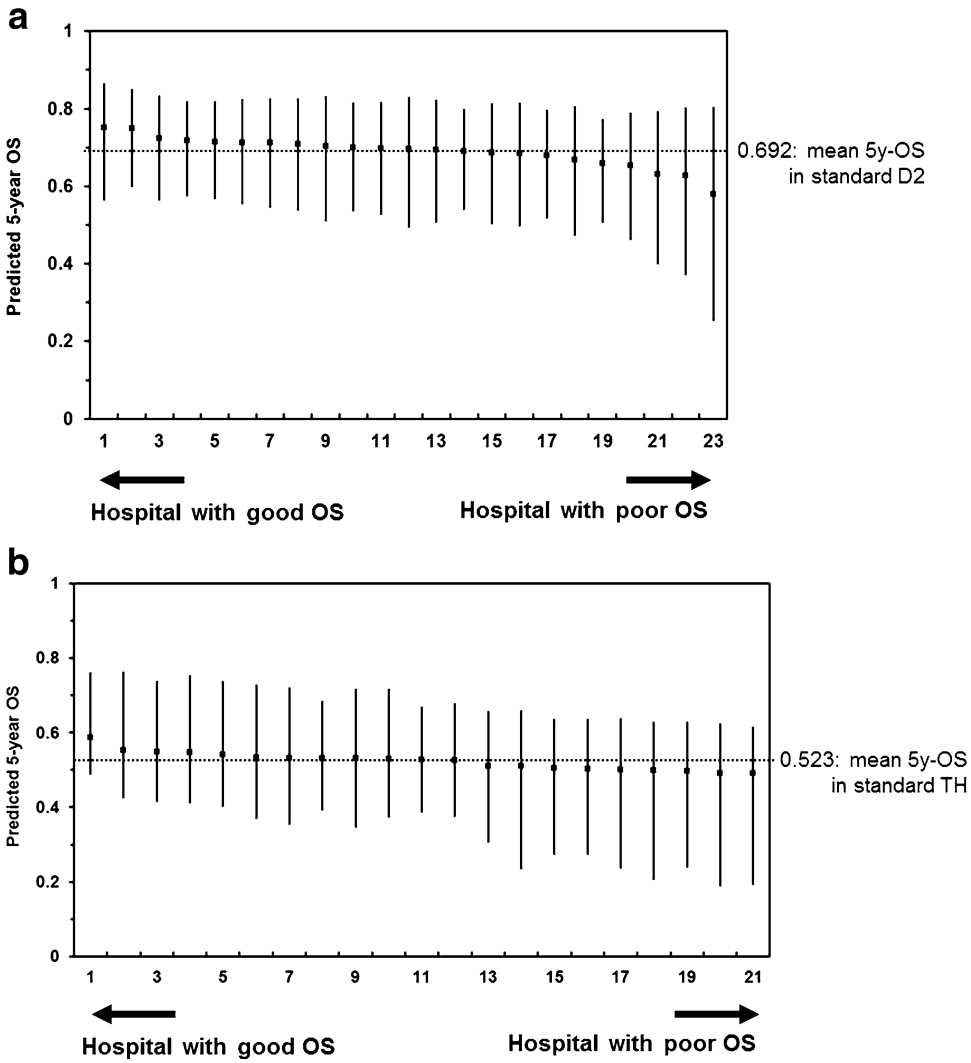

Fig. 2 Estimated 5-year overall survival (*OS*) rates for standard D2 lymphadenectomy at the 23 hospitals in the JCOG9501 trial (**a**) and for surgery with the standard transhiatal (*TH*) approach at the 21 hospitals in the JCOG9502 trial (**b**)

JCOG9502. However, hospital volume did not affect OS at all. Surgeon volume can be associated with variations in postoperative outcomes. Xirasagar et al. reported that the adjusted HR for mortality within 6 months after gastrectomy was 1.3 ($P < 0.01$) for low-volume surgeons relative to very high-volume surgeons [29]. Two other studies also showed a positive relationship between surgeon volume and short-term outcomes [30, 31]. Our study showed nonstatistically significant correlations between surgeon volume and the number of dissected lymph nodes and blood loss volume. Surgeon volume was not correlated with OS. Differences in OS among the hospitals might have been due to (unknown) differences in the prognostic factors of the patients, even those who fulfilled the inclusion criteria for the study, or due to differences in surgical skills that were not linked to the hospital or surgeon volume.

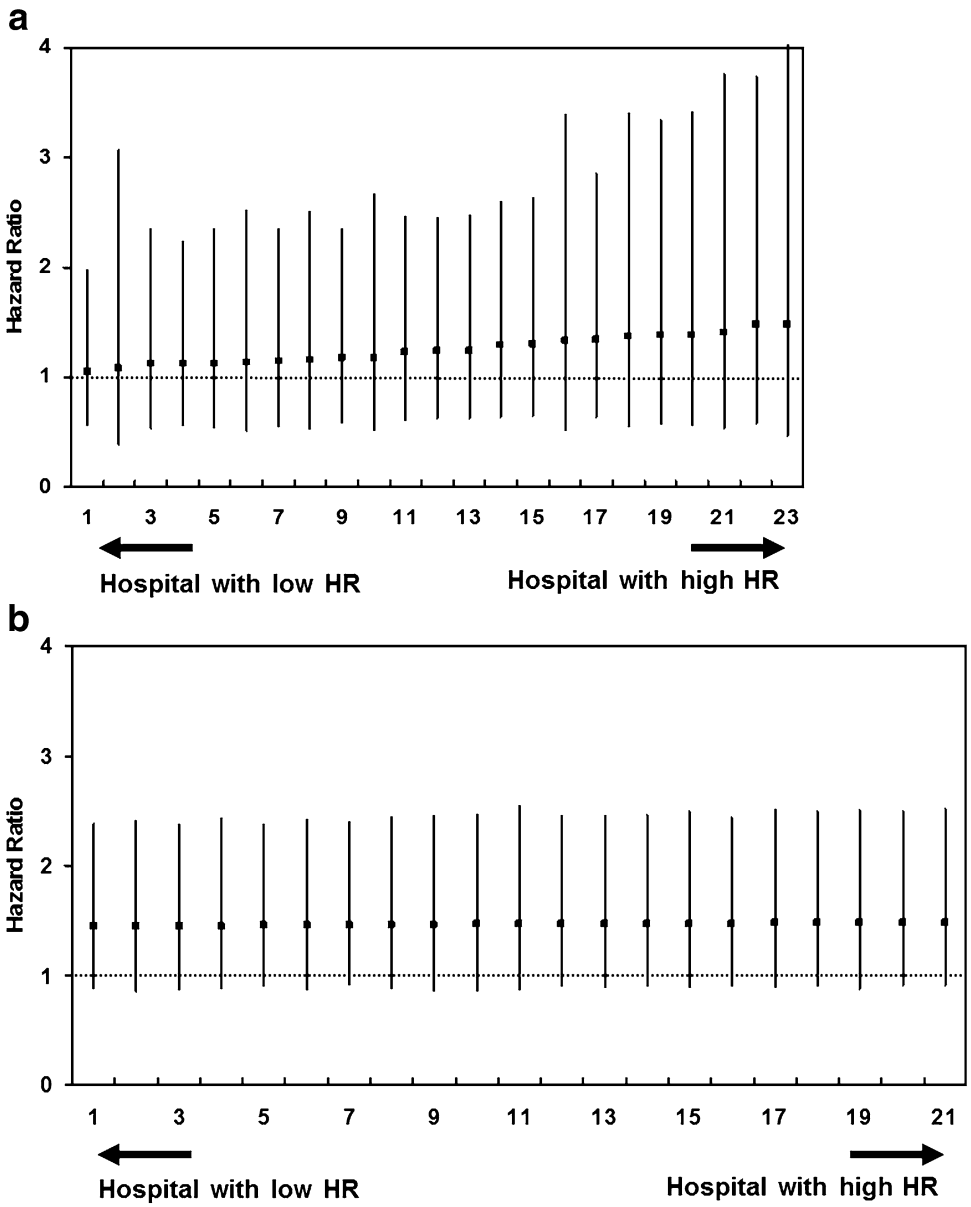

Fig. 3 Estimated hazard ratio (*HR*) for overall survival in the experimental D2 lymphadenectomy plus paraaortic lymph node dissection group compared to the standard D2 lymphadenectomy group at the 23 hospitals in the JCOG9501 trial (**a**) and in the experimental left thoracoabdominal approach group compared to the standard transhiatal approach group at the 21 hospitals in the JCOG9502 trial (**b**)

A possible limitation of our study is that the JCOG 9501 and JCOG9502 trials were conducted between 1995 and 2003, and the field of gastric or esophagogastric junction adenocarcinoma surgery may have changed significantly over this time period. Nomura et al. evaluated the relationship between hospital volume and long-term outcomes after gastric cancer surgery during four time periods: 1975–79, 1980–84, 1985–89, and 1990–94, using data from population-based cancer registries [32]. They reported that the strength of the association was attenuated in later time periods and disappeared during 1990–1994, except at very low-volume hospitals. The authors commented that improvements in medical technology and cancer care became widespread in various types of hospitals in Japan in the 1990s, although the standard surgical procedure for gastric cancer as stated in the JGCA guidelines has not changed over the last few decades in Japan.

In conclusion, substantial interinstitutional variations in short- and long-term outcomes after standard surgery were observed, even in "expert" hospitals in Japan. A positive relationship between higher hospital volume and lower morbidity and between higher hospital volume and reduced blood loss was estimated, while hospital or surgeon volume did not affect long-term outcomes. Variation in the HR for OS for experimental versus standard surgery was small, indicating that the final results of JCOG9501 and JCOG9502 can be generalized to the target population. This study also demonstrated the high reliability of the JCOG gastric cancer study group.

Table 3 Correlations between estimated outcomes for standard surgery and hospital or surgeon volume

	Hospital volume		Surgeon volume	
	JCOG9501 ($n = 263$)	JCOG9502 ($n = 76$)	JCOG9501 ($n = 263$)	JCOG9502 ($n = 76$)
Number of dissected lymph nodes	$\rho = 0.074$	$\rho = 0.340$	$\rho = 0.367$	$\rho = 0.387$
	($P = 0.738$)	($P = 0.131$)	($P = 0.085$)	($P = 0.083$)
Operative time	$\rho = -0.309$	$\rho = -0.292$	$\rho = -0.284$	$\rho = -0.183$
	($P = 0.151$)	($P = 0.200$)	($P = 0.189$)	($P = 0.428$)
Blood loss volume	$\rho = -0.398$	$\rho = -0.442$	$\rho = -0.388$	$\rho = -0.231$
	($P = 0.060$)	($P = 0.045$)	($P = 0.067$)	($P = 0.315$)
Proportion of patients with postoperative complications	$\rho = -0.524$	$\rho = 0.087$	$\rho = -0.254$	$\rho = -0.105$
	($P = 0.010$)	($P = 0.708$)	($P = 0.242$)	($P = 0.652$)
Overall survival rate	$\rho = -0.110$	$\rho = 0.289$	$\rho = -0.063$	$\rho = 0.179$
	($P = 0.617$)	($P = 0.204$)	($P = 0.776$)	($P = 0.439$)

Acknowledgments The study was supported in part by grants-in-aid for cancer research (17S-3, 17S-5, 20S-3, 20S-6, 23-A-16, 23-A-19) from the Ministry of Health, Labour and Welfare, Japan and the National Cancer Center Research and Development Fund (26-A-4).

Compliance with ethical standards

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

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients before they were included in the study.

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