ORIGINAL ARTICLE

Improving Outcomes After Gastroesophageal Cancer Resection

Can Japanese Results Be Reproduced in Western Centers?

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Hypothesis: Extended lymphadenectomy in gastroesphageal cancer leads to improved long-term survival without compromising postoperative outcomes in Western patients to attain the standard achieved in Japanese centers.

Design: Cohort study comparing postoperative outcomes and long-term survival with data from the National Cancer Center (NCC) of Tokyo, Japan. Outcomes were also compared with data from the UK National Oesophago-Gastric Cancer Audit (NOGCA) and a representative cohort from southeast England. Prospectively collected data were independently audited.

Setting: University medical center.

Patients: From 2003 to 2010, 100 patients underwent gastrectomy and 109 underwent esophagectomy.

Main Outcome Measures: Postoperative mortality and morbidity and long-term overall survival. Lymph node count was used as a measure for the extent of lymphadenectomy.

Results: One death occurred after esophagectomy and none after gastrectomy. Anastomotic leak rate was approximately 2% in both cohorts. Kaplan-Meier estimates of 5-year overall survival after gastrectomy and esophagectomy were 58.4% and 47.8%, respectively. Postoperative mortality and technical complications for gastric and esophageal cancer resections were similar to NCC rates ($P=.20$). Stage for stage 5-year survival rates in patients with esophageal cancer and stages II and III gastric cancer were similar to outcomes in the NCC. The 5-year survival for patients with gastric cancer was worse for those with stage I ($P<.001$) and better for those with stage IV ($P<.001$) disease compared with NCC rates. Postoperative outcomes and long-term survival were significantly better than those reported by the NOGCA and the data from the southeast of England ($P<.05$).

Conclusions: This study demonstrates that postoperative outcomes and long-term survival after gastroesophageal cancer resection can be improved in Western patients to the highest standard achieved in Japan.

Arch Surg. 2012;147(8):738-745

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PATIENTS UNDERGOING RESECTION for gastroesophageal cancer in Japan consistently have been shown to have the lowest postoperative mortality and best long-term survival worldwide.[1-4] This finding holds true despite significant improvements in the long-term survival of Western patients because of perioperative chemotherapy and postoperative chemoradiotherapy.[5-7] The key difference in surgical technique between Japanese and Western centers is the extent of lymphadenectomy. The long-term survival benefit of systematic nodal dissection in Japan was not initially observed in major randomized controlled trials in the United Kingdom and the Netherlands,[8,9] although the Dutch trial reported a significant survival benefit from extended lymphadenectomy at the 15-year follow-up.[10] Those trials also showed a higher postoperative morbidity and mortality with extended lymphadenectomy compared with limited resection. Postoperative outcomes in Western centers have been explained by the difference in age, weight, and comorbidity, whereas the poor long-term survival was attributed to tumor stage and location.[3,4,11] Nevertheless, some surgeons argued that we should not blame

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poor results on the patients and must strive toward achieving outcomes reported in the Japanese literature.[12]

Mixed evidence notwithstanding, the consistency of reported superior outcomes in Japan has inspired Western surgeons to adopt techniques of extended lymphadenectomy. The clinical guide-

lines in the United Kingdom have also recommended extended lymphadenectomy for gastroesophageal cancer resections.[13] The aim of this study was to determine (1) whether adherence to the principles of extended lymphadenectomy can lead to an improved long-term survival without compromising postoperative outcomes in gastroesophageal cancer resections in a Western population and (2) whether those outcomes can be achieved to a comparable standard as reported by the National Cancer Center (NCC) of Tokyo, Japan.

METHODS

From July 1, 2003, through September 23, 2010, we reviewed a complete series by a single surgeon (G.B.H.) at 3 London hospitals (St Mary's Hospital, Harefield Hospital, and Harley Street Clinic). Patient information was maintained prospectively in a comprehensive database. The end points of the study included mortality and morbidity as early outcome measures and long-term overall survival. We used lymph node count as a measure for the extent of lymphadenectomy.

MANAGEMENT STRATEGY

All patients were discussed at multidisciplinary meetings at Imperial College London for cancers of the upper gastrointestinal tract. Staging of gastric cancers entailed computed tomography of the chest, abdomen, and pelvis and a staging laparoscopy. Esophageal staging included computed tomography of the chest, abdomen, and pelvis; positron emission tomography; endoscopic ultrasonography; and staging laparoscopy. Neoadjuvant chemotherapy was administered except in cases of (1) early disease (T1 and T2a primary tumors with no lymph node involvement); (2) multiple comorbidity and elderly patients who were unlikely to tolerate chemotherapy and a surgical procedure; and (3) bleeding or gastric outlet obstruction at presentation that required urgent surgical intervention. Perioperative chemotherapy was given as 3 cycles of treatment before and 3 cycles after the operation. Cycles consisted of epirubicin hydrochloride, 50 mg/m^2, and cisplatin, 60 mg/m^2, given intravenously on day 1, followed by oral capecitabine, 625 mg/m^2 twice daily.[5]

The surgical policy for gastric cancer is D2 gastrectomy in strict accordance with Japanese guidelines.[14] Gastric tumors extending more than 2 cm into the esophagus were treated with D2 total gastrectomy, lower esophagectomy, and lower mediastinal lymphadenectomy via left thoracolaparotomy.[15] In summary, D2 lymphadenectomy for total gastrectomy entailed resection of the perigastric lymph nodes (D1 stations along the cardia, lesser and greater curvature, suprapyloric and infrapyloric regions, and left gastric artery) and the second tier of lymph nodes along the common hepatic, proper hepatic, celiac, proximal, and distal splenic arteries and the splenic hilum. In all patients, gastrectomy was completed with Roux-en-Y reconstruction. The surgical approach for gastroesophageal junctional adenocarcinoma was an Ivor Lewis esophagectomy with abdominal and chest infracarinal lymphadenectomy. For lower and middle esophageal tumors, the lymphadenectomy was extended to include the superior mediastinum and the area around the recurrent laryngeal nerves. In upper esophageal tumors, a neck lymphadenectomy was also performed. The extent of resection was determined according to the results of the prechemotherapy staging.

We performed oral studies using meglumine diatrizoate and diatrizoate sodium (Gastrografin; Bracco Diagnostics Inc) for all patients undergoing total gastrectomy or esophagectomy on the fifth postoperative day before allowing oral intake. Prompt investigation using computed tomography with intravenous and oral contrast and upper gastrointestinal tract endoscopy was performed on deviation from the predicted recovery course. Patients were followed up every 3 months for 2 years, every 6 months for the subsequent 3 years, and yearly thereafter. Surveillance with computed tomography was performed annually for the first 3 years and when clinically indicated.

POSTOPERATIVE EVALUATION

Postoperative death was defined as death during the period of postoperative hospitalization or death from any cause within 60 days of the operation. Definitions of the complications are provided as online supplementary material (eAppendix 1; http://www.archsurg.com). Failure to rescue was defined as death in a patient with 1 or more of these complications (excluding wound infection, which is a non–life-threatening complication). The rate of failure to rescue was determined by dividing the number of deaths in patients who developed a postoperative complication (numerator) by the total number of patients who developed a postoperative complication (denominator).[16] All tumors were staged in accordance with the American Joint Committee on Cancer/International Union Against Cancer TNM classification–version 6.[17] Lymph nodes were not individually dissected by the surgical team after resection to preserve the circumferential margin for examination by pathologists.

COMPARATIVE ASSESSMENT

Postoperative outcomes and long-term survival in the present study were compared with data from the NCC, which represent the criterion standard of technical performance of extended lymphadenectomy in Japan. Esophagectomy data were acquired from published literature[18] with the exception of lymph node count, which was obtained from the NCC Hospital.

We also compared rates of postoperative mortality and morbidity with those of patients from the UK National Oesophago-Gastric Cancer Audit (NOGCA) for England and Wales.[19] In this national audit, the outcomes of 1987 curative surgical procedures were reported from 38 cancer networks for patients diagnosed from October 1, 2007, through September 30, 2008. We compared long-term survival with regional data from 3870 patients in southeast England who underwent gastroesophageal cancer resection from January 1, 1998, through December 31, 2008.[20] This group is representative for comparison because it includes the London population with similar patient characteristics. Cases reported herein form part of the NOGCA and southeast England cohorts.

METHODS TO ASSESS BIAS

We examined reporting, operative, and selection biases that may influence a single-surgeon series. To exclude reporting bias, all resections since the first day of the surgeon's appointment as consultant were reviewed. Inclusion of all patients was verified by cross-referencing against operating theater records, hospital database, and records of multidisciplinary meetings for upper gastrointestinal tract cancer. The postoperative outcomes were audited against the department database by an independent consultant surgeon. Data were externally audited by one of us (M.S.) who visited St Mary's Hospital to review the case series. Survival data were independently verified through the Thames Cancer Registry, King's College London. Selection bias has 2 aspects. Bias due to selecting fit patients was examined by comparing the predicted mortality risk of the study

Table 1. Patient Characteristics

Characteristic	Patient Group[a] Gastrectomy (n = 100)	Esophagectomy (n = 109)
Age, mean (SD), y	63.7 (12.6)	62.2 (11.0)
Sex		
Female	33 (33.0)	23 (21.1)
Male	67 (67.0)	86 (78.9)
BMI, mean (SD)	25.5 (4.9)	26.2 (4.5)
Tumor type		
Adenocarcinoma	99 (99.0)	93 (85.3)
Squamous cell carcinoma	1 (1.0)	16 (14.7)
Tumor site		
Upper third	24 (24.0)	1 (0.9)
Middle third	18 (18.0)	7 (6.4)
Lower third	50 (50.0)	101 (92.7)
Linitus plastica	8 (8.0)	0
Pretreatment cancer stage		
I	27 (27.0)	21 (19.3)
II	19 (19.0)	27 (24.8)
III	36 (36.0)	58 (53.2)
IV	18 (18.0)	3 (2.8)
Pretreatment tumor stage		
T1 and T2	35 (35.0)	32 (29.4)
T3 and T4	65 (65.0)	77 (70.6)
Pretreatment nodal status		
Negative	42 (42.0)	43 (39.4)
Positive	58 (58.0)	66 (60.6)
Pathological cancer stage		
I	42 (42.0)	30 (27.5)
II	16 (16.0)	35 (32.1)
III	22 (22.0)	37 (33.9)
IV	20 (20.0)	7 (6.4)
Pathological tumor stage		
pT1	23 (23.0)	36 (33.0)
pT2	35 (35.0)	21 (19.3)
pT3	33 (33.0)	45 (41.3)
pT4	9 (9.0)	7 (6.4)
Pathological nodal status		
Negative	49 (49.0)	46 (42.2)
Positive	51 (51.0)	63 (57.8)
Lymph nodes retrieved, mean (SD) [range]	50.4 (20.4) [5-108]	60.3 (22.3) [5-138]
Positive lymph nodes retrieved, mean (SD) [range]	5.1 (9.2) [0-46]	4.7 (7.9) [0-44]

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and might not total 100.

population, calculated by a dedicated prediction model for risk-adjusted postoperative mortality in upper gastrointestinal tract cancer surgery (O-POSSUM model),[21] against the observed mortality. Bias due to selecting early cancer was assessed by examining the cancer stage case mix compared with NOGCA data.[19] Operative bias is defined as performing less than the standard extended lymphadenectomy because of patient factors such as comorbidity, obesity, and old age. Analysis of operative bias was performed by correlating lymph node count with O-POSSUM scores, body mass index (BMI), and age.

STATISTICAL ANALYSIS

The date of censoring for overall survival was October 1, 2010. Analysis was performed using commercially available software (SPSS [SPSS Inc] and R, version 2.11.1 for Mac OS X Cocoa application GUI [R Foundation for Statistical Computing]). A 2-sided $P \leq .05$ was considered statistically significant. Survival curves were estimated using the Kaplan-Meier method. We tested differences between the reported clinical outcomes and the NCC and NOGCA data using an unpaired t test for normally distributed continuous variables (ie, age and BMI), Wilcoxon signed rank test for hospital stay, χ^2 test for counted data, and Fisher exact test for counted data with small numbers (<5). Correlation between lymph node count and O-POSSUM scores, BMI, and age was examined by means of Pearson correlation coefficient (R^2).

RESULTS

PATIENTS AND MANAGEMENT

This study includes only patients who underwent potentially curative D2 gastrectomy (n=100) or esophagectomy (n=109) for cancer (eAppendix 2). Procedures for gastrectomy were subtotal (n=50), total (n=28), completion (n=2), and extended total with lower esophagectomy via left thoracolaparotomy (n=20). Procedures for esophagectomy were 2-field (n=107) and 3-field (n=2) lymphadenectomy with gastric tube reconstruction and anastomosis in the neck (n=34) or the chest (n=75).

Patients' demographic and tumor characteristics are shown in **Table 1**. Full details of patient comorbidity are provided in eTable 1 and eTable 2. The proportions of patients with American Society of Anesthesiologists grades 2:3:4 in the gastrectomy and esophagectomy groups were 77.0%:22.0%:1.0% and 68.8%:31.2%:0%, respectively. Mean (SD) predictive mortality scores using the O-POSSUM model for gastrectomy and esophagectomy were 9.7% (7.7%) and 10.3% (6.9%), respectively.

Perioperative chemotherapy[5,7] was administered in 40.0% of gastrectomy and 68.8% of patients undergoing esophagectomy (eTable 3). Adjuvant chemotherapy as the only oncological modality was given in 6 patients receiving gastrectomy and 3 receiving esophagectomy who underwent urgent resection for symptoms of obstruction or bleeding. Adjuvant chemoradiotherapy was administered in 2 patients with positive resection margins who underwent gastrectomy and 1 patient with extensive lymph node metastasis that was understaged preoperatively who underwent 2-field esophagectomy.

CLINICAL OUTCOMES

One death occurred after esophagectomy on postoperative day 26 owing to myocardial infarction and acute respiratory distress syndrome. Details of postoperative complications are outlined in **Table 2**. The reasons for unplanned reoperation are provided in the online supplementary material (eAppendix 3). The overall failure-to-rescue rate for the study was 0.68%. Kaplan-Meier overall survival curves for gastrectomy and esophagectomy are shown in the **Figure**. Median follow-up was 41.5 months for gastrectomy and 26.1 months for esophagectomy. The mean number of resected lymph nodes was 50.4 for gastrectomy and 60.3 for esophagectomy. No patients undergoing esophagectomy had involved proximal or distal resection margins with cancer, whereas 2

Table 2. Postoperative Complications

Complication	Patient Group[a]	
	Gastrectomy (n = 100)	Esophagectomy (n = 109)
Mortality	0	1 (0.9)
Surgical complications		
Anastomotic leak	2 (2.0)	2 (1.8)
Hemorrhage	2 (2.0)	0
Abdominal abscess	5 (5.0)	0
Bowel obstruction	5 (5.0)	1 (0.9)
RLN palsy (temporary)	0	5 (4.6)
Chyle leak	0	2 (1.8)
Wound infection	11 (5.0)	9 (8.3)
Pulmonary complications		
Pleural effusion	6 (6.0)	17 (15.6)
Pneumothorax	1 (1.0)	6 (5.5)
Pneumonia	22 (22.0)	35 (32.1)
ALI/ARDS	2 (2.0)	10 (9.2)
Pulmonary embolism	2 (2.0)	1 (0.9)
Cardiac complications		
Arrhythmia	6 (6.0)	25 (22.9)[b]
MI/ACS	3 (3.0)	5 (4.6)
Renal failure[c]	3 (3.0)[b]	1 (0.9)
Unplanned return to operating theater	8 (8.0)	6 (5.5)
Postoperative hospital stay, median (range), d	12 (6-97)	13 (8-124)

Abbreviations: ALI/ARDS, acute lung injury/acute respiratory distress syndrome; MI/ACS, myocardial infarction/acute coronary syndrome; RLN, recurrent laryngeal nerve.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

[b] Six patients with a documented history of atrial fibrillation before surgery are excluded.

[c] Two cases were acute-on-chronic renal failure.

undergoing gastrectomy had positive margins (1 proximal and 1 duodenal).

BIAS ASSESSMENT

There was no correlation between lymph node harvest and age, BMI, or predicted mortality ($R^2 \leq 0.025$, excluding operative bias) (eTable 4). Most of the patients were middle-aged men, similar to the NOGCA population. The predicted mortality of the study population was slightly higher than the observed mortality in the NOGCA cohort (7.1% for gastrectomy, 7.1% for open esophagectomy, and 5.2% for minimally invasive esophagectomy), excluding the bias of selecting low-risk patients. Compared with the NOGCA data, the present study includes more advanced gastric cancer and comparable esophageal cancer (eTable 5), eliminating the bias of selecting early cancer cases.

COMPARATIVE ASSESSMENT

Mortality and technical complications were significantly lower than in the NOGCA but comparable to the outcomes from the NCC. Pulmonary and cardiac complications, however, were higher than in both comparative groups (**Table 3** and **Table 4**). Year-by-year survival for the present study was significantly better than

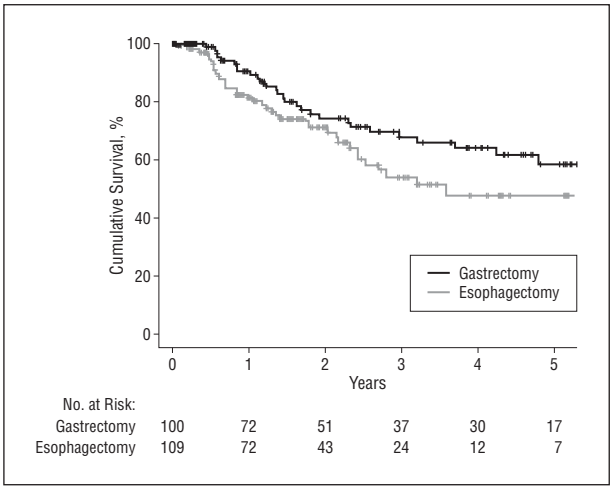

Figure. Kaplan-Meier curves depict overall survival in the present study.

for patients in southeast England (**Table 5**). In this study, stage-for-stage long-term survival in patients with esophageal and gastric cancer was similar to the outcomes in the NCC cohort (**Table 6** and **Table 7**). Using pathological staging, 5-year overall survival after gastrectomy was better in advanced cancer but worse in early cancer compared with the NCC cohort. The pathological staging of the present study was performed after chemotherapy and as such may reflect the downstaging by chemotherapy, whereas patients from the NCC rarely received neoadjuvant chemotherapy.

In the present study, 90.0% of patients who underwent gastrectomy had a lymph node yield of more than 25 compared with 39% of patients in the NOGCA cohort ($P<.001$), whereas 98.2% of patients undergoing esophagectomy had a lymph node harvest of more than 15 vs 68% to 78% of patients in the NOGCA cohort ($P<.001$). The mean lymph node count for gastrectomy in the NCC cohort was 57.4,[22] which is higher than the lymph node count reported for the entire series ($P<.001$) but significantly lower than the lymph node count during the last 3 years of the present study (mean number of lymph nodes, 64.6; $P=.006$). This discrepancy in lymph node harvest between the initial and late stages of the present study is a result of the initial practice of pathologists to retrieve only 15 lymph nodes in accordance with national recommendations for cancer staging.[23] The mean lymph node counts for 3- and 2-field lymphadenectomy in the NCC cohort were 70.2 and 48.5, respectively. This lymph node count in 2-field lymphadenectomy is significantly lower than that of the present study ($P<.001$). The involvement of the longitudinal resection margin was significantly lower in the study population compared with the NOGCA cohort.

COMMENT

The results of this study confirmed that extended lymphadenectomy in gastroesophageal cancer resection is safe for Western patients and can be improved to achieve the highest standard in Japan. These findings cannot be ex-

Table 3. Key Comparisons in Early Outcomes for Gastric Cancer Resections With NOGCA and NCC Data

	Present Study[a]	NOGCA	*P* Value[b]	NCC	*P* Value[b]
Age	63.7 (61.1-66.1)	67	.009	60.5	.14
BMI, median (95% CI)	25.5 (24.5-26.5)	NR		22.6	<.001
Pathological TNM staging, %					
I	42.0	45	<.001	58	.006
II	16.0	22		12	
III	22.0	25		13	
IV	20.0	8		17	
No. of positive lymph nodes, median	5.1 (3.3-7.1)	NR		NR	
Residual tumor, R1, %	2 (0-4.7)	7.8	.03	5.2	.15
Mortality, %	0 (0-1.8)	7.1	.006	0.15	>.99
Key complications					
Anastomotic leakage, %	2 (0-4.7)	6.3	.08	1.4	>.99
Abdominal abscess, %	5 (0-9.2)	NR		8.4	.22
Cardiac, %	9 (3.4-14.6)	5.2	.09	0	.003
Pneumonia, %	22 (13.9-30)	10	<.001	1.7	<.001
Hospital stay, d	12 (8.9-15.0)	12	.91	12	.91

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NCC, National Cancer Center of Tokyo, Japan; NOGCA, National Esophago-Gastric Cancer Audit[19]; NR, not reported; R1, residual microscopic disease.

[a] Unless otherwise indicated, data are reported as mean (95% CI).

[b] Generated by 1-sample *t* test for age and BMI, by Wilcoxon signed rank test for hospital stay, by χ^2 test for all counted data except for those less than 5 or less than 5%, in which case Fisher exact test was applied.

Table 4. Key Comparisons in Early Outcomes for Esophageal Cancer Resections With NOGCA and NCC Data

	Present Study[a]	NOGCA	*P* Value[b]	NCC	*P* Value[b]
Age	62.2 (60.1-64.3)	63	.47	62	.83
Tumor type			.76		<.001
Adenocarcinoma	85	86		7	
Squamous cell carcinoma	15	14		93	
Pathological TNM staging, %[c]					
0/I	27.5	21	.21	24/13	.19/<.001
II	31.2	37		29/35	
III	34.9	38		35/31	
IV	6.4	4		13/21	
Residual tumor, R1, %	0 (0-1.8)	6.8	.005	5.1	.02
Mortality, %[d]	1 (0-2.9)	7.1/ 5.2	.01/.048	2.6	.29
Key complications					
Anastomotic leakage, %[d]	2 (0-4.6)	7.8/10.6	.02/.004	35	<.001
Chyle leak[d]	2 (0-4.6)	3.7/1.9	.68/>.99	3	>.99
Temporary RLN palsy, %	5 (0.9-9)	NR		12	.02
Cardiac, %[d,e]	5 (0.9-9)	6.8/4.3	.45/>.99	1	.21
Pneumonia, %[d]	35 (26-44)	19.7/10.2	<.001	14	<.001
Hospital stay, days	13 (10.4-15.6)	14	.54	NR	
5-y Overall survival, %	47.8	NR		49.3	.75

Abbreviations: NCC, National Cancer Center of Tokyo, Japan; NOGCA, National Esophago-Gastric Cancer Audit[19]; NR, not reported; RLN, recurrent laryngeal nerve.

[a] Unless otherwise indicated, data are reported as mean (95% CI).

[b] *P* values are generated by 1-sample *t* test for age and body mass index, by Wilcoxon signed rank test for hospital stay, by χ^2 test for all counted data except for those less than 5 or less than 5%, in which case Fisher exact test was applied.

[c] The NCC data are expressed as 2-field/3-field lymphadenectomy.

[d] The NOGCA data are expressed as open/minimally invasive esophagectomy.

[e] Excludes arrhythmia.

plained by reporting, selection, or operative bias. The outcomes of the present study can be attributed to several factors. Appropriate training in techniques of extended lymphadenectomy is essential. The surgeon's training included a fellowship in the NCC. The clearance of appropriate lymph node stations was not compromised by case difficulty, as demonstrated by the lack of correlation with BMI. Even in the Japanese randomized controlled trial JCOG9501,[1] increased body weight was associated with significantly lower lymph node retrieval.[24] Also, accurate staging and optimization by a multidisciplinary team are essential. Extended lymphadenectomy without mortality was achieved in patients with a predicted mortality ranging from 11% to 20% and 21% or more who represented 29% and 8% of the study population, respectively. Finally, appropriate management of postoperative complications, as reflected by a low failure-to-rescue rate, is crucial to minimize mortality. All these contributing fac-

Table 5. Overall Survival of Study Population Compared With Southeast England Cohort[a]

	Patient Group, %			
	Gastrectomy		Esophagectomy	
Survival	Present Study Population	Southeast England Cohort	Present Study Population	Southeast England Cohort
30 d	100.0	90	99.1	94
1 y	90.6	64	81.4	67
2 y	74.3	48	71.2	46
3 y	67.8	38	53.9	37
4 y	64.0	32	47.8	32
5 y	58.4	27	47.8	28

[a] $P < .001$ for gastrectomy and $P = .001$ for esophagectomy, comparing Kaplan-Meier curves using the log-rank test.

Table 6. Five-Year Overall Stage-by-Stage Survival for Gastric Cancer Resections Compared With NCC Data

	Survival, %			*P* Value vs NCC Data[a]	
	ICL		NCC		
Stage	Prechemotherapy	Pathological	Pathological	Prechemotherapy	Pathological
I	77	77			
IA	NR	NR	94	<.001	<.001
IB	NR	NR	91	<.001	<.001
II	75	86	78	.47	.05
III	45	33			
IIIA	NR	NR	60	.002	<.001
IIIB	NR	NR	45	>.99	.01
IV	44	32	14	<.001	<.001

Abbreviations: ICL, Imperial College London; NCC, National Cancer Center of Tokyo, Japan; NR, not reported.
[a] Computed using the χ^2 test.

Table 7. Five-Year Overall Stage-by-Stage Survival for Esophageal Cancer Resections Compared With NCC Data

	Survival, %				*P* Values vs NCC Data[a]	
	ICL		NCC Pathological Stage			
TNM Stage	2-Field Lymphadenectomy	3-Field Lymphadenectomy	Prechemotherapy	Pathological	Trechemotherapy	Pathological
Tumor status						
T1 or T2	80.6	76.8	62.6	70.8	<.001/.02	.003/.19[b]
T3 or T4	35.4	24.1	30	38.1	.22/.56	>.1/.004[b]
Node status						
N0	81.3	90.3	73.6	75.1	.08/>.1[b]	<.001
N1	27.9	16.6	28.6	40.4	>.1/.01[b]	.006/<.001
Metastasis status						
M0	49.4	53.4	49.5	57.9	>.1/.07[b]	>.1
M1	0	0	14.3	27.8	<.001	<.001

Abbreviations: ICL, Imperial College London; NCC, National Cancer Center of Tokyo, Japan.
[a] Computed using the χ^2 test.
[b] Computed as the difference compared with 2-field/3-field lymphadenectomy.

tors are reproducible in high-volume Western cancer centers. The higher rates of postoperative pneumonia observed in the present study compared with the NCC cohort most likely reflect patient comorbidity and smoking habits, extended length of surgery and mechanical ventilation, and a low diagnostic threshold for this complication.

An important consideration for the surgical and oncological communities is why we took the evidence from a single-surgeon series against that of randomized controlled trials. In esophageal cancer, a meta-analysis of 52 comparative studies constituting 3389 transthoracic and 2516 transhiatal procedures showed no difference in 5-year survival. No study within the meta-analysis met

all minimum surgical quality standards. Lymphadenectomy and reported surgical quality were suboptimal in both groups, and the transthoracic group had significantly more advanced cancer. The study concluded that the finding of equivalent survival should therefore be viewed with caution.[25] Meta-analysis of 6 randomized controlled trials totaling 1876 patients concluded that D2 gastrectomy is associated with higher 30-day mortality and more postoperative complications and with a 5-year survival similar to that of the D1 cohort.[26] Recognized limitations of those trials now challenge this conclusion. Clinical practice during those randomized clinical trials performed 20 years ago in low-volume centers with inadequate surgical experience is different from modern practice. The annual average numbers of cases per hospital were 1.0 and 1.5 resections in the Dutch and Medical Research Council trials, respectively. About 82% and 75% of patients in the Dutch[27] and Medical Research Council trials, respectively, had a less-extensive lymphadenectomy than specified. Also, the high 30-day mortality offsets the effects of D2 dissection in the long term. Another factor is the outcome of managing postoperative complications. For instance, the mortality rates were 41.3% and 20.9%, respectively, for patients who developed anastomotic leakage and pancreatic fistula in the Dutch trial. Nevertheless, the 2 most recent trials from Italy and Taiwan demonstrated better 5-year survival with D2 gastrectomy.[28,29] Furthermore, the proven poor long-term survival of limited lymphadenectomy and the established safety of extended lymphadenectomy in specialized centers in modern practice[30-32] obviate the need for another randomized trial. The present study reproduced the Japanese standard in all aspects, including lymph node harvest, postoperative technical complications, and stage-for-stage long-term survival in gastric and esophageal cancer. Finally, D2 dissection was adopted in Japan after the pioneering work in the Cancer Institute Hospital in Tokyo[33] without the need for randomized trials.

In the present study, the practice of lymph node retrieval by pathologists changed over time. Initially, the search for lymph nodes was abandoned after retrieving 15 to 20 nodes in accordance with guidelines for the recommended minimum number of lymph nodes required for cancer staging. After a multidisciplinary team decision to aim to reproduce Japanese standards of lymph node retrieval, meticulous search by the digital feeling of lymph nodes was performed by the consultant pathologist (R.G.). An increase in surgical workload coupled with the time constraints on the pathologists led to the blocking of all perigastric fat, which produced higher lymph node counts than the feeling method and eliminated the effect of pathologist identity on lymph node yield. Factors that encouraged such change are pathologist specialization, cross-charging of costs to the surgical department, and the collaborative nature of multidisciplinary meetings concerning upper gastrointestinal tract cancer.

Limitations of this study include the following: (1) outcomes are from a single surgeon; (2) data include the proficiency gain curve for the surgeon and pathologists; (3) follow-up is incomplete (<5 years) for some patients; (4) small sample sizes are available for stage-by-stage survival analysis; (5) Western populations differ from Japanese; and (6) quality-of-life data are absent. Patients in the present study differ from the NCC because of the use of neoadjuvant chemotherapy, the nature of patient referral, and the proportion of squamous cell cancer. The use of neoadjuvant chemotherapy may account for improved survival in patients with stage IV cancer in the present study compared with the Japanese patients. Furthermore, the patients with pathological stage I cancer in the present study included patients whose disease had been downstaged by neoadjuvant chemotherapy. Survival of these patients may follow prechemotherapy clinical staging and may contribute to the better overall survival in Japanese patients with stage I disease. Finally, patients with significant comorbidity do not undergo their surgery in dedicated cancer centers in Japan; as such, this represents a bias against the present study.

In conclusion, extended lymphadenectomy leads to improved long-term survival without compromising postoperative outcomes. Those postoperative outcomes can be comparable to the standard reported by an expert Japanese center.

Accepted for Publication: February 28, 2012.
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Author Contributions: All authors approved the final manuscript. *Study concept and design:* Hanna, Goldin, and Sasako. *Acquisition of data:* Hanna, Boshier, Knaggs, Goldin, and Sasako. *Analysis and interpretation of data:* Hanna, Boshier, and Sasako. *Drafting of the manuscript:* Hanna. *Critical revision of the manuscript for important intellectual content*: Hanna, Boshier, Knaggs, Goldin, and Sasako. *Statistical analysis:* Hanna and Boshier. *Administrative, technical, and material support:* Hanna and Goldin. *Study supervision:* Hanna, Knaggs, Goldin, and Sasako.
Financial Disclosure: None reported.
Previous Presentation: This paper was presented at the 15th annual meeting of the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland; September 15, 2011; Belfast, Northern Ireland.
Online-Only Material: The eAppendixes and eTables are available at http://www.archsurg.com.
Additional Contributions: Hitoshi Katai, MD, and Yuji Tachimori, MD (Department of Surgical Oncology, NCC Hospital), provided gastric cancer data and lymph node counts, respectively. Henrik Møller, FFPH (Thames Cancer Registry), verified survival times and provided advice on analysis. Paul Ziprin, FRCS (Department of Surgery and Cancer, St Mary's Hospital, Imperial College London), provided internal auditing. Melody Ni, PhD, performed statistical analysis. Iakovos Amygdalos, MBBS (Department of Surgery and Cancer, Imperial College London), reviewed the pathology reports. Alfred Cuschieri, FRCS (Institute for Medical Science and Technology, University of Dundee), and Jane Blazeby, FRCS (Academic Unit of Surgical Research, Bristol University), provided feedback on the manuscript. Mark Harrison, FRCP (Department of Oncology, Mount Vernon Hospital), and

Danielle Power, MBBS (Department of Oncology, St Mary's Hospital), made oncological contributions. We thank members of the Northwest London Multidisciplinary Team and the physicians and staff of the intensive care unit for patients' care.

REFERENCES

1. Sasako M, Sano T, Yamamoto S, et al; Japan Clinical Oncology Group. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med*. 2008;359(5):453-462.
2. Jamieson GG, Mathew G, Ludemann R, Wayman J, Myers JC, Devitt PG. Postoperative mortality following oesophagectomy and problems in reporting its rate. *Br J Surg*. 2004;91(8):943-947.
3. Bollschweiler E, Boettcher K, Hoelscher AH, et al. Is the prognosis for Japanese and German patients with gastric cancer really different? *Cancer*. 1993;71(10):2918-2925.
4. Noguchi Y, Yoshikawa T, Tsuburaya A, Motohashi H, Karpeh MS, Brennan MF. Is gastric carcinoma different between Japan and the United States? *Cancer*. 2000;89(11):2237-2246.
5. Cunningham D, Allum WH, Stenning SP, et al; MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med*. 2006;355(1):11-20.
6. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med*. 2001;345(10):725-730.
7. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet*. 2002;359(9319):1727-1733.
8. Bonenkamp JJ, Hermans J, Sasako M, et al; Dutch Gastric Cancer Group. Extended lymph-node dissection for gastric cancer. *N Engl J Med*. 1999;340(12):908-914.
9. Cuschieri A, Fayers P, Fielding J, et al; The Surgical Cooperative Group. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. *Lancet*. 1996;347(9007):995-999.
10. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol*. 2010;11(5):439-449.
11. Strong VE, Song KY, Park CH, et al. Comparison of gastric cancer survival following R0 resection in the United States and Korea using an internationally validated nomogram. *Ann Surg*. 2010;251(4):640-646.
12. Griffin SM. Gastric cancer in the East: same disease, different patient. *Br J Surg*. 2005;92(9):1055-1056.
13. Allum WH, Griffin SM, Watson A, Colin-Jones D; Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland; British Society of Gastroenterology; British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer. *Gut*. 2002;50(suppl 5):v1-v23.
14. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 2nd English edition. *Gastric Cancer*. 1998;1(1):10-24.
15. Sasako M, Sano T, Yamamoto S, et al; Japan Clinical Oncology Group (JCOG9502). Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. *Lancet Oncol*. 2006;7(8):644-651.
16. Ghaferi AA, Birkmeyer JD, Dimick JB. Complications, failure to rescue, and mortality with major inpatient surgery in Medicare patients. *Ann Surg*. 2009;250(6):1029-1034.
17. American Joint Committee on Cancer. *Cancer Staging Manual*. Greene FL, Page DL, Fleming ID, et al; eds 6th ed. New York, NY: Springer; 2002.
18. Igaki H, Tachimori Y, Kato H. Improved survival for patients with upper and/or middle mediastinal lymph node metastasis of squamous cell carcinoma of the lower thoracic esophagus treated with 3-field dissection. *Ann Surg*. 2004;239(4):483-490.
19. Palser T, Cromwell D, van der Meulen J. *National Oesophago-Gastric Cancer Audit*. London: Clinical Effectiveness Unit, The Royal College of Surgeons of England; 2009.
20. Anderson O, Ni Z, Møller H, et al. Hospital volume and survival in oesophagectomy and gastrectomy for cancer. *Eur J Cancer*. 2011;47(16):2408-2414.
21. Tekkis PP, McCulloch P, Poloniecki JD, Prytherch DR, Kessaris N, Steger AC. Risk-adjusted prediction of operative mortality in oesophagogastric surgery with O-POSSUM. *Br J Surg*. 2004;91(3):288-295.
22. Noda N, Sasako M, Yamaguchi N, Nakanishi Y. Ignoring small lymph nodes can be a major cause of staging error in gastric cancer. *Br J Surg*. 1998;85(6):831-834.
23. Novelli MR. Dataset for the histopathological reporting of gastric carcinoma. *Standards and Datasets for Reporting Cancers*. 2nd ed. London, England: Royal College of Pathologists; 2007:12.
24. Tsujinaka T, Sasako M, Yamamoto S, et al; Gastric Cancer Surgery Study Group of Japan Clinical Oncology Group. Influence of overweight on surgical complications for gastric cancer: results from a randomized control trial comparing D2 and extended para-aortic D3 lymphadenectomy (JCOG9501). *Ann Surg Oncol*. 2007;14(2):355-361.
25. Boshier PR, Anderson O, Hanna GB. Transthoracic versus transhiatal esophagectomy for the treatment of esophagogastric cancer: a meta-analysis. *Ann Surg*. 2011;254(6):894-906.
26. Memon MA, Subramanya MS, Khan S, Hossain MB, Osland E, Memon B. Meta-analysis of D1 versus D2 gastrectomy for gastric adenocarcinoma. *Ann Surg*. 2011;253(5):900-911.
27. Bunt AM, Hermans J, Boon MC, et al. Evaluation of the extent of lymphadenectomy in a randomized trial of Western- versus Japanese-type surgery in gastric cancer. *J Clin Oncol*. 1994;12(2):417-422.
28. Wu CW, Hsiung CA, Lo SS, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. *Lancet Oncol*. 2006;7(4):309-315.
29. Degiuli M, Sasako M, Calgaro M, et al; Italian Gastric Cancer Study Group. Morbidity and mortality after D1 and D2 gastrectomy for cancer: interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial. *Eur J Surg Oncol*. 2004;30(3):303-308.
30. Sue-Ling HM, Johnston D, Martin IG, et al. Gastric cancer: a curable disease in Britain. *BMJ*. 1993;307(6904):591-596.
31. Lerut T, Nafteux P, Moons J, et al. Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. *Ann Surg*. 2004;240(6):962-974.
32. Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari L; Italian Gastrointestinal Tumor Study Group. Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. *Ann Surg*. 1999;230(2):170-178.
33. Nakajima T, Nishi M, Kajitani T. Improvement in treatment results of gastric cancer with surgery and chemotherapy: experience of 9,700 cases in the Cancer Institute Hospital, Tokyo. *Semin Surg Oncol*. 1991;7(6):365-372.