Improving Outcomes After Gastroesophageal Cancer Resection

Can Japanese Results Be Reproduced in Western Centers?

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Hypothesis: Extended lymphadenectomy in gastroesophageal 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.

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lines in the United Kingdom have also recommended extended lymphadenectomy for gastroesophageal cancer resections. 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.

### 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/m², and cisplatin, 60 mg/m², given intravenously on day 1, followed by oral capecitabine, 625 mg/m² twice daily.

The surgical policy for gastric cancer is D2 gastrectomy in strict accordance with Japanese guidelines. 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.

### 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.

### 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 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. 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. 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
population, calculated by a dedicated prediction model for risk-adjusted postoperative mortality in upper gastrointestinal tract cancer surgery (O-POSSUM model),12 against the observed mortality. Bias due to selecting early cancer was assessed by examining the cancer stage case mix compared with NOGCA data.19

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 ≤ .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, χ² test for counted data, and Fisher exact test for counted data with small numbers (<3). Correlation between lymph node count and O-POSSUM scores, BMI, and age was examined by means of Pearson correlation coefficient (R²).

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 chemotherapy5,7 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 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Gastrectomy Group (n = 100)</th>
<th>Esophagectomy Group (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>63.7 (12.6)</td>
<td>62.2 (11.0)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>25.5 (4.9)</td>
<td>26.2 (4.5)</td>
</tr>
<tr>
<td>Tumor type</td>
<td>Adenocarcinoma</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Pretreatment cancer stage</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Pretreatment tumor stage</td>
<td>T1 and T2</td>
<td>T3 and T4</td>
</tr>
<tr>
<td>Pretreatment nodal status</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Pathological cancer stage</td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Pathological tumor stage</td>
<td>pT1</td>
<td>pT2</td>
</tr>
<tr>
<td>Pathological nodal status</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Lymph nodes retrieved, mean (SD) [range]</td>
<td>50.4 (20.4) [5-108]</td>
<td>4.7 (7.9) [0-44]</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared). Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and might not total 100.

The date of censoring for overall survival was October 1, 2010. Analysis was performed using commercially available software (eAppendix 4).
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 (R² = 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 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 37.4,22 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.

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-
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, increased body weight was associated with significantly lower lymph node retrieval. 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 3. Key Comparisons in Early Outcomes for Gastric Cancer Resections With NOGCA and NCC Data

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

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; 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 χ² test for all counted data except for those less than 5 or less than 5%, in which case Fisher exact test was applied.

d The NCC data are expressed as open/minimally invasive esophagectomy.
e Excludes arrhythmia.

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

<table>
<thead>
<tr>
<th></th>
<th>Present Study*</th>
<th>NOGCA</th>
<th>P Valueb</th>
<th>NCC</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62.2 (60.1-64.3)</td>
<td>63</td>
<td>.47</td>
<td>62</td>
<td>.83</td>
</tr>
<tr>
<td>Tumor type</td>
<td></td>
<td></td>
<td>&lt;.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>85</td>
<td>86</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>15</td>
<td>14</td>
<td>93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathological TNM staging, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>27.5</td>
<td>21</td>
<td>24/13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>31.2</td>
<td>37</td>
<td>29/35</td>
<td></td>
<td></td>
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<tr>
<td>III</td>
<td>34.9</td>
<td>38</td>
<td>.21</td>
<td>35/31</td>
<td>.19/-.001</td>
</tr>
<tr>
<td>IV</td>
<td>6.4</td>
<td>4</td>
<td>13/21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual tumor, R1, %</td>
<td>0 (0-1.8)</td>
<td>6.8</td>
<td>.005</td>
<td>5.1</td>
<td>.02</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>1 (0-2.9)</td>
<td>7.1/5.2</td>
<td>.01/0.048</td>
<td>2.6</td>
<td>.29</td>
</tr>
<tr>
<td>Key complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastomotic leakage, %</td>
<td>2 (0-4.6)</td>
<td>7.8/10.6</td>
<td>.02/-.004</td>
<td>35</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chyle leak</td>
<td>2 (0-4.6)</td>
<td>3.7/1.9</td>
<td>.69/-.99</td>
<td>3</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Temporary RLN palsy, %</td>
<td>5 (0-9.9)</td>
<td>NR</td>
<td>12</td>
<td></td>
<td>.02</td>
</tr>
<tr>
<td>Cardiac, %</td>
<td>5 (0-9.9)</td>
<td>6.8/4.3</td>
<td>.45/-.99</td>
<td>1</td>
<td>.21</td>
</tr>
<tr>
<td>Pneumonia, %</td>
<td>35 (26-44)</td>
<td>19.7/10.2</td>
<td>&lt;.001</td>
<td>14</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hospital stay, d</td>
<td>13 (10.4-15.6)</td>
<td>14</td>
<td>.54</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>5-y Overall survival, %</td>
<td>47.8</td>
<td>NR</td>
<td>49.3</td>
<td></td>
<td>.75</td>
</tr>
</tbody>
</table>

Abbreviations: NCC, National Cancer Center of Tokyo, Japan; NOGCA, National Esophago-Gastric Cancer Audit; 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 χ² 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.
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

<p>| Table 5. Overall Survival of Study Population Compared With Southeast England Cohort |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>Survival</th>
<th>Present Study Population</th>
<th>Southeast England Cohort</th>
<th>Present Study Population</th>
<th>Southeast England Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 d</td>
<td>100.0%</td>
<td>90%</td>
<td>99.1%</td>
<td>94%</td>
</tr>
<tr>
<td>1 y</td>
<td>90.6%</td>
<td>64%</td>
<td>81.4%</td>
<td>67%</td>
</tr>
<tr>
<td>2 y</td>
<td>74.3%</td>
<td>48%</td>
<td>71.2%</td>
<td>46%</td>
</tr>
<tr>
<td>3 y</td>
<td>67.8%</td>
<td>38%</td>
<td>53.9%</td>
<td>37%</td>
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<tr>
<td>4 y</td>
<td>64.0%</td>
<td>32%</td>
<td>47.8%</td>
<td>32%</td>
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<tr>
<td>5 y</td>
<td>58.4%</td>
<td>27%</td>
<td>47.8%</td>
<td>28%</td>
</tr>
</tbody>
</table>

\(P < .001\) for gastrectomy and \(P < .001\) for esophagectomy, comparing Kaplan-Meier curves using the log-rank test.

<p>| Table 6. Five-Year Overall Stage-by-Stage Survival for Gastric Cancer Resections Compared With NCC Data |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>Stage</th>
<th>ICL Prechemotherapy</th>
<th>ICL Pathological</th>
<th>NCC Prechemotherapy</th>
<th>NCC Pathological</th>
<th>(P) Value vs NCC Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>77</td>
<td>77</td>
<td>NR</td>
<td>94</td>
<td>(&lt;.001)</td>
</tr>
<tr>
<td>IA</td>
<td>NR</td>
<td>NR</td>
<td>91</td>
<td>(&lt;.001)</td>
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<tr>
<td>IB</td>
<td>NR</td>
<td>NR</td>
<td>91</td>
<td>(&lt;.001)</td>
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<tr>
<td>II</td>
<td>75</td>
<td>86</td>
<td>78</td>
<td>(.47)</td>
<td></td>
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<tr>
<td>III</td>
<td>45</td>
<td>33</td>
<td>60</td>
<td>(.002)</td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
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<td>(&lt;.001)</td>
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<tr>
<td>IV</td>
<td>44</td>
<td>32</td>
<td>14</td>
<td>(&lt;.001)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ICL, Imperial College London; NCC, National Cancer Center of Tokyo, Japan; NR, not reported.

\(a\) Computed using the \(\chi^2\) test.

<p>| Table 7. Five-Year Overall Stage-by-Stage Survival for Esophageal Cancer Resections Compared With NCC Data |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>TNM Stage</th>
<th>ICL 2-Field Lymphadenectomy</th>
<th>ICL 3-Field Lymphadenectomy</th>
<th>NCC Pathological Stage</th>
<th>Prechemotherapy</th>
<th>Pathological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 or T2</td>
<td>80.6%</td>
<td>76.8%</td>
<td>62.6%</td>
<td>70.8%</td>
<td>(&lt;.001/102)</td>
</tr>
<tr>
<td>T3 or T4</td>
<td>35.4%</td>
<td>24.1%</td>
<td>30%</td>
<td>38.1%</td>
<td>(.22/56)</td>
</tr>
<tr>
<td>Node status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>81.3%</td>
<td>90.3%</td>
<td>73.6%</td>
<td>75.1%</td>
<td>(.08/=.1)</td>
</tr>
<tr>
<td>N1</td>
<td>27.9%</td>
<td>16.6%</td>
<td>28.6%</td>
<td>40.4%</td>
<td>(&lt;.1/01)</td>
</tr>
<tr>
<td>Metastasis status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>49.4%</td>
<td>53.4%</td>
<td>49.5%</td>
<td>57.9%</td>
<td>(&lt;.1/07)</td>
</tr>
<tr>
<td>M1</td>
<td>0%</td>
<td>0%</td>
<td>14.3%</td>
<td>27.8%</td>
<td>(&lt;.001)</td>
</tr>
</tbody>
</table>

Abbreviations: ICL, Imperial College London; NCC, National Cancer Center of Tokyo, Japan.

\(a\) Computed using the \(\chi^2\) test.

\(b\) Computed as the difference compared with 2-field/3-field lymphadenectomy.
all minimum surgical quality standards. Lymphadenec-
tomy and reported surgical quality were suboptimal in
both groups, and the transthoracic group had signifi-
cantly more advanced cancer. The study concluded that
the finding of equivalent survival should therefore be
viewed with caution.29 Meta-analysis of 6 randomized con-
trolled trials totaling 1876 patients concluded that D2 gas-
trectomy is associated with higher 30-day mortality and
more postoperative complications and with a 5-year sur-

vival similar to that of the D1 cohort.30 Recognized limi-
tations of those trials now challenge this conclusion.
Clinical practice during those randomized clinical trials
performed 20 years ago in low-volume centers with in-
adquate surgical experience is different from modern
practice. The annual average numbers of cases per hos-
pital were 1.0 and 1.5 resections in the Dutch and Medi-
cal Research Council trials, respectively. About 82% and
75% of patients in the Dutch32 and Medical Research
Council trials, respectively, had a less-extensive lymph-
adenectomy than specified. Also, the high 30-day mor-
tality offsets the effects of D2 dissection in the long term.
Another factor is the outcome of managing postopera-
tive complications. For instance, the mortality rates were
41.3% and 20.9%, respectively, for patients who de-
veloped 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.30,31 Furthermore, the proven poor long-
term survival of limited lymphadenectomy and the es-

ed safety of extended lymphadenectomy in special-
cized centers in modern practice10-32 obviate the need
for another randomized trial. The present study repro-
duced the Japanese standard in all aspects, including
lymph node harvest, postoperative technical complica-
tions, 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 Insti-
tute Hospital in Tokyo15 without the need for random-
ized trials.

In the present study, the practice of lymph node re-
trieval 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 rec-
ommended minimum number of lymph nodes required
for cancer staging. After a multidisciplinary team deci-
sion to aim to reproduce Japanese standards of lymph
node retrieval, meticulous search by the digital feeling
of lymph nodes was performed by the consultant pa-
thologist (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 elimi-
nated the effect of pathologist identity on lymph node
yield. Factors that encouraged such change are patholo-
gist specialization, cross-charging of costs to the surgi-
cal department, and the collaborative nature of multi-
disciplinary meetings concerning upper gastrointestinal
tract cancer.

Limitations of this study include the following: (1) out-
comes are from a single surgeon; (2) data include the pro-

iciency 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 sur-

vival analysis; (5) Western populations differ from Japa-
nese; 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 re-

deral, and the proportion of squamous cell cancer. The
use of neoadjuvant chemotherapy may account for im-
proved survival in patients with stage IV cancer in the
present study compared with the Japanese patients. Fur-
thermore, the patients with pathological stage I cancer in
the present study included patients whose disease had
been downstaged by neoadjuvant chemotherapy. Sur-
vival of these patients may follow prechemotherapy clini-
cal staging and may contribute to the better overall sur-
vival 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 post-

operative outcomes. Those postoperative outcomes can
be comparable to the standard reported by an expert Japa-
nese center.

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din, and Sasako. Analysis and interpretation of data: Hanna,
Boshier, and Sasako. Drafting of the manuscript: Hanna.
Critical revision of the manuscript for important intellec-
Statistical analysis: Hanna and Boshier. Adminis-
trative, technical, and material support: Hanna and Goldin.
Study supervision: Hanna, Knaggs, Goldin, and Sasako.

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Online-Only Material: The eAppendices and eTables are

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REFERENCES


