Surgical and long-term outcomes of combined organ resection for esophageal cancer invading adjacent organs: Experience of 90 consecutive cases

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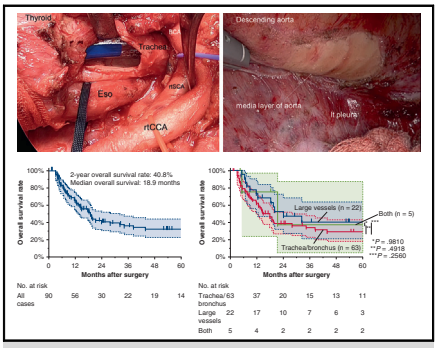
ABSTRACT

Objective: To evaluate the feasibility of and long-term survival with combined organ resection for esophageal cancer (EC). The optimal treatment strategy for EC that is invading adjacent organs is not established.

Methods: Ninety patients with EC invading adjacent organs who underwent combined organ resection after induction treatments during the time period 2003-2023 in our institute were eligible for the study. Short- and long-term outcomes were assessed, and survival analysis was performed to identify prognostic parameters in this cohort.

Results: Most patients had primary tumors (78.9% vs 21.1% with recurrent disease). The resected organs were the trachea/bronchus in 75.6%, large vessels in 24.4%, and both in 5.6%. All but 1 patient underwent chemotherapy or chemoradiotherapy as prior induction treatment, and had R0 resection. The overall complication rate (Clavien-Dindo grade II or greater) was 54.4%, and in-hospital mortality was 2.2% (30- and 90-day mortality: 0% and 2.2%, respectively). Of the deaths, 47 (87.0%) were attributed to EC and 7 (13.0%) to other causes. Median disease-free survival was 6.5 months, and overall survival (OS) was 18.9 months. The 2-year OS values were 47.2% with trachea/bronchus resection, 38.4% with large-vessel involvement, and 37.5% if both were involved. Univariate analysis of OS demonstrated significant associations of operation time (hazard ratio [HR], 2.11; $P = .0080$), blood loss (HR, 2.85; $P = .0003$), all-layer tracheal resection (HR, 3.51; $P = .0045$), ypT (HR, 2.04; $P = .022$), and pathologic response (HR, 2.77; $P = .0089$).

Conclusions: If patient selection is highly selected, combined organ resection may be a feasible and promising option as a part of the multidisciplinary treatment for EC invading an adjacent organ. (J Thorac Cardiovasc Surg 2025;170:957-68)



Outcomes of combined organ resection for esophageal cancer invading adjacent organs.

CENTRAL MESSAGE

With optimized patient selection, combined organ resection for esophageal cancer that is invading adjacent organs might be a feasible and promising option as a part of multidisciplinary treatment.

PERSPECTIVE

This study reported short- and long-term outcomes for the largest series of 90 patients with esophageal cancer undergoing combined resection of invaded organs, including the trachea/bronchus and large arteries. We also conducted a survival analysis to identify important prognostic parameters in this population for the optimization of indications for this extended surgery.

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Abbreviations and Acronyms

5-FU = 5-fluorouracil
AMT = anterior mediastinal tracheostomy
BCA = brachiocephalic artery
CCA = common carotid artery
CI = confidence interval
CRT = chemoradiation
CS = conversion surgery
CT = computed tomography
DCF = docetaxel, cisplatin, and 5-FU
DFS = disease-free survival
EC = esophageal cancer
HR = hazard ratio
MRI = magnetic resonance imaging
OS = overall survival
PET = positron emission tomography
SCA = subclavian artery

Esophageal cancer (EC) is an aggressive malignancy often identified at an advanced stage.[1-4] Because of a lack of serosa, EC can easily penetrate the esophageal wall and directly involve adjacent organs, such as the trachea, bronchus, and aorta.[5] *The TNM Classification of Malignant Tumours*, 8th Edition, published by the Union for International Cancer Control, defines tumor involvement of these adjacent organs as clinical T4b (cT4b) disease, which reportedly accounts for 7.5% to 9.3% of thoracic EC.[6-8] This disease presents a challenging therapeutic dilemma with no established standard therapy. Chemoradiation (CRT)[8] per guidelines for EC is often ineffective, yielding only 0% to 39% complete response rates.[9] Reports suggest that 5% to 22% of patients develop fistula formation between the tumor and adjacent vital organs, which can easily be fatal.[9] Accordingly, the prognosis for cT4b remains extremely poor, with a 5-year overall survival (OS) rate of 7% to 33%.[9]

Conversion surgery (CS) is an operation in which T4b tumor invasion is relieved by induction treatments.[9-12] CRT or chemotherapy followed by this surgery has been reported to improve survival rates in patients with cT4b EC and is considered a treatment option.[9] In fact, CS has been performed after induction treatments in 32% to 96% of T4b EC cases with relatively high curative resection rates.[9,13,14] CS for cT4b cases is technically demanding, particularly in cases with previous irradiation at a definitive dose, and postoperative complication and mortality rates are reportedly high.[9,14-16] Cases involving insufficient tumor response with no relief of T4b invasion after definitive CRT or induction treatments apparently have no chance of "cure," usually with less than 6 months of estimated OS.

For these cases, combined resection of adjacent organs together with the tumor presents the only alternative, but the surgery is extremely challenging,[17] and few surgeons have experience with these extended resections. The cases that have been described are associated with high morbidity and mortality with no apparent survival improvement.[18] For these reasons, recent reports no longer address the usefulness of this approach as a potential option in multidisciplinary treatment for patients with T4b EC.

Here, we analyzed short- and long-term outcomes for 90 patients with EC undergoing combined resection of invaded organs, including the trachea/bronchus and large arteries. We also conducted a survival analysis to identify important prognostic parameters in this population for the optimization of indications for this surgery. To our knowledge, this study represents the largest series of extended surgeries for EC invading adjacent vital organs and analysis of related outcomes.

METHODS

Patients and Methods

From 2003 to 2023, a total of 260 consecutive patients with primary/recurrent EC invading adjacent structures (cT4b) without distant metastasis were surgically treated at Osaka University Hospital. Patients with supraclavicular lymph node metastasis, or cM1 according to the TNM classification, were eligible for inclusion because we recognized this status as involving regional lymph nodes. Pretreatment clinical staging (Union for International Cancer Control, 8th Edition[7]) was on the basis of endoscopy, computed tomography (CT),[19] and positron emission tomography (PET)-CT,[10,20-23] as described previously.[7] Involvement of adjacent organs was determined by endoscopy, CT, PET-CT, bronchoscopy and magnetic resonance imaging,[24] if needed.

To summarize, regardless of biopsy, tumor protrusion into the lumen of the trachea or bronchus was considered T4 invasion. Invasion of the aorta was diagnosed when the fatty surface of the triangular space between the esophagus, aorta, and spine had disappeared; when a tumor mass shadow was observed between the aorta and spine; and when the degree of direct contact between the tumor and the aorta exceeded 90° on CT.[10] This last criterion also was used to diagnose tumor invasion to other large arteries including the common carotid artery (CCA), subclavian arrtery (SCA), and brachocephalic artery (BCA). Among the 260 consecutive patients, 170 underwent radical resection (R0) after tumors became resectable after induction treatments. The remaining 90 patients underwent combined organ resection with the aim of achieving R0 resection and were eligible for inclusion in this study. The Human Ethics Review Committee of Osaka University Graduate School of Medicine approved the protocol for this retrospective study, and each participant provided signed consent.

Induction Therapy and Surgical Procedure

The induction CRT regimen in our hospital consisted of simultaneous radiation with the administration of a cisplatin and 5-fluorouracil (5-FU) or a docetaxel, cisplatin, and 5-FU (DCF) regimen.[21,22,25-28] In the cisplatin and 5-FU regimen, the 5-FU was administered by continuous intravenous infusion at a dose of 400 mg/m^2 in combination with the administration of cisplatin at 10 mg/m^2 by drip infusion for 5 days per week. In the DCF regimen, the 5-FU was administered by continuous intravenous infusion at a dose of 400 mg/m^2 in combination with the administration of cisplatin at 10 mg/m^2 by drip infusion for 5 days per week, and docetaxel at 30 mg/m^2 by rapid intravenous infusion on days 1 and 8. External-beam radiation therapy was administered by a 10-MV X-ray linear accelerator at 2 Gy per fraction per day and 5 fractions per week for 4-6 weeks, for a total dose of 40-60 Gy. The induction chemotherapy

regimen comprised triple therapy with 5-FU, cisplatin, and doxorubicin or DCF.[21,22,25-28] In the 5-FU, cisplatin, and adriamycin regimen, 700 mg/m^2 5-FU was given by continuous intravenous infusion on days 1-7, and 70 mg/m^2 cisplatin by intravenous infusion and 35 mg/m^2 doxorubicin by rapid intravenous infusion on day 1. For the DCF regimen, the cisplatin was administered at 70 mg/m^2 and docetaxel at 70 mg/m^2 by rapid intravenous infusion on day 1, and 5-FU at 700 mg/m^2 by continuous intravenous infusion on days 1 through 5. Two courses of these triplet therapies were used with a 3- to 4-week interval. If T4 invasion was not relieved by induction chemotherapy alone, second-line CRT with the same treatment protocol as first-line CRT was performed. CS was performed within 8 weeks of the last induction therapy, and the surgical procedure for the primary cases was basically a subtotal esophagectomy and 2- or 3-field lymph node dissection modified according to the tumor status.[10] The decision to perform open or minimally invasive surgery was made by the surgeon on the basis of the general condition of the patient. In the recurrent cases after esophagectomy, only resection of recurrent tumor along with invaded organ was performed.

Evaluation of Adverse Events and Clinical Responses

Adverse events during induction CRT or chemotherapy were graded according to the Common Terminology Criteria for Adverse Events, version 4.0. After completion of the induction treatments, all patients were restaged by endoscopy, CT, PET-CT, and magnetic resonance imaging (MRI) (if needed) to evaluate the clinical response and assess resectability.[19-21,28] The response was categorized on the basis of the World Health Organization response criteria for measurable disease and the criteria of the Japanese Society for Esophageal Disease.[27] We classified cases involving progressive disease or stable disease as nonresponders, and those involving a partial response or complete response as responders. In cases involving an inadequate tumor response to induction therapy and persistent invasion to an adjacent organ, combined resection of the invaded organ was considered. After surgery, the pathologic response was categorized according to the criteria of the Japanese Society for Esophageal Diseases.[27-29] Pathologic stage was determined according to the 8th edition of the Union for International Cancer Control staging system.[7]

Surgical procedure for partial- or all-layer treacheal/bronchial resection. A scalpel was used to shave a partial layer of the tracheal/broncheal membrane portion or cartilage, depending on the tumor location (ie, "tracheal shaving"; Figure 1, *A*). The shaved area of the trachea/bronchus was usually covered with the great omentum or mesentery, depending on the reconstruction organ, for reinforcement wherever possible. If the circumferential margin was suspicous, a frozen section was submitted to confirm curability. If the tumor was diagnosed as infiltrating the tracheal lumen or inner layer, an all-layer resection of the trachea/bronchus was attemped. Our strategy for intrathoracic tracheal reconstruction is as follows: (1) when the defect size is smaller than one-quarter of the tracheal circumference, muscle or musculocutaneous flap is applied without cartilage grafting. In these cases, the pectoralis major muscle flap with/without denuded skin was freed from the chest wall with an additional caudal incision and transposed to the tracheal window defect with a 4-0 polypropylene interrupted suture to reinforce the cervical/mediastinal structures and fill in the dead space of the cervicothoracic region (Figure 1, *B*). In the cases of with pectoralis major musclocutaneous, the skin paddle was used as the membranous surface/inner layer of the tracheal/bronchial reconstruction. (2) If the defect is smaller than one-half of the tracheal circumference, cartilage grafting per the procedure mentioned above is considered.[30] (3) If the trachea must be resected wider than one-half circumferentially with remnant trachea length of >30 mm, anterior mediastinal tracheostomy (AMT) will be performed.

Surgical procedure for AMT. AMTs were performed using a transcervical approach with the patient in a supine position. These procedures were performed using cervical collar and anterior chest midline incisions, regardless of whether the cancer was initial or recurrent. The manubrium, the medial half of the clavicle, and the adjacent first and second ribs on both sides were removed. After complete tumor resection, AMT was performed. The tracheal stoma was translocated inferior to the brachiocephalic artery in all but seven patients. The stoma was created using interrupted stitching to attach the tracheal stump to the native chest skin. The dead space in the upper mediastinum around the trachea and major arteries was covered using the pectoral myocutaneous flap, omentum, and mesentery to prevent infection in the upper mediastinum.[17]

Resection of aortic adventitia after insertion of an endovascular aortic stent. A thoracic stent graft (Conformable TAG; W.L. Gore & Associates) was prophylactically inserted to cover the aortic segment where tumor invasion was suspected. Occasionally, the position of the tumor was precisely detected with DynaCT guiding, as previously described.[31] After 2 to 3 days, radical surgical resection (subtotal esophagectomy with resection of aortic adventitia with/without replacement by gastric conduit through the retrosternal route) was performed through the right chest approach without fatal hemorrhage[32] (Figure 1, *C*).

Resection of the descending aorta replaced with a synthetic vascular graft. After systemic heparinization (300 U/kg) to achieve an activated clotting time >450 seconds, cardiopulmonary bypass was established with right atrium drainage and arterial perfusions through the femoral artery. The patient was cooled to 34 °C. After clamping the descending aorta proximal and distal to the tumor with an appropriate margin of 2 to 3 cm, the tumor of the esophagus was resected together with the invaded aorta with a sufficient resection margin. Regarding reconstruction with a synthetic graft, a rifampicin-soaked graft (Hemashield; Boston Scientific) was usually selected. Cardiac arrest was not triggered at any time during the entire procedure (Figure 1, *D*). In cases of CCA/SCA/BCA resection, the tumor and invaded artery were resected with a resection margin using a simple clamping method. Reconstruction with a synthetic graft or autogenous vessel (eg, great saphenous vein) was performed within an acceptable time frame for single-sided cerebral perfusion (Figure 1, *E*).

Postoperative Complications and Follow-up

All postoperative complications were graded on the basis of the Clavien–Dindo classification, and events classified as grade II or greater were documented as complications. Postoperative follow-up occurred at 3- to 4-month intervals in all patients during the first 2 years and then every 6 months for another 3 years using CT scans and tumor markers. Tumor recurrence was assessed by endoscopy with esophageal biopsy or CT. When the results indicated recurrence, further investigations were performed by more selective methods, such as PET-CT, bone scintigraphy, and MRI.[33,34]

Statistical Analysis

Data were analyzed using JMP16 software (SAS Institute Inc). Results are expressed as median (range) for continuous variables and percentages for categorical variables. Kaplan-Meier survival curves and log-rank analysis demonstrated survival differences between curves. OS was defined as the period from surgery to death, and surviving patients were censored at the last follow-up. Disease-free survival (DFS) was from the date of surgery to the date of recurrence as assessed by RECIST 1.1. or other cause of death. Hazard ratios (HRs) and 95% confidence intervals (CIs) were derived from a Cox proportional hazard model. Only variables significant in univariate analysis were included in multivariate analysis.

RESULTS

Patient Characteristics

The characteristics of all patients (N = 90) are summarized in Table 1. Median age was 61 years (range 42-80), 72 (80.0%) patients were male, and 63 (70%) were

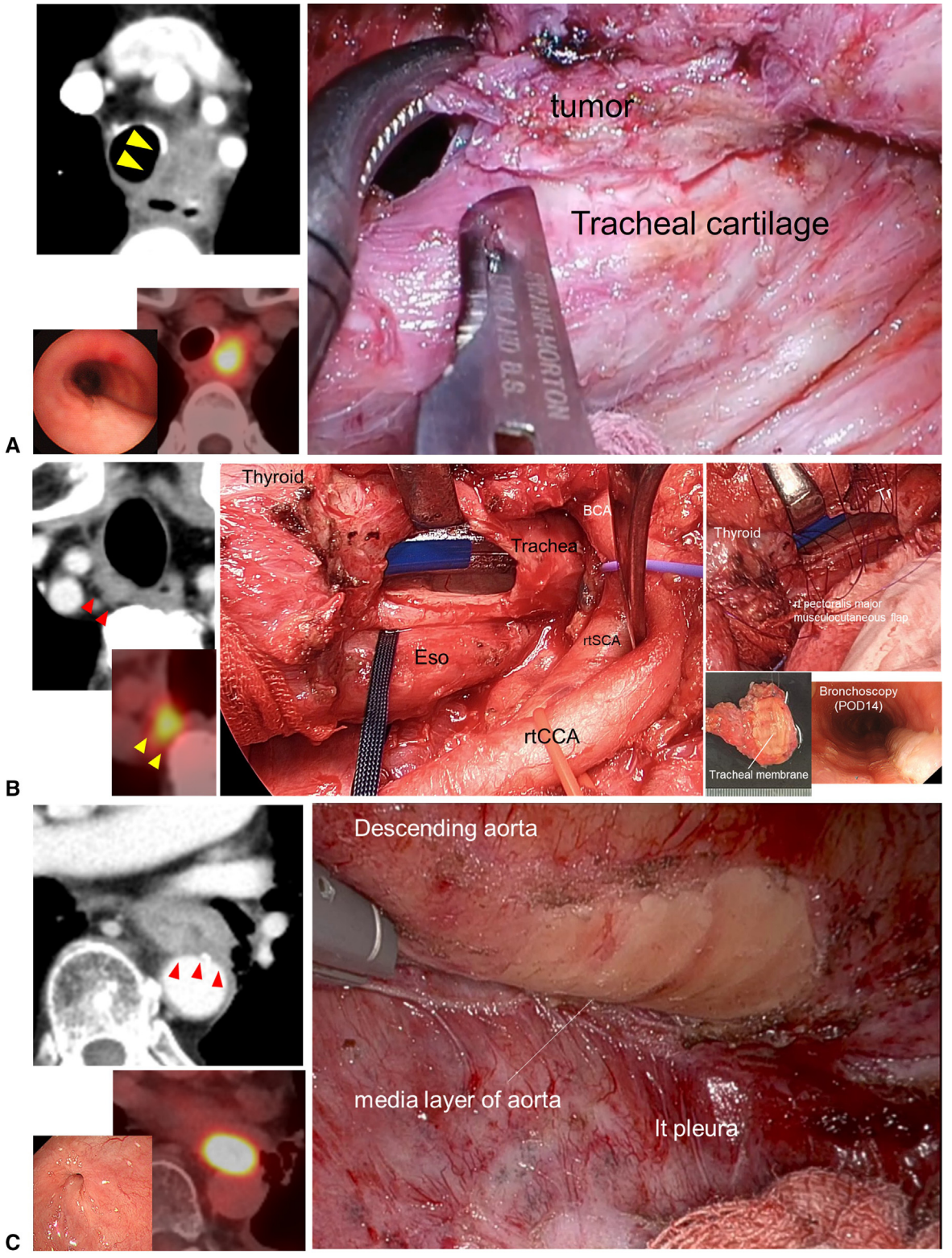

FIGURE 1. A representative case with tracheal shaving (A), all-layer resection of the trachea (B), resection of aortic adventitia layer via a robotic approach (C), synthetic graft replacement following descending aortic resection (D), and synthetic graft replacement after resection of the BCA/SCA/CCA and trachea (E). *Red* and *yellow arrow* indicate recurrent tumor. *BCA*, Brachiocephalic artery; *Eso*, esophagus; *rtSCA*, right subclavian artery; *rtCCA*, right common carotid artery; *POD*, postoperative; *Ao*, aorta; *SCA*, subclavian artery; *CCA*, common carotid artery.

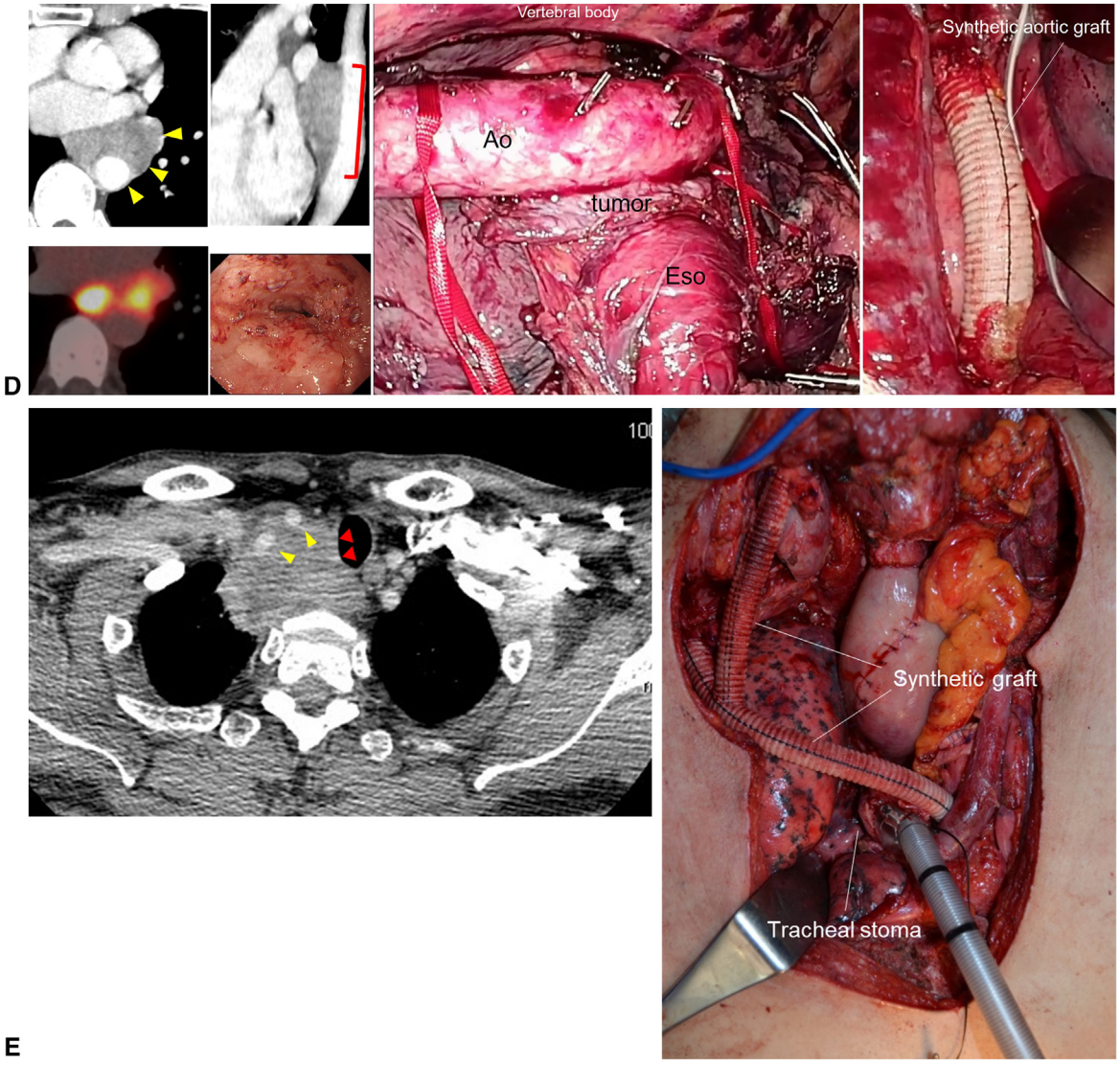

FIGURE 1. (*continued*).

American Society of Anesthesiologists Classification physical status class II. Tumor status was primary in 71 (78.9%) and recurrent in 19 (21.1%). The most commonly involved organ was the trachea/bronchus (n = 68; 75.6%), followed by a large artery (CCA, SCA, or BCA; n = 28; 31.1%), and both (n = 5; 5.6%). Among patients with primary disease, 62 (89.9%) were cN0-1, and 54 (78.2%) had cM0 disease.

Treatment Details and Clinicopathologic Features

Treatment details and clinicopathologic features are provided in Table 2. Initial induction treatment regimens included chemotherapy in 56 (62.2%) patients, CRT in 33 (36.7%), and none in 1 (1.1%) patient. The median radiation dose was 50 (28-66) Gy in CRT cases. The most commonly resected organ was the trachea/bronchus in 63 (70.0%), followed by a large vessel in 22 (24.4%). Types of tracheal/broncheal resection comprised partial-layer resection ("tracheal shaving") in 19 (27.9%) cases and all-layer resection in 49 (72.0%). An anterior mediastinal tracheostomy was performed in 32 patients as reconstruction after all-layer tracheal resection.

The large-vessel resections involved CCA/SCA/BCA in 14 (51.9%) cases, aortic replacement with a synthetic graft in 7 (25.9%), and aortic adventitia resection in 6 (22.2%). Representative images of each surgical procedure are shown in Figure 1, *A-E*. The median (range) operation time was 564 minutes (276-1053), and median blood loss was 710 mL (30-3750). Among all cases, minimally invasive surgeries including thoracoscopic or robotic approach were applied in 18 (20.0%) cases.

TABLE 1. Patient characteristics and treatment details (N = 90)

Median age, y (range)	61 (42-80)
Gender, n (%)	
Male	72 (76.1)
Female	18 (23.9)
ASA-PS, n (%)	
Class I/II/III/IV/V	10 (11.1)/63 (70.0)/ 17 (18.9)/0 (0)/0 (0)
Tumor status, n (%)	
Primary disease	71 (78.9)
Recurrent disease	19 (21.1)
Tumor location (primary disease), n (%)	
Cervical	14 (20.3)
Upper third	30 (43.5)
Middle third	22 (31.9)
Lower third	3 (4.3)
Tumor histology	
Squamous cell carcinoma	89 (98.9)
Other	1 (1.1)
Type of tumor invading adjacent organ, n (%)	
Primary	79 (87.8)
Lymph node	11 (12.2)
Invaded organ, n (%)	
Trachea/bronchus	63 (70.0)
Large vessel	22 (24.4)
Both	5 (5.6)
cN (n = 69), n (%)	
0/1/2/3	5 (7.2)/57 (82.6)/ 6 (8.7)/1 (1.4)
cM (n = 69), n (%)	
0/1 (#104)	54 (78.2)/15 (11.8)
Median body mass index, kg/m^2 (range)	19.9 (13.6-26.5)
Median albumin, g/dL (range)	3.6 (2.4-4.5)
Median C-reactive protein, mg/dL (range)	0.21 (0.04-5.3)
Median CAR (range)	0.058 (0.009-1.60)
Initial induction treatments, n (%)	
Chemotherapy	56 (62.2)
Chemoradiation	33 (36.7)
None	1 (1.1)
Secondary induction treatments, n (%)	
Chemotherapy	4 (4.4)
Chemoradiation	40 (44.4)
None	46 (51.1)
Radiation dose, n (%)	50 (28-66)
Organ with combined resection, n (%)	
Trachea/bronchus	63 (70.0)
Large vessel	22 (24.4)
Both	5 (5.6)
Tracheal/bronchial resection type (n = 68), n (%)	
Shaving (partial layer resection)	19 (27.9)
All-layer resection	49 (72.0)
Anterior mediastinal tracheostomy	32 (35.6)
Type of large vessel resection (n = 27), n (%)	
Aortic adventitia resection	6 (22.2)
Aortic replacement with synthetic graft	7 (25.9)
Resection of CCA/SCA/BCA	14 (51.9)
Surgical approach	
Open	72 (80.0)
Thoracoscopy	17 (18.9)
Robot	1 (1.1)

Values are n (%) unless otherwise noted. *ASA-PS*, American Society of Anesthesiologists physical status; *CAR*, C-reactive protein/albumin ratio; *CCA*, common carotid artery; *SCA*, subclavian artery; *BCA*, brachiocephalic artery.

Pathologic findings and postoperative complications. Table 3 summarizes the pathologic findings and postoperative complications. R0 resection was achieved in 89 (98.9%) patients. Of this group, 25 (36.2%) had ypT4 tumors, and 44 (63.8%) had ypT3 or less tumors. The most common pathologic response was grade 1b in 34 (37.8%) patients, followed by grade 1a in 28 (31.1%) and grade 2 in 12 (13.3%) cases. Overall postoperative morbidity (Clavien-Dindo classification grade II or greater) was 54.4%, and the most frequent complication (grade II or greater) was pneumonia (n = 13, 14.4%), followed by pleural effusion (n = 8, 8.9%) and palsy of the recurrent laryngeal nerve (n = 6, 6.7%). In-hospital death occurred in 2 (2.2%) patients, with grade V pneumonia in one case, and fatal hemorrhage from compression necrosis between the brachiocephalic artery and the remnant trachea in the other case. Overall postoperative morbidity rates (Clavien-Dindo classification grade II or greater) according to type of surgery were 52.4% with trachea/bronchus resection, 59.1% with large vessel resection, and 60.0% with both, indicating no significant difference among types of surgery.

OS and Univariate and Multivariate Analyses

The median follow-up period was 44.4 months. Of the patients who died during follow-up period, 47 (87.0%) deaths were attributed to EC, and 7 (13.0%) to other causes, which included 2 in-hospital death as shown earlier. The median and 2-year OS rate were 18.9 (95% CI, 13.4-27.9) months and 40.8%, respectively (Figure 2, *A*). Respective 2- and 5-year OS rates were 38.4% and 28.9% with trachea/bronchus resection, 47.2% and

TABLE 2. Surgical parameters and pathologic findings (n = 90)

Median operative time, min (range)		564 (276-1053)
Median blood loss, mL (range)		710 (30-3750)
Transfusion (yes), n (%)		48 (53.3)
Median postoperative hospital stay, d (range)		35 (11-201)
Postoperative complication, n (%)*		49 (54.4)
Pneumonia		13 (14.4)
Atelectasis		0 (0)
Tracheal necrosis		2 (2.2)
Anastomotic leakage		4 (4.4)
Recurrent nerve palsy		6 (6.7)
Arrhythmia (cardiac)		5 (5.6)
Pleural effusion		8 (8.9)
Chylothorax		0 (0)
Others		23 (25.6)
Reoperation, n (%)		8 (8.9)
In-hospital death, n (%)		2 (2.2)
Curability, n (%)	R0/1/2	89 (98.9)/1 (1.1)/0 (0)
pT (n = 69), n (%)†	0/1/2/3/4	6 (8.7)/3 (4.3)/4 (5.8)/31 (44.9)/25 (36.2)
pN (n = 69), n (%)†	0/1/2/3	29 (42.0)/21 (30.4)/14 (20.3)/5 (7.2)
pM (n = 69), n (%)†	0/1	61 (88.4)/8 (11.6)
Histologic grade, n (%)	0/1a/1b/2/3/X	1 (1.1)/28 (31.1)/34 (37.8)/12 (13.3)/8 (8.9)/7 (7.8)

*Clavien–Dindo classification grade III or greater. †Primary disease.

40.5% with large vessel resection, and 37.5% and 37.5% with both (Figure 2, *B*). Among the cases of tracheal/bronchial resection, tracheal shaving (ie, partial-layer resection) was associated with significantly better OS compared with all-layer resection (respective 2- and 5-year OS: 70.8% and 62.0% with partial vs 26.3% and 18.4% with all-layer; $P = .0025$) (Figure 2, *C*). Regarding resection of the aorta/large arteries, the respective 2- and 5-year OS rates were 66.7% and 33.3% for aortic adventitia, 34.3% and 34.3% for aorta (synthetic graft), and 44.0% and 44.0% for CCA, SCA, or BCA (Figure 2, *D*). A grade 2-3 pathologic response was associated with significantly better OS compared with a grade 0-1 response (respective 2- and 5-year OS rates: 75.0% and 54.7% with grade 2-3 vs 26.5% and 21.2% with grade 0-1; $P = .0065$; Figure 2, *E*). Univariate analysis of OS demonstrated statistically significant associations of longer operation time (HR, 2.11, $P = .0080$), greater blood loss (HR, 2.85; $P = .0003$), all-layer resection of trachea (HR, 3.51; $P = .0045$), ypT4 (HR, 2.04; $P = .022$), and grade 0-1 pathologic response (HR, 2.77; $P = .0089$; Table 3).

DFS and Recurrence Pattern

The median and 2-year DFS rate were 6.5 (95% CI, 4.1-8.7) months and 26.5%, respectively (Figure 2, *F*). Univariate analysis of DFS demonstrated statistically significant associations of greater blood loss (HR, 1.77; $P = .021$), all-layer resection of trachea (HR, 2.45; $P = .0090$), ypT4 (HR, 1.83; $P = .038$), and grade 0-1 pathologic response (HR, 4.01; $P = .0003$; Table 3). In terms of recurrence, 64 (71.1%) patients overall postoperatively developed recurrence, and the most common site was lymph node (62.5%; 43.8% outside of the surgical field and 21.9% within it). Hematogenous recurrence was identified in 36 (56.3%) patients, and 13 (20.3%) developed local recurrence, as shown in Table 4.

DISCUSSION

In the present study, we evaluated outcomes for 90 patients with EC invading an adjacent organ who underwent combined organ resection. R0 resection was achieved eventually in all but 1 patient. Postoperative morbidity (Clavien-Dindo grade II or greater) was 54.4%, and overall in-hospital mortality was 2.2%, whereas 30-day mortality was zero. Median DFS was 6.5 months, and OS was 18.9 months. The 2-year OS rates were 47.2% with trachea/bronchus resection, 38.4% with large-vessel resection, and 37.5% with both. Univariate analysis of OS demonstrated significant associations of operation time, blood loss, all-layer tracheal resection, ypT, and pathologic response. To the best of our knowledge, this study involves the largest series to date for evaluating the feasibility and utility of combined organ resection in EC.

The standard guidelines-based algorithm for T4b esophageal squamous-cell carcinoma is definitive CRT followed

TABLE 3. Univariate analyses of overall and disease-free survival (n = 90)

	Category	HR	95% CI	*P*
Overall survival				
Age	≥70 y	1.64	0.91-2.97	.099
Gender	Male	1.32	0.65-2.73	.43
ASA-PS	1-3	3.02	0.94-9.73	.064
Tumor status	Primary	1.21	0.61-2.40	.59
Invasion of trachea/bronchus	Present	1.41	0.74-2.69	.29
Invasion of large vessels	Present	0.68	0.37-1.25	.21
cN	2-3	1.33	0.53-3.36	.54
cM	1	0.84	0.42-1.67	.62
Body mass index (cutoff 18.5)	Low	1.63	0.94-2.82	.081
CAR (cutoff 0.095)	High	1.70	0.99-2.91	.051
Operative time (cutoff 564 min)	High	2.11	1.21-3.65	.0080
Blood loss (cutoff 710 mL)	High	2.85	1.61–5.04	.00030
All layer resection of trachea	Yes	3.51	1.47-8.37	.0045
Postoperative complication	Yes	1.31	0.79-2.34	.27
ypT	4	2.04	1.11-3.74	.022
Pathologic response (grade)	0-1	2.77	1.29-5.93	.0089
Disease-free survival				
Age	≥70 y	1.35	0.79-2.31	.27
Gender	Male	1.19	0.64-2.23	.58
ASA-PS	1-3	2.38	0.95-5.94	.064
Tumor status	Primary	1.09	0.62-1.92	.75
Invasion of trachea/bronchus	Present	1.63	0.90-2.94	.10
Invasion of large vessels	Present	0.73	0.43-1.25	.25
cN	2-3	1.89	0.93-3.84	.08
cM	1	0.94	0.50-1.77	.85
Body mass index (cutoff 18.5)	Low	1.04	0.62-1.76	.88
CAR (cutoff 0.095)	High	1.57	0.97-2.54	.067
Operative time (cutoff 564 min)	High	1.56	0.96-2.53	.071
Blood loss (cutoff 710 mL)	High	1.77	1.09-2.88	.021
All layer resection of trachea	Yes	2.45	1.25-4.80	.0090
Postoperative complication	Yes	1.14	0.70-1.86	.59
ypT	4	1.83	1.03-3.24	.038
Pathologic response (grade)	0-1	4.01	1.88-8.53	.0003

HR, Hazard ratio; *CI*, confidence interval; *ASA–PS*, American Society of Anesthesiologists physical status; *CAR*, C-reactive protein/albumin ratio.

by observation. The rate of clinical complete response in these cases has remained low, but cT4 (including cT4a) EC cases with R0 resection have been reported to involve relatively favorable long-term survival, with 5-year OS rates of 37.9%-63.6%.[9,14,16] Therefore, the establishment of effective induction treatments to achieve R0 resection is critical to improving survival for patients with cT4b. Triplet induction chemotherapy with DCF is promising for this population,[25,27,34] and given that the response rates of 52% to 74% are almost comparable with rates with CRT,[35] DCF is expected to be effective in local and systemic control of cT4b EC.[25,36] Yokota and colleagues,[13] when assessing chemo-selection with DCF followed by CS as a multidisciplinary treatment strategy, reported promising signs of tolerability and efficacy in patients with locally advanced unresectable EC. In our multicenter randomized phase 2 trial, we identified superiority of upfront CRT over DCF as initial induction therapy for T4b EC in terms of 2-year survival and local and regional control.[37] More recently, the JCOG1510 TRIANgLE trial has begun, intended to confirm the superiority of induction DCF followed by CS or definitive CRT over definitive CRT alone for OS in patients with locally advanced unresectable EC.[38]

In the current study, overall postoperative complications (grade II or greater) occurred in 54.4% of all cases, which is greater than with esophagectomy for resectable EC.[27] This greater risk might be justified when considering these challenging surgeries for all patients with ycT4b disease, most of whom have been heavily treated with CRT-based induction treatments. However, we note the limited in-hospital mortality in this study (n = 2; 2.2%), with 1 death from the primary disease (EC) and one from massive hemorrhage postoperatively. A hemorrhage from compression necrosis between the brachiocephalic artery and the remnant trachea has been described as the complication with the highest mortality risk after AMT.[17] Modification in the creation of a tracheal stoma enabled us to avoid this risk in later cases. Regarding the quality of life associated with AMT, our recent report showed that 93% of patients with AMT were eventually (21 days to 3 months) able to live at home although some patients were temporarily transferred to a rehabilitation facility. In addition, all patients tolerated oral intake and could have normal meals without enteral or parenteral nutrition by discharge, indicating that AMT may be feasible to some extent in terms of life function. An investigation of postoperative quality of life would be the target of a future prospective study. In terms of combined aortic resection with invading tumor, the 2 treatment options are aortic graft replacement and endovascular aortic stent.[32,39] Despite its invasiveness with a potential risk of mediastinal contamination, the advantage of aortic graft replacement is to enable complete tumor resection by all-layer removal of the aortic wall,[18] but few reports have discussed aortic replacement for EC resection.[18] In contrast, insertion of an aortic stent before surgery is less invasive and facilitates partial-layer resection of the aorta (we try to avoid all-layer resection with exposure of the stent surface due to potential risk of subsequent stent infection). Others have also demonstrated the utility of endovascular stent insertion for aortic wall resection.[32,39] Potential risk of infection associated with inserted endovascular stent needs to be considered particularly in the case of concurrent esophagectomy. Therefore, we often plan 2-stage operation (ie, separating reconstruction from esophagectomy) for

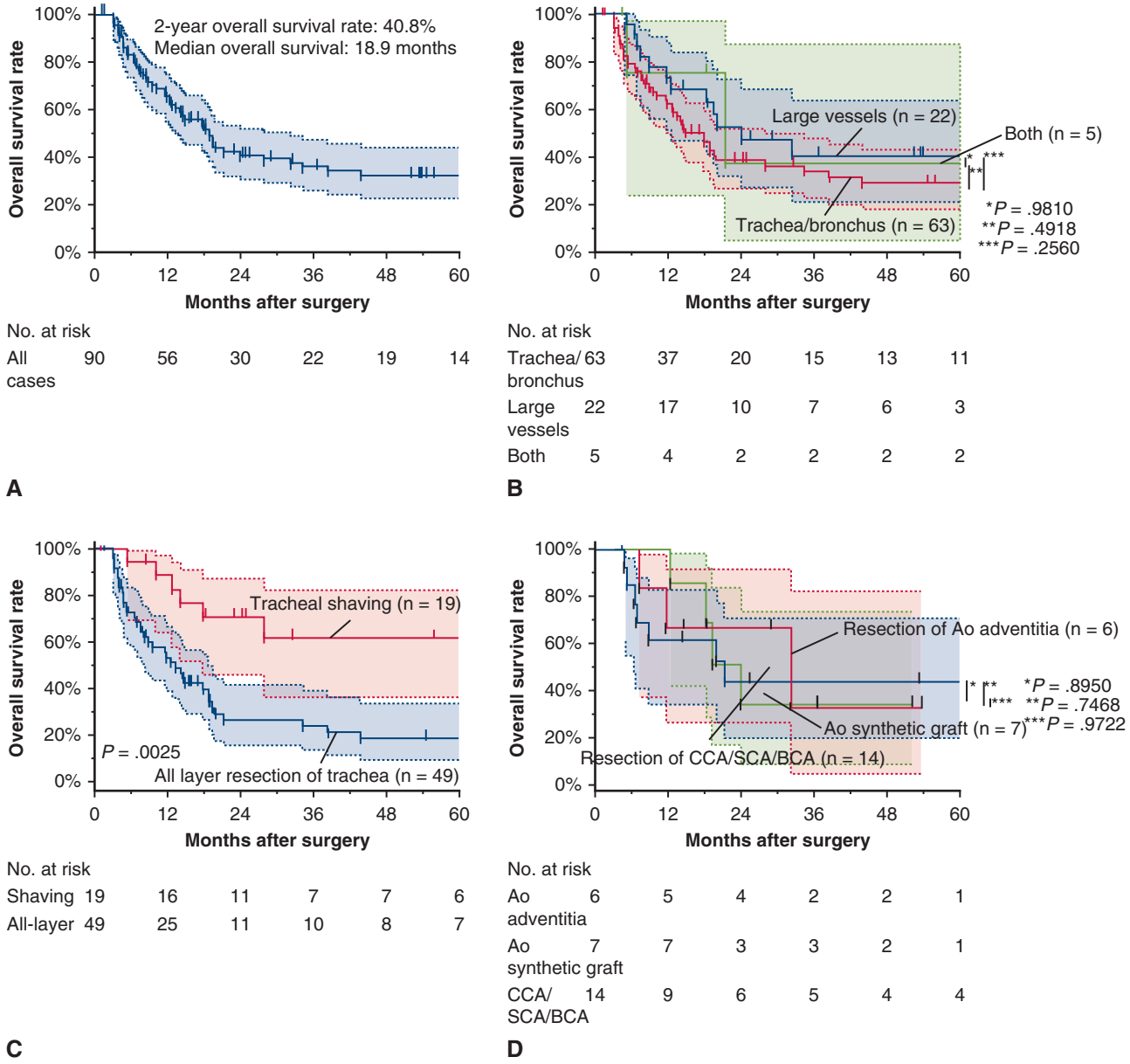

FIGURE 2. Kaplan-Meier survival curves for overall survival in all patients (95% CI, 13.4-27.9 months) (A), classified by type of resected organ (95% CI of trachea, bronchus/large vessels/both = 11.9-27.9/11.7-NA/5.2-NA months) (B), type of tracheal/bronchial resection (95% CI of shaving/all-layer resection = 14.0-NA/8.0-18.9 months) (C), type of large arterial resection (95% CI of Ao adventitia/Ao synthetic graft/CCA, SCA, BCA = 7.3-NA/12.4-NA/6.5-NA months) (D), according to pathological response (95% CI of grade 0-1/grade 2-3 = 10.1-18.9/13.4-NA months) (E), and for disease-free survival in all cases (95% CI, 4.1-8.7 months) (F). *CI*, Confidence interval; *NA*, not available; *CCA*, common carotid artery; *SCA*, subclavian artery; *BCA*, brachiocephalic artery; *Ao*, aorta.

such cases to avoid further contamination of endovascular stent. Other surgical measures to reduce the risk of infection would be the use of the greater omentum, mesentery, or pectoralis muscle flap, to cover endovascular stent graft as needed. Also, long-term use of postoperative antibiotic therapy should be considered. Fortunately, we have to date detected no serious infection at the synthetic graft in this cohort. To further decrease this risk, we have recently adopted reconstruction using an autogenous vessel (eg, great saphenous vein) for BCA/CCA/SCA resection if the clinical situation permits. Nonetheless, it is to be noted that the present procedures should be performed only at high-volume centers with multidisciplinary discussion before surgeries.

A quarter of a century ago, Watanabe and colleagues[18] performed combined resection of esophageal tumor and adjacent involved organs in 14 patients with A3 (ie, T4) EC, but none survived to 3 years and resecting

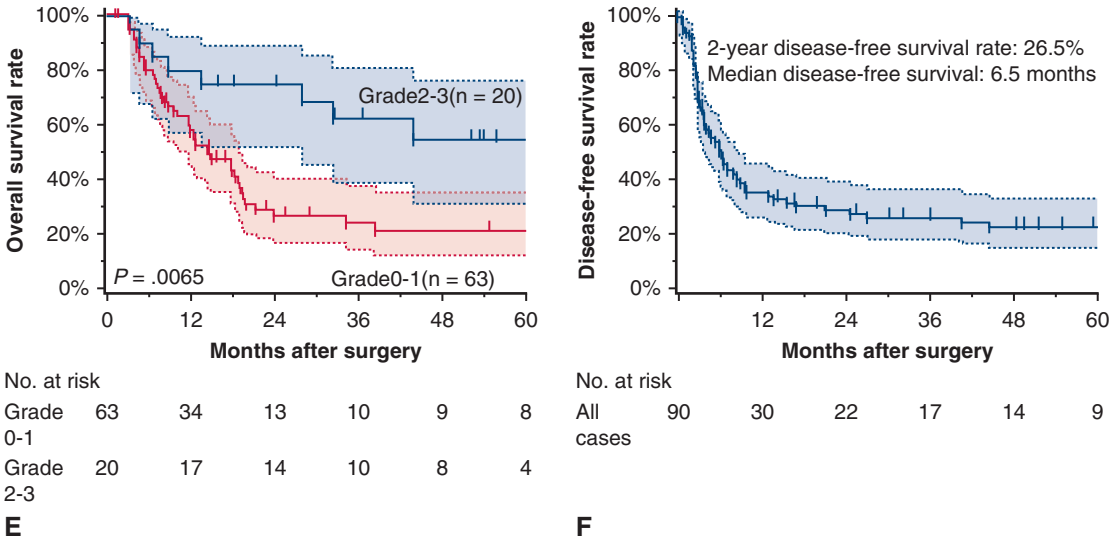

FIGURE 2. (*continued*).

tumor-invaded organs did not improve patient survival, as other small reports also describe.[40] In contrast, this study showed promising survival results, with 40.8% and 26.5% 2-year OS and recurrence-free survival rates. Remarkably, when confined to responders (pathologic response greater than grade 2) to induction treatments, 5-year OS was 54.7%. According to our clinical data, the median overall survival and 2-year overall survival rate of cT4b esophageal cancer patients (n = 22) who had not received surgery due to no relief of cT4b after series of induction treatments were 7.4 months and 10.4%, respectively (data not shown), implying potential survival benefit of these extended surgeries.

Few studies have focused on the pattern of recurrence after CS for T4b EC, with reported rates of 21% to 35% for lymphatic, 16% to 35% for hematogenous, and 15% to 47% for local recurrences.[41-43] In the present study, 64 patients (71.1%) postoperatively developed disease recurrence, with lymphatic recurrence (62.5%) predominantly out of the surgical field (43.8%) as the most common, followed by hematogenous (56.3%), whereas local recurrence was 20.3% among overall recurrences. This pattern suggests that perioperative control of systemic micrometastases is critical for improving survival in this patient population. The CheckMate 577 trial demonstrated that adjuvant nivolumab significantly improves survival by controlling distant metastases in patients with EC who undergo curative surgery following preoperative CRT.[44] Accordingly, adjuvant nivolumab therapy may be a good indication for the present cohort mostly with preoperative induction CRT.

TABLE 4. Pattern of disease recurrence, n (%); N = 90

Overall	64 (71.1)
Local	13 (20.3)
Lymphatic	40 (62.5)
Within surgical field	14 (21.9)
Out of surgical field	28 (43.8)
Hematogenous	36 (56.3)
Liver	5 (7.8)
Lung	25 (39.1)
Brain	0 (0)
Bone	6 (9.4)
Others	3 (4.7)
Dissemination	4 (6.3)

This study has several limitations. First, our data are gathered from a single institutional experience; however, this study is the largest series to date involving this type of extended surgery for far-advanced EC. The current data needs to be compared to survival with other treatments and validated with an independent cohort. Second, it was difficult to diagnose T4b and resectability after induction therapy, particularly CRT; edema due to inflammation from previous treatments tend to increase adipose tissue density around tumor tissue and make organ boundaries unclear, thus leading it difficult to judge the tumor margins. An enhanced CT scan was mandatory for a T4b diagnosis, but endoscopic ultrasonography and bronchoscopy were not. In fact, only 36.2% of patients were categorized as ypT4 in this study, indicating room for improvement in resectability evaluation. We recently started using MRI to evaluate resectability of cT4b cases because MRI is better at identifying organ layer structures given its higher tissue resolution compared with CT. In fact, our recent study showed the MRI had a superior diagnostic performance to CT for diagnosing T4b EC invading the surrounding organs. Adding endoscopic ultrasonography, bronchoscopy, or

other modalities including MRI might improve the diagnostic accuracy in T4b disease work-up and support treatment optimization. Also, from surgical point of view, planned en bloc tumor dissection together with "invaded" organ would be sometime better applied rather than bearing the risk of ending up with cutting into tumor when trying to forcedly perform organ preservation. A third limitation is a risk of selection bias for inclusion, as the indication for surgical resection or type of applied surgical procedure depended on the general condition or nutritional status of patients, in addition to physician or patient preference. Lastly, the present cohort included patients treated at our institution over the course of 20 years, and advances in perioperative management and treatments, including the introduction of immune-checkpoint inhibitors,[45,46] could have affected treatment outcomes.

CONCLUSIONS

Combined organ resection for EC invading adjacent organs might be feasible and promising in selected patients. Optimizing indications for surgery and establishing more effective perioperative treatments may further improve outcomes in this patient population. The current findings offer important information that could ultimately lead to improved clinical outcomes in patients with EC that persistently invades adjacent organs after a series of induction treatments.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: esophageal cancer, cT4b, combined organ resection, conversion surgery