ANTICANCER RESEARCH *39*: 5123-5133 (2019)
doi:10.21873/anticanres.13707

A Randomized Phase III Trial on the Role of Esophagectomy in Complete Responders to Preoperative Chemoradiotherapy for Esophageal Squamous Cell Carcinoma (ESOPRESSO)

SOOK RYUN PARK[1*], DOK HYUN YOON[1*], JONG HOON KIM[2], YONG-HEE KIM[3], HYEONG RYUL KIM[3], HYUN JOO LEE[4], HWOON-YONG JUNG[5], GIN-HYUG LEE[5], HO JUNE SONG[5], DO HOON KIM[5], KEE DON CHOI[5], JEONG HOON LEE[5], JI YONG AHN[5], JIN-SOOK RYU[6], KYUNG-JA CHO[7] and SUNG-BAE KIM[1]

[1]Department of Oncology, [2]Department of Radiation Oncology, [3]Department of Thoracic Surgery, [4]Department of Radiology, [5]Department of Gastroenterology, [6]Department of Nuclear Medicine, and [7]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

Abstract. *Background/Aim: We investigated the role of esophagectomy after clinical complete response (cCR) to chemoradiotherapy for esophageal squamous cell carcinoma (ESCC). Patients and Methods: Patients with resectable cT3-T4a/anyN/M0 or anyT/N+/M0 thoracic ESCC received two cycles of induction chemotherapy and then chemoradiotherapy (50.4 Gy/28 fractions). Patients with cCR were randomized to surgery or observation. Results: Among 86 patients, 38 (44.2%) achieved cCR after chemoradiotherapy; 37 were randomized to surgery (n=19) or observation (n=18). Although there were trends of better disease-free survival (DFS) toward the surgery arm in the intent-to-treat analysis (2-year DFS, 66.7% vs. 42.7%; p=0.262) or as-treated analysis (66.7% vs. 50.2%; p=0.273), overall survival was not different between the two arms in the intent-to-treat (HR=1.48; p=0.560) or as-treated analysis (HR=1.09; p=0.903). Among the 11 patients having recurrence during observation, 8 underwent surgery (n=7) or endoscopic dissection (n=1). Conclusion: Close observation with salvage surgery might be a reasonable option in resectable ESCC patients achieving cCR after chemoradiation.*

*These Authors contributed equally to this work.

Correspondence to: Prof. Sung-Bae Kim, MD, Ph.D., Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro, 43-gil, Songpa-gu, Seoul, 05505, Republic of Korea. Tel: +82 230103217, Fax: +82 230106961, e-mail: sbkim3@amc.seoul.kr

Key Words: Esophageal squamous cell carcinoma, chemoradiotherapy, induction chemotherapy, clinical complete response, surgery, observation.

Despite recent advances in treatment, esophageal cancer is still one of the deadliest malignancies (1). Even patients with potentially resectable disease have a poor prognosis with 5-year overall survival (OS) rates of 15-20% with surgery alone, which underscores the value of multidisciplinary treatment approaches (2, 3). Currently, neoadjuvant chemoradiation followed by surgery is the preferred treatment for potentially resectable stage II-III thoracic esophageal cancer (EC) based on the survival benefits compared to surgery alone (4-7). However, it is unclear whether surgery is required in patients who have received chemoradiation, given that radical esophagectomy is associated with significant morbidity and mortality.

In a randomized phase III study comparing induction chemotherapy followed by chemoradiotherapy with or without surgery for locally advanced esophageal squamous cell carcinoma (ESCC), the addition of surgery resulted in better locoregional control but did not translate to survival benefits due to a higher risk of treatment-related death (8). Patients with tumor response to induction chemotherapy had a high 3-year survival rate, regardless of the treatment group (8). Another phase III study (FFCD 9102) compared continuation of chemoradiotherapy to surgery in patients responding to chemoradiation for advanced EC, which also did not demonstrate survival benefits of the addition of surgery (9). A recent Cochrane analysis also suggested that chemoradiotherapy appears to be at least equivalent to surgery in terms of short- and long-term survival in ESCC patients who are fit for surgery and are responsive to induction chemoradiotherapy (10). Although chemoradiation followed by surgery remains the preferred treatment approach for resectable EC in medically fit patients, the role of surgery in long-term outcomes needs to be elucidated, particularly for patients responding to chemoradiation. Therefore, in this single-center, open-label, randomized,

phase III trial, we investigated the role of esophagectomy in patients who achieved a clinical complete response (cCR) after chemoradiation for locally advanced ESCC.

Patients and Methods

Eligibility criteria. The key eligibility criteria were: histologically confirmed, resectable cT3-T4a/anyN/M0 or anyT/N+/M0 (the 7th edition of the AJCC staging system) thoracic ESCC, age 20-75 years, Eastern Cooperative Oncology Group performance status 0-2, adequate major organs function, and no history of other cancers within 5 years. Pre-treatment staging work-up included esophagogastroduodenoscopy with biopsy, thoracic/abdominal/pelvic computed tomography (CT), endoscopic ultrasonography, bone scan, ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET), and bronchoscopy when needed. All patients gave written informed consent before study enrolment. The study was approved by the institutional review board of Asan Medical Center, Korea (IRB approval number: 2012-0817), and conducted in accordance with the principles of the Declaration of Helsinki. The trial was registered at ClinicalTrials.gov (NCT01740375).

Treatment and evaluation. Patients received two cycles of induction chemotherapy (capecitabine 1,000 mg/m^2 twice daily on D1-14 and cisplatin 60 mg/m^2 intravenously on D1 every 3 weeks) and proceeded to chemoradiation if they had a response or stable disease (SD) on PET after induction chemotherapy, according to European Organization for Research and Treatment of Cancer criteria (11). Radiotherapy was delivered once a day to a total dose of 50.4 Gy in 28 fractions of 1.8 Gy with a 15-MV linear accelerator. The clinical target volume included the primary tumor with a 5-cm cranio-caudal margin and 2-cm lateral margin and regional lymph nodes (LNs). Supraclavicular LNs were routinely encompassed in upper thoracic EC and celiac LNs in distal or middle thoracic EC. During radiotherapy, concurrent chemotherapy was administered with capecitabine 800 mg/m^2 twice daily for 5 days/week and cisplatin 30 mg/m^2 weekly. Adverse events were assessed using the Common Terminology Criteria for Adverse Events v4.03.

Four weeks after completing chemoradiation, patients were re-evaluated with endoscopy with biopsy, chest CT, and PET-CT. cCR was defined as no radiographic or metabolic evidence of disease without residual tumor on endoscopy with biopsy. Complete metabolic response was complete resolution of FDG uptake within all lesions, making them indistinguishable from surrounding tissue. Otherwise, the response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (12). Only patients who achieved a cCR after chemoradiation were randomized (1:1) through the block randomization method to surgery or observation, stratified by the presence of LN metastasis.

Surgical resection *via* an abdominal–right thoracic approach (Ivor–Lewis) or right thoracic–abdominal–cervical approach (McKeown) with two-field LN dissection was preferentially performed within 6-8 weeks and not exceeding 12 weeks after completing chemoradiation. The proximal and distal margins had to be at least 6-8 cm from the gross tumor. The pathologic response was evaluated according to the percentage of vital tumor tissue in relation to the macroscopically identifiable tumor bed: grade 1, >50% of residual tumor cells; grade 2, 10-50%; grade 3, <10%; and grade 4, no viable tumor (13). Pathologic CR (pCR) was defined by the absence of viable cancer cells in the esophagus and LNs.

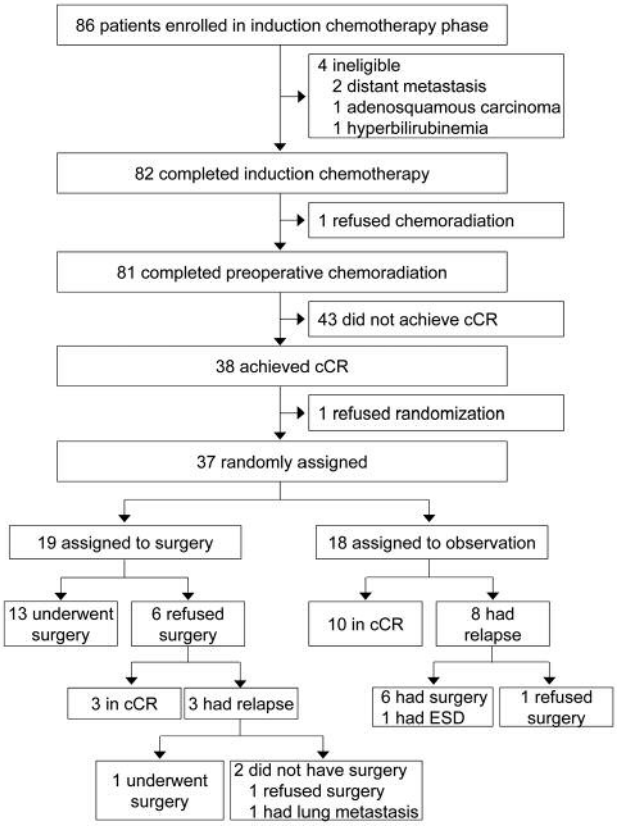

Figure 1. *CONSORT diagram. cCR: Clinical complete response; ESD; endoscopic submucosal dissection.*

Follow-up after randomization included OPD visits at 3-month intervals for the first 2 years and then every 6 months from 3-5 years with CT and endoscopy every 6 months.

Statistical analysis. The primary endpoint was disease-free survival (DFS), which was defined as the time between randomization and progression or death from any cause. The secondary endpoints included progression-free survival (PFS; the time between initiation of chemotherapy and progression or death), time to progression (TTP; the time between initiation of chemotherapy and progression), OS (the time between initiation of chemotherapy and death), the failure pattern, the pCR rate, treatment outcomes according to metabolic or clinical response, safety, and quality of life. For patients who had cCR and/or R0 or R1 resection, progression was defined as the first clinical evidence of relapse. Patients with R1 resection were regarded as having progressed only when there was clinical or radiological evidence of disease progression before surgery. For patients not macroscopically free of disease after surgery or not undergoing surgery due to progression, progression was defined as occurring at the time of surgery or at the time of clinical evaluation showing unresectable disease.

Sample size calculations showed that 194 patients (78 DFS events required) were needed to detect an increase in the 2-year DFS rate from 50% to 70% (hazard ratio [HR]=0.514) among

Table I. *Baseline characteristics*.

	Entire population (n=82)	Randomized population		
		Surgery arm (n=19)	Observation arm (n=18)	*p*-Value
Age (years)	60 (55-67)	62 (56-69)	61 (55-67)	0.819
Gender				0.230
Male	79 (96.3%)	19 (100%)	16 (88.9%)	
Female	3 (3.7%)	0 (0%)	2 (11.1%)	
ECOG performance status				0.582
0	48 (58.5%)	11 (57.9%)	12 (66.7%)	
1	34 (41.5%)	8 (42.1%)	6 (33.3%)	
Tumor location				0.788
Upper third	7 (8.5%)	0 (0%)	1 (5.6%)	
Middle third	26 (31.7%)	5 (26.3%)	6 (33.3%)	
Lower third	46 (56.1%)	13 (68.4%)	10 (55.6%)	
Multifocal/diffuse spreading	3 (3.7%)	1 (5.3%)	1 (5.6%)	
Histological grade				1.000
Well differentiated	13 (15.9%)	2 (10.5%)	3 (16.7%)	
Moderately differentiated	61 (74.4%)	15 (78.9%)	14 (77.8%)	
Poorly differentiated	7 (8.5%)	2 (10.5%)	1 (5.6%)	
Unknown	1 (1.2%)	0 (0%)	0 (0%)	
Clinical T stage				0.128
T1	8 (9.8%)	1 (5.3%)	6 (33.3%)	
T2	15 (18.3%)	2 (10.5%)	2 (11.1%)	
T3	55 (67.1%)	15 (78.9%)	10 (55.6%)	
T4	4 (4.9%)	1 (5.3%)	0 (0%)	
Clinical N stage				0.807
N0	16 (19.5%)	4 (21.1%)	5 (27.8%)	
N1	42 (51.2%)	10 (52.6%)	11 (61.1%)	
N2	20 (24.4%)	4 (21.1%)	2 (11.1%)	
N3	4 (4.9%)	1 (5.3%)	0 (0%)	
Clinical TNM stage				0.014*
IIA	8 (9.8%)	2 (10.5%)	3 (16.7%)	
IIB	21 (25.6%)	3 (15.8%)	9 (50.0%)	
IIIA	33 (40.2%)	9 (47.4%)	5 (27.8%)	
IIIB	13 (15.9%)	3 (15.8%)	1 (5.6%)	
IIIC	7 (8.5%)	2 (10.5%)	0 (0%)	

Data are median (interquartile range) or number (%). *p-value for stage 2 *vs*. 3. ECOG: Eastern Cooperative Oncology Group.

patients undergoing surgery with 80% power and a two-sided α of 0.05. Assuming a 40% rate of cCR, 486 patients were planned. Time to event endpoints were characterized by the Kaplan–Meier method, and treatment groups were compared using the log-rank test and Cox proportional hazard regression models (unadjusted). We compared variables with the χ^2 test, Fisher exact test, or a nonparametric Wilcoxon test, depending on their type and distribution. All statistical tests were two-sided, and we considered $p<0.05$ significant.

Results

Patient characteristics. Between November 2012 and March 2016, 86 patients (17.7% of the target number) were enrolled. The accrual was slower than expected, causing early study closure. Among the 82 eligible patients, 38 patients (44.2%) achieved a cCR after chemoradiation; of these, 37 were randomized to surgery (n=19) or observation (n=18) (Figure 1). Patient characteristics were well balanced between the treatment arms except for clinical TNM stages (stage >2, 73.7% in the surgery arm *vs*. 33.3% in the observation arm; $p=0.014$) (Table I).

Induction chemotherapy and chemoradiation. All eligible 82 patients completed induction chemotherapy, and post-chemotherapy PET showed a CR in 7 patients (8.5%), partial response (PR) in 62 (75.6%), and SD in 12 (14.6%); one patient (1.2%) refused PET. Eighty-one patients proceeded to chemoradiotherapy; of these, 78 (96.3%) received 50.4 Gy of radiotherapy, 2 received 46.0 Gy, and 1 received 46.8 Gy. The post-chemoradiation metabolic response evaluation showed a CR in 38 patients (46.3%), PR in 35 (43.2%), SD in 1 (1.2%), and progressive disease (PD) in 6 (7.3%); one patient was not

evaluable. According to RECIST, post-chemoradiation evaluation showed a CR in 39 patients (47.6%), PR in 6 (7.3%), SD or NonCR/NonPD in 31 (37.8%), and PD in 5 (6.1%). Adverse events during induction chemotherapy and chemoradiation are shown in Table II.

Compliance with the allocated arm. The compliance rates significantly differed between the allocated arms (68.4% in the surgery arm and 100% in the observation arm; p=0.020). In the surgery arm, only 13 patients (68.4%) underwent surgery; the remaining six declined surgery after chemoradiotherapy and were followed without any treatment until disease progression. In the observation arm, all patients were followed without any treatment until disease progression (Figure 1).

Surgery results. In the surgery arm, 12 of 13 patients (92.3%) undergoing surgery had R0 resection, whereas one patient (7.7%) had R1 resection. In the observation arm, eight patients experienced recurrence, all locoregional, during observation. Of these, one patient refused surgery, one patient received curative endoscopic dissection, and six patients underwent surgery: R0 resection in three patients (3 of 6, 50.0%) and R1 resection in three patients (3 of 6, 50.0%). In the intent-to-treat analysis, the surgery arm had a higher R0 resection rate (92.3% *versus* 50.0%; p=0.071), lower pathologic T (p=0.008) and TNM (p=0.002) stages, and higher degree of pathologic regression (p<0.0001) than the observation arm (Table III). In the as-treated analysis, the surgery arm also had a significantly higher R0 resection rate (92.3% *versus* 42.9%; p=0.031) and pathologic regression grade (p<0.0001) and lower pathologic T (p=0.003) and TNM (p=0.0005) stages than patients who underwent salvage surgery in the observation arm (Table III). Although there was no 30-day mortality after surgery in both arms, one patient in the surgery arm died of recurrent pneumonia 74 days after surgery which was considered surgery-related death.

Survival. Among the 82 eligible patients, patients who achieved a cCR had a better TTP [31.9 months (95%CI=not estimated (NE)) *vs*. 16.4 months (95%CI=NE); p=0.116], PFS [31.9 months (95%CI=NE) *vs*. 11.6 months (95%CI=4.4-18.8); p=0.041], and OS [not reached *vs*. 21.7 months (95%CI=6.5-36.9); p=0.002] than those who did not. For the 37 randomized patients, with a median follow-up of 29.9 months (IQR=13.9-36.3), the median OS and TTP were not reached, the median PFS was 31.9 months (95%CI=NE), and the median DFS was 27.7 months (95%CI=NE). In the intent-to-treat analysis, there were no significant differences in DFS, PFS, TTP, and OS between the two arms, although the surgery arm tended to have better DFS, PFS, and TTP than the observation arm (Figure 2). The median DFS was 21.7 months (95%CI=0-45.9) in the observation arm, whereas it was not reached in the surgery arm (p=0.262) (Figure 2a). The 2-year DFS rate was 66.7% [95%CI=44.9-88.5%] in the surgery arm *vs*. 42.7% (95%CI=17.0-68.4) in the observation arm (HR=1.75; 95%CI=0.65-4.72). The median PFS was not reached in the surgery arm and was 25.6 months (95%CI=2.4-48.8) in the observation arm (HR=1.71; 95%CI=0.63-4.61; p=0.282) (Figure 2b). The median TTP was not reached in the surgery arm and was 25.6 months (95%CI=2.7-48.5) in the observation arm (HR=1.83; 95%CI=0.63-5.30; p=0.257) (Figure 2c). The median OS was not reached in either arm (HR=1.48; 95%CI=0.40-5.51; p=0.560) (Figure 2d).

In the as-treated analysis, there were similar trends to the intent-to-treat analysis (Figure 2e-h). Although the surgery arm tended to have better DFS (HR=1.87; 95%CI=0.60-5.82), PFS (HR=1.81; 95%CI=0.58-5.63; p=0.300), and TTP (HR=2.25; 95%CI=0.62-8.10; p=0.203) than the observation arm, OS was not different between the two arms.

In the intent-to-treat analysis, the recurrence rate was 31.6% (6 of 19) in the surgery arm and 44.4% (8 of 18) in the

Table II. *Adverse events during induction chemotherapy and chemoradiotherapy.*

	Induction chemotherapy (n=82)		Chemo-radiotherapy (n=81)	
Adverse events*	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Hematologic				
Leukopenia	23 (28.0)	1 (1.2)	44 (54.3)	30 (37.0)
Neutropenia	44 (53.7)	3 (3.7)	51 (63.0)	24 (29.6)
Anemia	14 (17.1)	0 (0)	45 (55.6)	3 (3.7)
Thrombocytopenia	28 (34.1)	0 (0)	44 (54.3)	30 (37.0)
Non-hematologic				
Abdominal pain	10 (12.2)	1 (1.2)	14 (17.3)	0 (0)
Odynophagia	18 (22.0)	0 (0)	40 (49.4)	1 (1.2)
Dysphagia	14 (17.1)	1 (1.2)	29 (35.8)	1 (1.2)
Esophagitis	0 (0)	0 (0)	26 (32.1)	0 (0)
Dyspepsia	4 (4.9)	0 (0)	9 (11.1)	0 (0)
Anorexia	8 (9.8)	0 (0)	40 (49.4)	0 (0)
Nausea	22 (26.8)	1 (1.2)	33 (40.7)	0 (0)
Vomiting	2 (2.4)	4 (4.9)	12 (14.8)	1 (1.2)
Constipation	13 (15.9)	0 (0)	15 (18.5)	0 (0)
Fatigue	39 (47.6)	0 (0)	53 (65.4)	0 (0)
Dizziness	16 (19.5)	0 (0)	35 (43.2)	0 (0)
Hiccup	18 (22.0)	0 (0)	5 (6.2)	0 (0)
Hand-foot syndrome	10 (12.2)	0 (0)	20 (24.7)	0 (0)
Skin hyperpigmentation	12 (14.6)	0 (0)	20 (24.7)	0 (0)
Cough	3 (3.7)	0 (0)	10 (12.3)	0 (0)
Sputum	0 (0)	0 (0)	9 (11.1)	0 (0)
Hyperbilirubinemia	3 (3.7)	0 (0)	22 (27.2)	0 (0)

Data are numbers of patients (%). *Reported in ≥10% of patients.

Table III. *Surgical and pathologic details*.

	Entire population (n=82)	Intent-to-treat analysis			As-treated analysis		
		Surgery (n=19)	Observation (n=18)	*p*-Value	Surgery (n=13)	Observation (n=24)	*p*-Value
Surgery*							
Yes	51 (62.2%)	13 (68.4%)	6 (33.3%)		13 (100%)	7 (29.2%)	
Extent of surgery**				0.071			0.031
R0	41 (80.4%)	12 (92.3%)	3 (50.0%)		12 (92.3%)	3 (42.9%)	
R1	6 (11.8%)	1 (7.7%)	3 (50.0%)		1 (7.7%)	4 (57.1%)	
R2	3 (5.9%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Open & Closure	1 (2.0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Types of surgery**				1.000			1.000
Ivor-Lewis operation	29 (56.9%)	9 (69.2%)	4 (66.7%)		9 (69.2%)	5 (71.4%)	
McKeown operation	20 (39.2%)	3 (23.1%)	2 (33.3%)		3 (23.1%)	2 (28.6%)	
Others	2 (3.9%)	1 (7.7%)	0 (0%)		1 (7.7%)	0 (0%)	
Postoperative hospital stay (days)**	15 (13-21)	14 (14-18)	15 (12-27)	0.894	14 (14-18)	15 (13-18)	1.000
Postoperative death within 30 days after surgery**	1 (2.2%)	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
Postoperative complications**							
Vocal cord palsy	19 (37.3%)	3 (23.1%)	4 (66.7%)	0.129	3 (23.1%)	4 (57.1%)	0.174
Pneumonia	10 (19.6%)	2 (15.4%)	1 (16.7%)	1.000	2 (15.4%)	1 (14.3%)	1.000
Cardiac arrhythmia	4 (7.8%)	2 (15.4%)	0 (0%)	1.000	2 (15.4%)	0 (0%)	0.521
Wound infection	3 (5.9%)	0 (0%)	1 (16.7%)	0.316	0 (0%)	1 (14.3%)	0.350
Chylothorax	2 (3.9%)	0 (0%)	1 (16.7%)	0.316	0 (0%)	1 (14.3%)	0.350
Anastomosis site leakage	5 (9.8%)	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
Mediastinitis	3 (5.9%)	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
Bronchial fistula	1 (2.0%)	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
Pathologic T stage***				0.008			0.003
T0	17 (34.0%)	9 (69.2%)	0 (0%)		9 (69.2%)	0 (0%)	
Tis	2 (4.0%)	1 (7.7%)	0 (0%)		1 (7.7%)	0 (0%)	
T1	6 (12.0%)	0 (0%)	1 (16.7%)		0 (0%)	1 (14.3%)	
T2	6 (12.0%)	1 (7.7%)	0 (0%)		1 (7.7%)	0 (0%)	
T3	13 (26.0%)	2 (15.4%)	3 (50.0%)		2 (15.4%)	4 (57.1%)	
T4a	2 (4.0%)	0 (0%)	1 (16.7%)		0 (0%)	1 (14.3%)	
T4b	4 (8.0%)	0 (0%)	1 (16.7%)		0 (0%)	1 (14.3%)	
Pathologic N stage***				0.148			0.220
N0	27 (54.0%)	9 (69.2%)	2 (33.3%)		9 (69.2%)	3 (42.9%)	
N1	15 (30.0%)	4 (30.8%)	2 (33.3%)		4 (30.8%)	2 (28.6%)	
N2	7 (14.0%)	0 (0%)	1 (16.7%)		0 (0%)	1 (14.3%)	
N3	1 (2.0%)	0 (0%)	1 (16.7%)		0 (0%)	1 (14.3%)	
Pathologic TNM stage***				0.002			0.0005
pCR	15 (30.0%)	8 (61.5%)	0 (0%)		8 (61.5%)	0 (0%)	
0	2 (4.0%)	1 (7.7%)	0 (0%)		1 (7.7%)	0 (0%)	
IA	0 (0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
IB	3 (6.0%)	0 (0%)	1 (16.7%)		0 (0%)	1 (14.3%)	
IIA	4 (8.0%)	0 (0%)	1 (16.7%)		0 (0%)	2 (28.6%)	
IIB	10 (20.0%)	1 (7.7%)	0 (0%)		1 (7.7%)	0 (0%)	
IIIA	4 (8.0%)	2 (15.4%)	0 (0%)		2 (15.4%)	0 (0%)	
IIIB	3 (6.0%)	0 (0%)	1 (16.7%)		0 (0%)	1 (14.3%)	
IIIC	5 (10.0%)	0 (0%)	3 (50.0%)		0 (0%)	3 (42.9%)	
IV	2 (4.0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Other (T0N1M0)	2 (4.0%)	1 (7.7%)	0 (0%)		1 (7.7%)	0 (0%)	
Tumor regression grade***				<0.0001			<0.0001
Grade 1	15 (30.0%)	0 (0%)	6 (100%)		0 (0%)	7 (100%)	
Grade 2	7 (14.0%)	1 (7.7%)	0 (0%)		1 (7.7%)	0 (0%)	
Grade 3	10 (20.0%)	3 (23.1%)	0 (0%)		3 (23.1%)	0 (0%)	
Grade 4	18 (36.0%)	9 (69.2%)	0 (0%)		9 (69.2%)	0 (0%)	

Data are median (interquartile range) or number (%). *Immediate surgery in the surgery arm and delayed surgery at recurrence in the observation arm; **Among patients who underwent surgery; ***Among patients who underwent esophagectomy. pCR: Pathologic complete response.

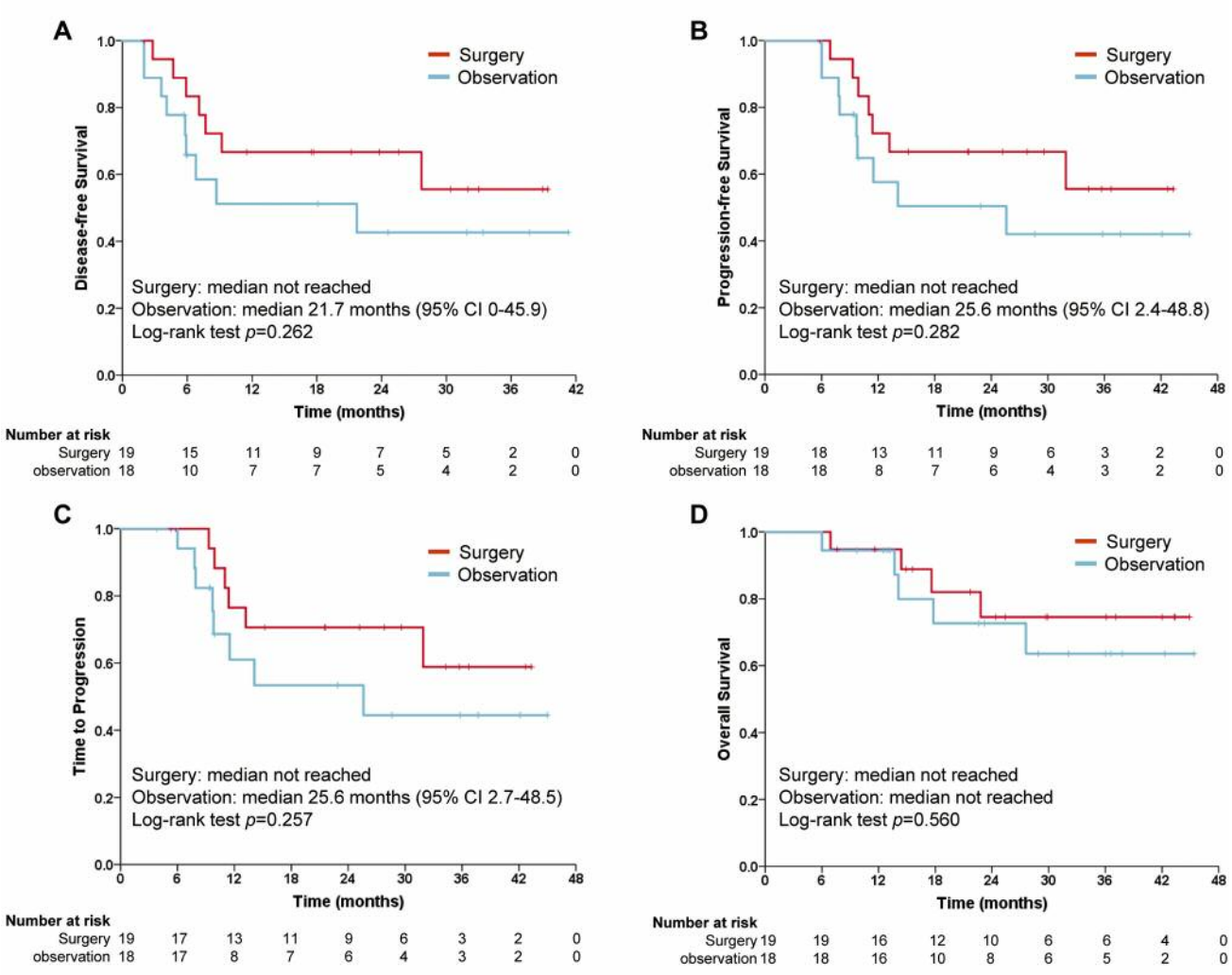

Figure 2. *Continued*

observation arm (p=0.420). The observation arm was more likely to have locoregional-only relapse at the first recurrence than the surgery arm (44.4% *vs*. 15.8%; p=0.056) (Table IV). In the as-treated analysis, the recurrence rate was 23.1% (3 of 13) in the surgery arm and 45.8% (11 of 24) in the observation arm (p=0.288). All 10 locoregional-only recurrences in the observation arm were considered resectable; eight patients underwent surgery (n=7) or endoscopic submucosal dissection (n=1), whereas two patients refused surgery. In those patients who had local therapy for locoregional recurrence during observation, the median OS was 27.6 months (95%CI=7.5-47.7). In the patients who had recurrence during observation, the median time to recurrence after randomization was 5.9 months (95%CI=4.6-7.2).

In the entire populations, when TTP, PFS, and OS were analyzed according to the metabolic response after induction chemotherapy and chemoradiation (Figure 3), there were significant associations between treatment outcomes and metabolic response after chemoradiation (p<0.0001), whereas metabolic response after induction chemotherapy was associated with non-significant trends toward better outcomes.

Discussion

Our results revealed that surgery did not significantly prolong survival compared to observation in ESCC patients who achieved a cCR after induction chemotherapy and chemoradiation. Although DFS, PFS, and TTP tended to be better in the surgery arm than in the observation arm, the differences were not statistically significant. In particular, OS was similar between the two arms in both the intent-to-treat and as-treated analyses. The recurrence rate was numerically higher in the observation arm than in the surgery arm [44.4% *vs*. 31.6% in the intent-to treat analysis (p=0.420); 45.8% *vs*.

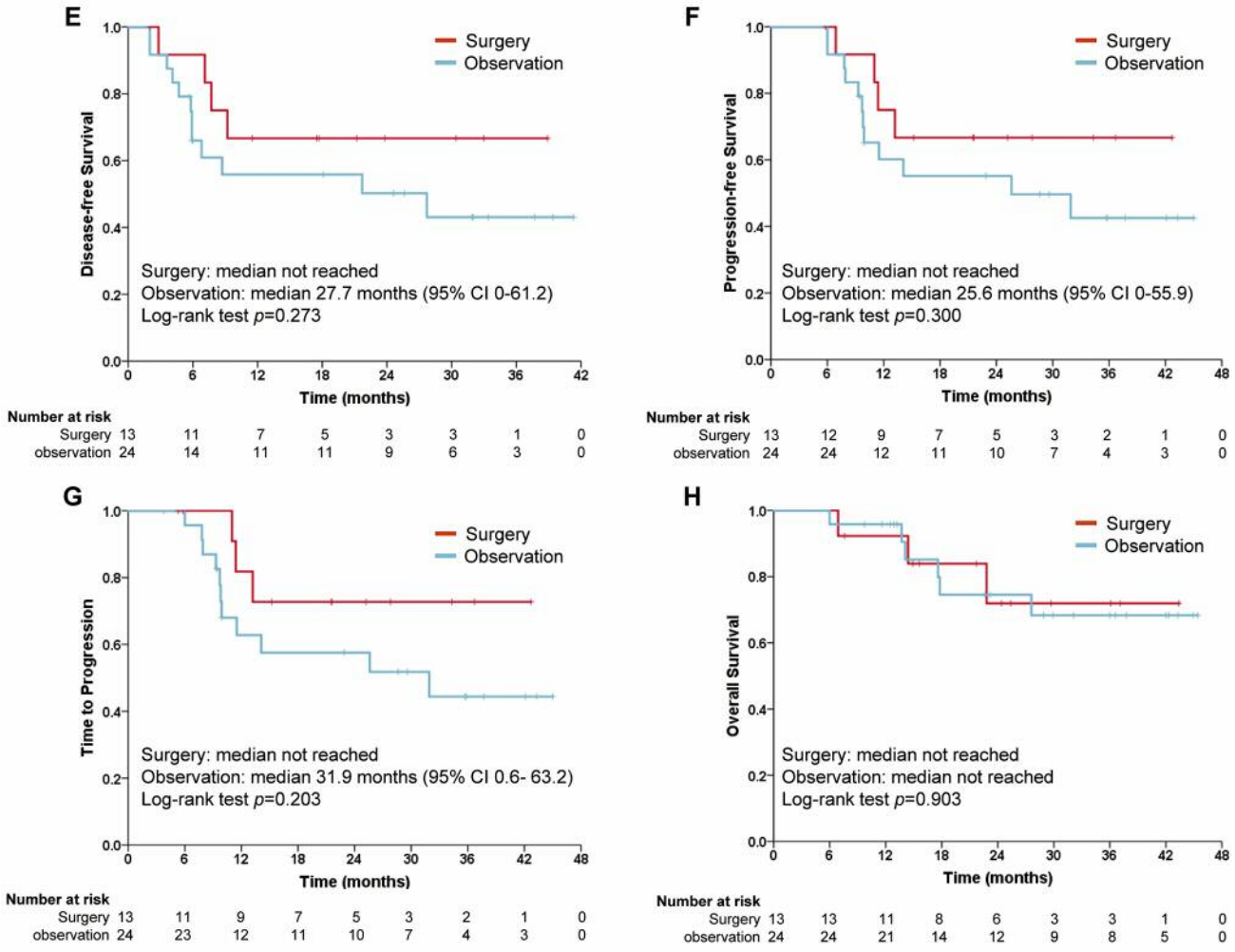

Figure 2. *Disease-free survival, progression-free survival, time to progression, and overall survival according to treatment arm in the intent-to-treat analysis (a-d) and in the as-treated analysis (e-h) for the randomized patients.*

23.1% in the as-treated analysis (p=0.288)], but most recurrences in the observation arm were resectable locoregional recurrences. Therefore, most patients (72.7%) who had recurrence during observation could undergo salvage surgery or curative endoscopic dissection. This might have contributed to the lack of difference in survival between the two arms. In addition, a higher surgery-related mortality rate in the surgery arm (5.3% *vs*. 0% in the intent-to-treat analysis; 7.7% *vs*. 0% in the as-treated analysis) might have negatively impacted survival in the surgery arm. Further research is needed in order to understand how minimally invasive esophagectomy affects the risk benefit ratio for surgery *vs*. surveillance in this setting (14).

Our results are consistent with those of previous studies comparing chemoradiation with or without surgery in EC. In a randomized phase III study by Stahl *et al*. (8), 172 patients with thoracic ESCC (cT3-4/N0-1/M0) were randomized to induction chemotherapy followed by chemoradiotherapy (40 Gy) and surgery or the same induction chemotherapy followed by chemoradiotherapy alone (≥65 Gy). Chemoradiotherapy alone resulted in an equivalent OS to chemoradiotherapy plus surgery (14.9 *vs*. 16.4 month; p=0.007 for equivalence test) with less treatment-related mortality (3.5% *vs*. 12.8%; p=0.03). In a larger randomized phase III study (FFCD 9102), 259 patients with thoracic EC (mostly squamous cell carcinoma) (cT3/N0-1/M0) were randomized to continued chemoradiation or surgery once they achieved a clinical response to induction chemoradiation (9). Chemoradiation alone was equivalent to chemoradiation plus surgery in terms of OS (19.3 *vs*. 17.7 months; p=0.49) with a low 3-month mortality rate (0.8% *vs*. 9.3%; p=0.002) and shorter hospital stay (52 *vs*. 68 days; p=0.02).

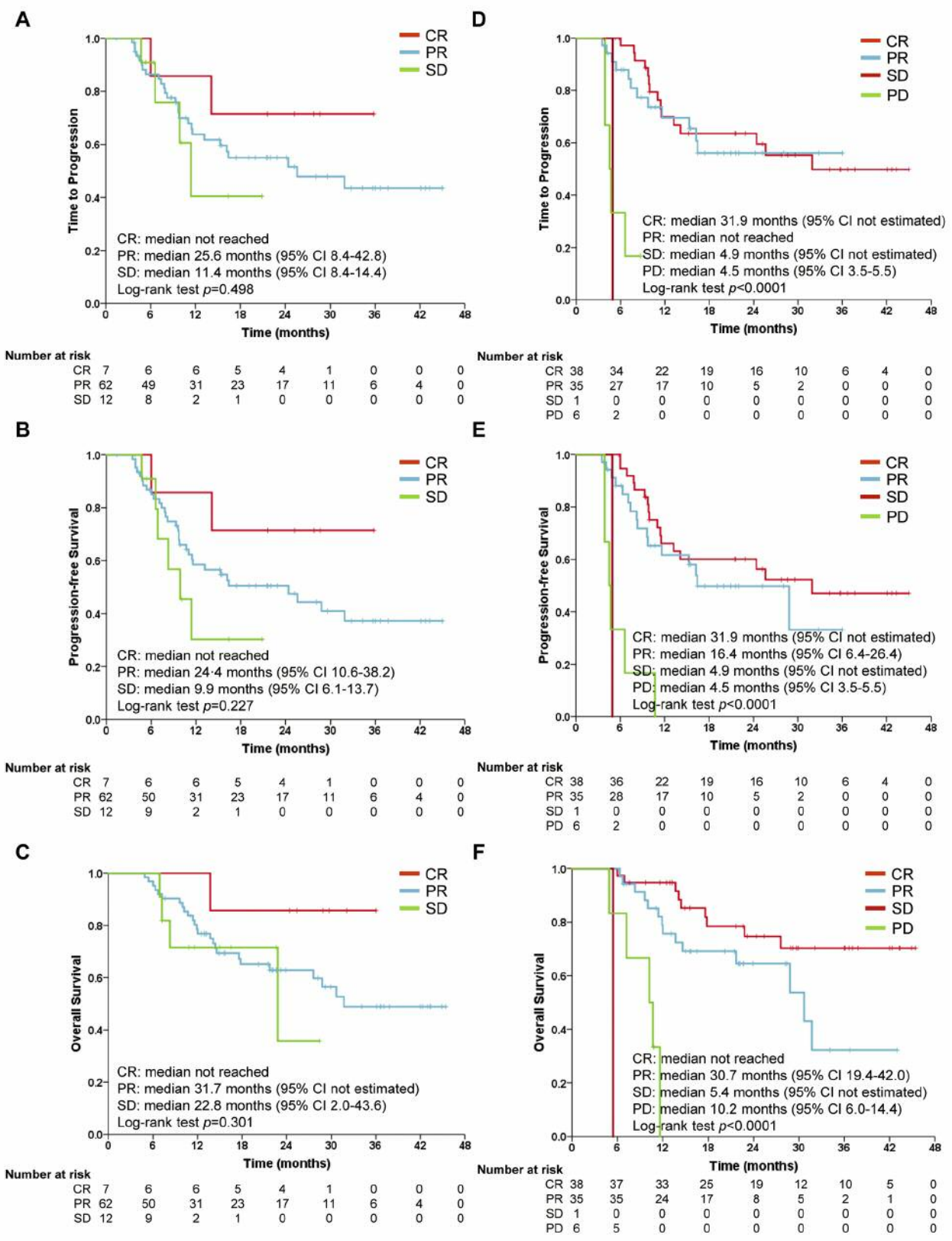

Figure 3. *Time to progression, progression-free survival, and overall survival according to the metabolic response after induction chemotherapy (a-c) and chemoradiotherapy (d-f) in all eligible patients. CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease.*

Table IV. *Failure patterns*.

	Intent-to-treat analysis				As-treated analysis		
	Entire population (n=82)	Surgery (n=19)	Observation (n=18)	*p*-Value	Surgery (n=13)	Observation (n=24)	*p*-Value
Alive	52 (63.4%)	15 (78.9%)	13 (72.2%)	0.736	10 (76.9%)	18 (75.0%)	0.465
Without recurrence or disease progression	41 (50.0%)	12 (63.2%)	9 (50.0%)		9 (69.2%)	12 (50.0%)	
With recurrence	11 (13.4%)	3 (15.8%)	4 (22.2%)		1 (7.7%)	6 (25.0%)	
Deaths	30 (36.6%)	4 (21.1%)	5 (27.8%)	0.762	3 (23.1%)	6 (25.0%)	0.744
Cancer-related	19 (23.2%)	3 (15.8%)	4 (22.2%)		2 (15.4%)	5 (20.8%)	
Surgery-related	6 (7.3%)	1 (5.3%)	0 (0%)		1 (7.7%)	0 (0%)	
Other cause	2 (2.4%)	0 (0%)	1 (5.6%)		0 (0%)	1 (4.2%)	
Unknown	3 (3.7%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
First failure pattern				0.056			0.067
Locoregional relapse	13 (15.9%)	3 (15.8%)	8 (44.4%)		1 (7.7%)	10 (41.7%)	
Distant metastasis	4 (4.9%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Locoregional relapse + distant metastasis	3 (3.7%)	3 (15.8%)	0 (0%)		2 (15.4%)	1 (4.2%)	

Data are numbers (%).

The role of surgery is more controversial in patients achieving a cCR after chemoradiotherapy because they have favorable survival regardless of whether they undergo surgery (15-17). This issue will bring forth more attention when increased cCR is achieved with incorporation of immune checkpoint inhibitors in the neoadjuvant setting (18, 19). A retrospective study by Castoro *et al*. (15) showed that there were no significant differences in 5-year OS (50.0% *vs*. 57.0%; p=0.99) and 5-year DFS (55.5% *vs*. 34.6%; p=0.15) between chemoradiotherapy plus surgery and chemoradiotherapy alone in thoracic ESCC patients obtaining a cCR after chemoradiation. Although the recurrence rate was numerically higher in chemoradiotherapy alone than in chemoradiotherapy plus surgery (58% *vs*. 44%; p=0.25), 36.6% patients in the chemoradiation alone group had R0 salvage surgery at recurrence. A recent meta-analysis also showed that the addition of surgery to thoracic locally advanced EC patients with a cCR after neoadjuvant chemoradiotherapy provided no advantage to long-term survival (HR=1.361, 95% CI=0.572-3.239; p=0.486), while 2-year DFS could be improved (HR=3.186, 95%CI=2.071-4.901; p=0.000) (20). These results along with ours suggest that watchful waiting then salvage surgery at recurrence could be a treatment option in the setting of cCR after chemoradiation. However, considering that patients in our study who underwent delayed salvage surgery were less likely to receive R0 resection and had significantly higher pathologic stages than patients who underwent immediate surgery after chemoradiation, close monitoring for early detection of recurrence may be needed during the observation period. Given that the median time to recurrence after randomization was 5.9 months (95%CI=4.6-7.2) in patients who had recurrence during observation under a follow-up schedule involving endoscopy and CT scans every 6 months, more frequent, short-term follow-up strategies need to be considered, particularly in the early observation period after cCR achievement.

On the other hand, because surgery after chemoradiation was associated with less local recurrence, less dysphagia before death (46% *vs*. 63%; p=0.04), and less requirement for procedures for dysphagia (24% *vs*. 46%; p<0.001) compared with chemoradiation alone in the FFCD 9102 study (9), there may be a role for surgery even in patients responding to chemoradiation. Furthermore, a retrospective case-control study suggested the survival benefits of surgery in patients who had a cCR after chemoradiation and were fit for surgery compared with surveillance (5-year OS, 58.9% *vs*. 33.4%; p=0.001) (21). In contrast to our study, this study included adenocarcinoma (15.9%) as well as squamous cell carcinoma (84.1%) and did not always use PET to assess cCR. To further optimize the treatment decision for individual patients, predictive factors for treatment efficacy and toxicity profiling need to be identified and efficacy and toxicity should be balanced for the two treatment strategies. In particular, a more accurate clinical assessment tool for predicting pCR and long-term survival after chemoradiation would help in the therapeutic decision making. A recent systemic review and meta-analysis suggested insufficient accuracy of endoscopic biopsies, endoscopic ultrasonography, and ^{18}FDG-PET(-CT) as single modalities for detecting residual disease after neoadjuvant chemoradiotherapy for EC; pooled sensitivities and specificities were 33% and 95% for endoscopic biopsies, 96% and 8% for qualitative endoscopic ultrasonography, 74% and 52% for qualitative PET, 69% and 72% for PET-SUVmax, and 73% and 63% for PET-%ΔSUVmax (22). In

our study using the combination of endoscopy with biopsy, chest CT, and PET-CT, the sensitivity, specificity, and accuracy of residual disease detection was 82.8%, 53.3%, and 72.7%, respectively, and a miss rate of residual disease was 39% (5 of 13). A Dutch prospective cohort study (preSANO) suggested that the miss rate for residual disease (>10% residual carcinoma in the resection specimen) using endoscopy with regular biopsy and fine-needle aspiration of suspicious LNs decreased from 31% to 10% after introduction of bite-on-bite biopsies, and the negative predictive value increased from 35% to 45% (23). For any residual disease (>0% residual carcinoma), however, this diagnostic strategy still had a high miss rate of 55% (23). The ongoing, randomized, phase III SANO trial has incorporated this diagnostic strategy and is comparing active surveillance with standard surgery in patients who achieve cCR after neoadjuvant chemoradiotherapy (24). Novel biomarkers such as circulating tumor DNA are an intriguing research area in predicting pCR and monitoring disease recurrence in the post-chemoradiation period.

A limitation of our study is the small sample size and because of that, this study is underpowered for drawing conclusions. Although we designed a high-volume single-institutional trial to avoid inevitable differences in surgical techniques among surgeons from a multi-institutional trial, a high rate of non-adherence to treatment assignment in the surgery arm led to early study closure. This high rate of drop-out for assigned treatment was attributed to 1) timing of randomization which was performed after obtaining cCR with chemoradiation while patient consent was obtained before initiating study treatment, and 2) change in treatment patterns in South Korea where non-surgical approach in locally advanced esophageal cancer is more often used than before. Another limitation includes that quality of life data were not available due to a low response rate.

In conclusion, our study suggests that close observation with salvage surgery as appropriate might be a reasonable option in patients with thoracic ESCC achieving a cCR to chemoradiation. Further large-scale prospective studies are necessary to confirm our results and optimize the treatment decision in individual patients.

Conflicts of Interest

The Authors declare no conflict of interest relevant to this article.

Authors' Contributions

DHY, JHK, YHK, HYK, and SBK contributed to study design. SRP, DHY, JHK, YHK, HRK, HJL, HYJ, GHL, HJS, DHK, KDC, JHL, JYA, JSR, KJC, and SBK contributed to data collection. SRP, DHY, and SBK contributed to data analysis and interpretation. All Authors read and approved the final manuscript.

Acknowledgements

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Received June 30, 2019
Revised July 29, 2019
Accepted August 1, 2019