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Improved prognosis with induction chemotherapy in pathological complete responders after trimodality treatment for esophageal squamous cell carcinoma: Hypothesis generating for adjuvant treatment

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A B S T R A C T

Purpose: To compare the locations of recurrences and survival outcomes in esophageal squamous cell carcinoma (ESCC) patients with pathological complete response (pCR) after neoadjuvant concurrent chemoradiotherapy (CCRT) with or without preceding induction chemotherapy (IC) followed by esophagectomy.

Methods: Among 276 patients with locally advanced ESCC undergoing trimodality treatment during 2004–2014, 94 (34.1%) with pCR were eligible. The cohort included 26 patients undergoing IC before CCRT (IC group), and 68 patients who did not receive IC (non-IC group).

Results: At a median follow-up of 51.4 months (95% confidence interval; 42.9–62.1), 19 patients experienced recurrences. There was a trend toward fewer distant failures in the IC group (0% vs.14.7%, $p = 0.057$), while locoregional recurrence was similar (7.7% vs. 7.4%). IC was associated with significantly improved survivals with the 5-year RFS and OS rates for the IC group of 85.1% and 90.5%, respectively, compared to of 46.2% and 48.1% for the non-IC group ($p = 0.008$ for RFS, and $p = 0.015$ for OS). By multivariable analyses, IC remained the only significant factor associated with survivals (HR:0.18 for RFS, $p = 0.020$ and HR:0.18 for OS, $p = 0.025$). The effect of IC in the whole cohort, irrespective of pathological response, was also assessed. Patients with non-pCR in the IC group had a trend toward worse survivals compared to the non-IC group

Conclusions: In ESCC patients with pCR after trimodality treatment, IC was associated with favorable survivals. The benefits of IC might be a hypothesis generation for adjuvant treatment for patients with pCR.

Introduction

Esophageal cancer is the 6th most common cause of cancer death worldwide [1]. Trimodality treatment with neoadjuvant concurrent chemoradiotherapy (CCRT) followed by esophagectomy offers a convincing survival benefit [2,3] and is becoming the standard of care for locally advanced esophageal cancer, especially for esophageal squamous cell carcinoma (ESCC) [2]. Neoadjuvant

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CCRT yields a pathological complete response (pCR) in 18–52% of patients undergoing trimodality therapy and a significantly higher 5-year survival rate in patients with pCR than in patients with residual disease [4–7]. However, 14–39% of patients achieving pCR eventually experience recurrences, with the majority (44% up to 90%) of relapses occurring at distant sites [4,5,7–11].

Several studies have investigated prognosticators in patients with pCR. Old age [8,10], advanced clinical stages [4], postoperative complications [8], number of dissected lymph nodes [12], and histology of adenocarcinoma [8] were associated with more recurrences and worse survivals. However, variations in treatment protocol, radiation dose, and chemotherapy regimen complicate the interpretation of prognosticators. Most importantly, no clinical or treatment factors have been identified for possible improvement on the systemic control after an effective trimodality treatment.

ESCC is a notorious disease associated with distant spread. Induction chemotherapy (IC) prior to neoadjuvant CCRT may provide additional disease control, especially for the patients who are responsive to chemotherapy/radiotherapy. Previous researches revealed that IC before neoadjuvant CCRT was associated with improvements on pCR rate and survivals [13,14]. A prognostic scoring model for adenocarcinoma have also been developed, characterizing high-risk patients who might get the most benefits from additional IC [15]. There is, however, no exploration on the effects of IC in pathological complete responders. We hypothesize that IC might be associated with improved outcomes in patients with pCR, who pose unique sensitivities to preoperative CCRT. The present study sought to compare the locations of recurrence and survival outcomes of ESCC patients achieving pCR after IC and neoadjuvant CCRT followed by esophagectomy, with patients undergoing trimodality treatment without IC.

Methods and materials

Patients population and pre-treatment workups

From 2004 to 2014, a cohort of 276 patients with locally advanced ESCC treated by trimodality therapy was retrospectively investigated. Pre-treatment evaluations included complete medical history, physical examination, esophagram, computed tomography (CT) of the chest and abdomen, endoscopic ultrasonography (EUS), and pulmonary function tests. ^{18}F-FDG-PET (PET) was initially optional and became mandatory after 2007. Patients were eligible with clinical stage T3-4 or N+ disease, without any distant lymph node or metastasis shown on CT or PET, which excluded patients of the 6th edition of the American Joint Committee on Cancer (AJCC-6) M1a/M1b stages. At the time of the analyses, diseases were (re) staging according to the latest AJCC-8 system. Among 276 patients undergoing trimodality treatment, 94 (34.1%) patients with pCR on esophagectomy was selected for further analyses.

Chemotherapy

Patients received one of the two regimens for concurrent radiotherapy, as following.

(1) TP-CCRT: weekly TP regimen comprised 1-h IVF of paclitaxel (35 mg/m^2) on day 1 and day 4, 2-h IVF of cisplatin (15 mg/m^2) on day 2 and 5. (2) PF-CCRT: weekly cisplatin 30 mg/m^2 and 5-fluorouracil 450 mg/m^2 started on day 1 of each week.

One cycle of induction chemotherapy before CCRT was given based on medical oncologist's decision or protocol-defined treatment. IC involved paclitaxel 70 mg/m^2 on days 1 and 8, cisplatin 30 mg/m^2 on days 2 and 9, and continuous infusion of fluorouracil 2000 mg/m^2 with leucovorin 300 mg/m^2 for 24 h on days 2 and 9 (TP-HDFL). CCRT would start from day 22 of the IC.

Radiotherapy

All patients were treated with neoadjuvant CCRT, typically by intensity-modulated radiation therapy (IMRT) to a total dose of 40 Gy in 20×2 Gy fractions. Radiotherapy started on day 1 of concurrent weekly TP or PF. Elective nodal irradiation (ENI) was given at the radiation oncologist's discretion. Details of the radiotherapy technique have been previously reported [16,17] and described in the Supplementary material.

Surgery

Surgery with curative intent was performed 4–8 weeks after completion of CCRT. The methods consisted of an Ivor-Lewis procedure with 2- field lymphadenectomy for lower-third tumor, and tri-incision esophagectomy with 3-field lymphadenectomy for upper and middle-third tumor. Tri-incision esophagectomy was the preferred approach for lower-third tumor with proximal extension near carina. All involved nodes ever demonstrated by CT ((short-axis> 1 cm) or PET/CT (SUVmax > 2.5) were excised. Postoperative complications, including pulmonary, gastrointestinal, cardiac, and wound complications were defined and graded in accordance with literature [18,19].

Pathological complete response (pCR)

Resected specimens were fixed in formalin, embedded in paraffin blocks; the blocks were sectioned (5-μm thick); and the sections were stained with hematoxylin and eosin. A pathological complete response was defined as no residual tumor in the esophagus or dissected lymph nodes. Immunohistochemical staining was not performed routinely.

Post-treatment surveillances

No adjuvant treatment was given to any patient with pCR. Patients were followed up with regularly scheduled physical examinations (every 2–3 months) and periodic surveys by esophagogastroduodenoscopy and computed tomography every 3–6 months for 5 years. A PET scan or biopsy of suspected recurrence for histological confirmation was not mandatory but performed as clinically indicated.

Outcome assessment and statistical analysis

Overall survival (OS) was calculated from the date of surgery to the date of death from any cause or the date of last follow-up. Recurrence-free survival (RFS) was calculated from the date of surgery to the date of first observation of any recurrence or death from any cause or the most recent follow-up. Median follow-up was reported with reverse Kaplan-Meier estimate [20]. Categorical variables were compared using the Chi-square test or Fisher's exact test. Survival analysis was performed by the Kaplan–Meier method. Prognosticators for survival-endpoints were assessed by Cox proportional hazards regression model. All statistical tests were two-tailed, with the significance level set at $p < 0.05$. Variables associated ($p < 0.1$) with OS or RFS on univariable analyses, and relevant prognosticators reported in the literature were all included in the multivariable regression model. The analyses were conducted using MedCalc Statistical Software version 16.8 (MedCalc Software bvba, Ostend, Belgium; 2016).

Results

Patients and treatment characteristics

Patient and treatment characteristics are summarized in Table 1. The median age was 57 years (range, 39–79). The cohort included 26 (27.7%) patients undergoing induction TP-HDFL regimen before neoadjuvant CCRT (IC group) and 68 (72.3%) patients who did not receive IC (non-IC group). At diagnosis, most patients had T3 (89.4%) or N1(76.6%) disease. The clinical stage according to the AJCC-8 was IIA-B, III, and IVA (T4 or N3) disease in 6 (6.4%), 81 (86.2%), and 7 (7.4%) patients, respectively. Seventy-three (77.7%) patients received TP-CCRT. The median number of dissected lymph nodes during esophagectomy was 22. The study subjects comprised 35 patients (37.2%) enrolled in two prospective phase II trials evaluating taxane/cisplatin regimens between 2000 and 2005, and 2008 to 2012 [21,22].

As shown in Table 1, there was no significant difference in age, ECOG performance score, tumor locations, clinical stages, maximum of PET standardized uptake value (SUV_{max}), surgery year, surgery method, or rate of postoperative complications of grade 2 or higher between IC group and non-IC group. However, more than

Table 1
Clinical and treatment characteristics of patients.

Factors	Total n = 94, (%)	IC group n = 26, (%)	Non-IC group n = 68, (%)	*p* value
Age (years)				0.294
<60	57 (60.6)	18 (69.2)	39 (57.4)	
≥60	37 (39.4)	8 (30.8)	29 (42.6)	
Gender				0.749
Male	88 (93.6)	24 (94.4)	64 (94.1)	
Female	6 (6.4)	2 (5.6)	4 (5.9)	
ECOG performance				0.951
0–1	61 (64.9)	17 (65.4)	44 (64.7)	
2	33 (35.1)	9 (34.6)	24 (35.3)	
Clinical trial participants				0.002
Yes	33 (35.1)	16 (61.5)	17 (25.0)	
No	61 (64.9)	10 (29.5)	51 (75.0)	
Surgery year				0.558
2004–2010	46 (48.9)	14 (53.8)	32 (47.1)	
2011–2014	48 (51.1)	12 (46.2)	36 (52.9)	
Tumor location				0.587
Upper	29 (30.9)	8 (30.8)	21 (30.9)	
Middle	33 (35.1)	11 (42.3)	22 (32.3)	
Lower-third	32 (34.0)	7 (26.9)	25 (36.8)	
Clinical T stages				0.767
T2	5 (5.3)	1 (3.8)	4 (5.9)	
T3	84(89.4)	23 (88.5)	61 (89.7)	
T4	5 (5.3)	2 (7.7)	3 (4.4)	
Clinical N stages				0.830
N0	4 (4.3)	1 (3.8)	3 (4.4)	
N1	72 (76.6)	20 (76.9)	52 (76.5)	
N2	16 (17.0)	5 (19.2)	11 (16.2)	
N3	2 (2.1)	0 (0)	2 (2.9)	
AJCC-8 clinical stages				0.824
II	6 (6.4)	1 (3.8)	5 (7.4)	
III	81 (86.2)	23 (88.5)	58 (85.3)	
IVA (T4 or N3 disease)	7 (7.4)	2 (7.7)	5 (7.3)	
Concurrent regimen during radiotherapy				
Taxane and platinum	73 (77.7)	25 (96.1)	48 (70.6)	0.008
Platinum and 5-FU	21 (22.3)	1 (3.9)	20 (29.4)	
Surgery method				0.391
Tri-incision	74 (78.7)	22 (84.6)	52 (76.5)	
Ivor-Lewis	20 (21.3)	4 (15.4)	16 (23.5)	
Number of lymph nodes dissected				
<20	36 (38.4)	11 (42.3)	25 (36.8)	
≥20	58 (61.7)	15 (57.7)	43 (63.2)	
Elective nodal irradiation				0.955
Yes	87 (92.6)	24 (92.4)	63 (92.6)	
No	7 (7.4)	2 (7.6)	5 (7.4)	
Postoperative complications				0.732
Yes	12 (12.8)	4 (15.4)	8 (11.8)	
No	82 (87.2)	22 (84.6)	60 (88.2)	
^{18}F-FDG-PET for staging purpose				0.319
Yes	73 (77.7)	22 (84.6)	51 (75.0)	
No	21 (22.3)	4 (15.4)	17 (25.0)	
High^{18}F-FDG-PET SUV_{max} (higher than median)				0.714
Pre-operation				
Yes	24 (47.1)	6 (42.9)	18 (47.4)	
No	27 (52.9)	8 (57.1)ss	19 (52.6)	
Pre-IC or RT				0.659
Yes	30 (44.8)	9 (40.9)	21 (56.7)	
No	37 (55.2)	13 (59.1)	24 (53.3)	

Abbreviations: IC: induction chemotherapy; AJCC: American Joint Committee on Cancer Staging; ^{18}F-FDG-PET: ^{18}F-fluorodeoxyglucose-positron emission tomography; SUV_{max}: maximum of standardized uptake value; 5-FU: 5-flurorouracil; Postoperative complications: complication of grade 2 or higher.

a half (61.5%) of patients in IC group were trial participants, compared to 25% in non-IC group. Besides, patients in IC group more likely to receive TP-CCRT, but not PF-CCRT.

Recurrences and patterns of failure

At a median follow-up time of 51.4 months (95% confidence interval (CI); 42.9–62.1), 19 (20.2%) patients with pCR experienced disease recurrences. The median follow-up time for IC group and non-IC group was 56.7 months (95%CI; 47.9–73.5), and 47.6 months, respectively. The first sites of failure were locoregional in 7 patients, distant in 10, and synchronous local/distant in 2. The most common sites of recurrence were lung and mediastinal node metastasis. Three of 26 patients (11.5%) in the IC group developed recurrences, compared to 16 of 68 patients (23.5%) in the non-IC group did ($p = 0.257$). Table 2 demonstrated the differences in the locations of recurrence between IC group and non-IC group. The locoregional alone recurrence rate was similar between the IC group (7.7%) and the non-IC group (7.4%, $p = 0.996$). There was a no distant failure alone in the IC group, while 14.7% of patients in the non-IC group developed distant metastases ($p = 0.057$).

Survival and prognostic factor analyses

By the time of analysis, 28 (41.2%) patients had died. The causes of death included disease recurrence (n = 19), pneumonia (n = 2), second cancer (n = 3), perioperative mortality (n = 3), and other diseases (n = 1). Postoperative complications of grade 2 or higher occurred in 12 (12.8%) patients. The 5-year RFS and OS rates for all patients with pCR were 57.0% and 60.7%, respectively. The median RFS and OS were not reached. Univariable analyses of prognostic factors associated with RFS and OS are shown in Table 3. IC was significantly associated with RFS ($p = 0.008$) and OS ($p = 0.015$). The 5-year RFS and OS rates for the IC group were 85.1% and 90.5%, respectively, compared to 46.2% and 48.1% for the non-IC group (Fig. 1). There was no significant association between the use of IC and the occurence of postoperative complications (15.4% in IC group vs. 17.8% in non-IC group, $p = 0.732$). Postoperative complication was associated with significantly worse RFS and OS ($p = 0.015$ for RFS, and $p = 0.003$ for OS). High PET-SUV_{max} (higher than median) before IC or RT was associated with inferior survivals with non-significance ($p = 0.075$ for RFS and $p = 0.098$ for OS).

Relevant prognosticators that were reported in the literature [old age ($\geq$60), ECOG performance score, number of dissected lymph nodes <20, concurrent chemotherapy regimen, and clinical T/N stages,] were also included into multivariable analyses, in addition to IC, postoperative complications of grade $\geq$2, high SUV_{max} before IC/RT, and enrollment of clinical trials, (Table 4). IC remained the only significant prognosticator (HR = 0.18 for RFS, $p = 0.020$ and HR = 0.18 for OS, $p = 0.025$).

As most patients in IC-group underwent TP-CCRT, the association of IC and survival outcomes were further checked for patients receiving TP regimen (n = 73). The IC group still demonstrated significantly favorable OS and RFS compared to the non-IC group. The 5-year RFS and OS rates were 85.0% and 90.1%, respectively, for patient receiving IC and TP-CCRT, compared to 39.6% and 43.1%, respectively, for patients receiving TP-CCRT without IC ($p = 0.004$ for RFS and $p = 0.010$ for OS).

With the strong associations of IC and favorable outcomes in patient achieving pCR, we also investigated the effects of IC in the entire cohort, irrespective of pathological response.

Among all the patients undergoing trimodality treatment (n = 276), IC was given in 47 (17.0%) patients. IC was associated with a higher pCR rate (45.3% vs. 33.5, $p = 0.005$). In contrast to the improved outcomes in patients with IC achieving pCR, patients with non-pCR in the IC group had a trend toward worse survivals compared to the non-IC group (5-year RFS rate:11.9% vs. 24.7%, $p = 0.093$; 5-year OS rates: 13.4% vs. 32.0%, $p = 0.100$). Across the entire cohort, IC was not significantly associated with survival outcomes (HR = 0.65, $p = 0.096$ for RFS, and HR = 0.70, $p = 0.158$ for OS).

Discussion

In the present cohort, 20.2% of patients with pCR developed recurrences, and distant failures accounted for 13%.The large proportion of distant metastasis is in line with previously published results [4,5,8,9,11]. Notably, there was no distant relapse among patients in the IC group. For patients in the non-IC group, the 5-year survival was 48.1%, which was in line with previous reports [4,5,8,11]. The apparent improvement on survivals associated with IC could be attributed to fewer distant relapses. Pathological complete responders after trimodality treatment are a subgroup with unique biological features, which responded well to modest-intensity preoperative CCRT. The additional one cycle of IC might help eradicate micro-metastasis before neoadjuvant CCRT. Although patients undergoing TP-CCRT were more likely to have induction TP-HDFL compared to those receiving PF-CCRT, survival outcomes did not significantly differ among patients undergoing concurrent TP or PF regimen by univariable and multivariable analyses. Besides, the IC group still demonstrated significantly favorable OS and RFS in patients underwent TP-CCRT.

By contrast, there was a trend toward worse survivals in patients with non-pCR. Our interpretation is that the inherent sensitivity to chemotherapy/radiotherapy is the most important prognosticator for patient undergoing trimodality treatment. If the disease nature responds well to chemoradiation with pCR achieved, the additional IC before neoadjuvant CCRT might facilitate elimination of occult micro-metastasis and therefore extend the survivals. On the other hand, if the inherent response to chemoradiation is not satisfactory enough to achieve pCR, the additional IC before CCRT would carry out a negative impact on survivals. The possible reasons might be the delayed start of locoregional treatment, the attenuation of the dose intensity of CCRT, and the increased postoperative morbidity and mortality. Across our cohort irrespective of pathological response, IC was not significantly associated with survival outcomes, which was compatible with the two small randomized trials failing to demonstrate a survival advantage from IC [23,24]. Interestingly, the Cancer and Leukemia Group B (CALGB) 80803 recently showed the benefits of adaptive CCRT regimen based on FDG-PET response after 2 or 3 cycles of IC [25]. This randomized phase II trial demonstrated a significantly improved pCR rate in the PET

Table 2
The comparison of the first sites of recurrences.

	Locoregional alone recurrence	Distant metastasis alone	Synchronous locoregional recurrence and distant metastasis
IC group (n = 26)	2 (7.7%)	0 (0%)	1 (3.8%)
Non-IC group (n = 68)	5 (7.4%)	10(14.7%)	1 (1.5%)
p value of Fisher's exact test	0.996	0.057	0.479

Abbreviations: IC: induction chemotherapy.

Table 3
Univariate analysis on prognostic factors associated with recurrence-free survival (RFS) and overall survival (OS) of patients.

Factors	RFS		OS	
	5-year survival (%)	*p* value	5-year survival (%)	*p* value
Age		0.715		0.900
≥60 y/o	54.2		59.0	
<60 y/o	60.8		61.9	
Gender (%)		0.296		0.365
Male	56.2		60.1	
Female	66.7		66.7	
ECOG performance		0.919		0.543
0–1	57.8		64.7	
2	55.2		52.5	
Clinical trial participants		0.237		0.437
Yes	64.9		64.3	
No	51.9		58.7	
Surgery year		0.510		0.762
2004–2010	60.6		64.5	
2011–2014	73.7		68.1	
Tumor location		0.472		0.709
Upper	49.9		57.6	
Middle	53.8		62.0	
Lower-third	61.6		61.5	
Clinical T stage		0.232		0.263
T2	100.0		100.0	
T3	52.7		57.6	
T4	80.0		66.7	
Clinical N stage		0.478		0.709
N0	50.0		33.3	
N1	53.8		59.7	
N2	77.3		76.7	
N3	censored		censored	
AJCC-8 clinical stages		0.451		0.516
II	83.3		80.0	
III	53.4		58.8	
IVA (T4 or N3 disease)	85.7		66.7	
Use of induction chemotherapy		0.008		0.015
Yes	85.1		90.5	
No	46.2		48.1	
Concurrent regimen during radiotherapy		0.782		0.902
Taxane and platinum	55.5		60.7	
Platinum and 5-FU	62.4		60.6	
Surgery method		0.558		0.361
Tri-incision	54.5		59.0	
Ivor-Lewis	69.7		64.0	
Number of lymph nodes dissected		0.482		0.273
≥20	58.7		56.8	
<20	58.7		67.2	
Elective nodal irradiation		0.270		0.330
Yes	55.5		59.1	
No	80.0		80.0	
Postoperative complications		0.015		0.003
Yes	62.0		66.2	
No	0.0		0.0	
^{18}F-FDG-PET for staging purpose		0.639		0.780
Yes	54.1		62.2	
No	63.0		59.9	
High ^{18}F-FDG-PET SUV_{max} (higher than median)Pre-operation		0.520		0.229
Yes	47.2		46.5	
No	57.7		76.7	
Pre-IC or RT		0.075		0.098
Yes	47.5		56.9	
No	62.8		67.0	

Abbreviations: AJCC: American Joint Committee on Cancer Staging; ^{18}F-FDG-PET: ^{18}F-fluorodeoxyglucose-positron emission tomography; SUV_{max}: maximum of standardized uptake value; IC: induction chemotherapy; 5-FU: 5-flurorouracil; Postoperative complications: complication of grade 2 or higher.

non-responders when those patients crossed over to alternative chemotherapy during neoadjuvant CCRT. These findings, along with the present results, emphasize the importance of inherent sensitivity when considering any additional chemotherapy or radiotherapy. In this context, adjuvant treatment might be considered in these pathological complete responders with favorable sensitivities to chemoradiation.

The data supporting adjuvant therapy after trimodality treatment are scanty and inconsistent, especially for ESCC [26]. A large National Cancer Database study recently examined the effects of adjuvant chemotherapy following trimodality treatment for resectable gastroesophageal carcinoma, mostly adenocarcinoma

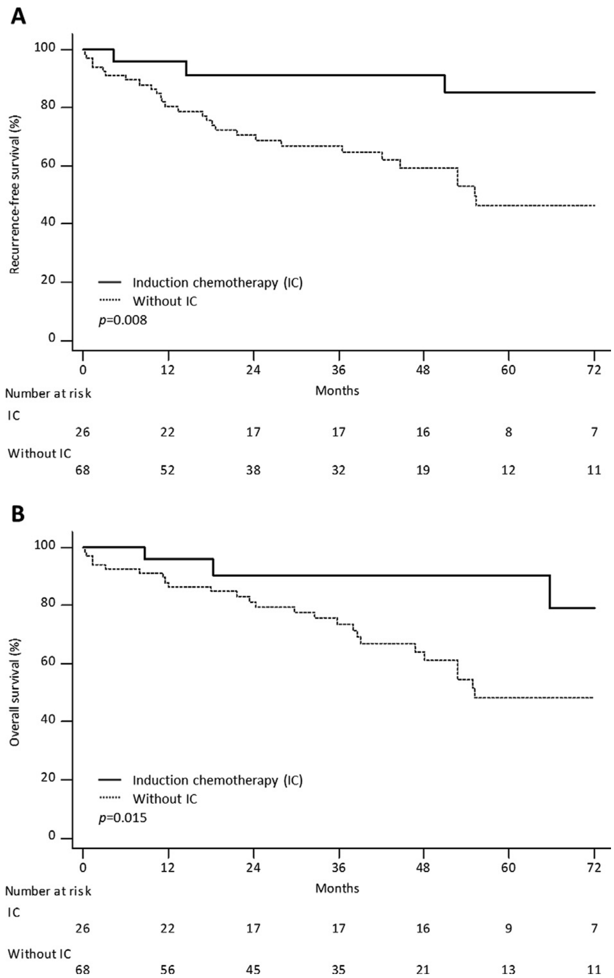

Fig. 1. Kaplan-Meier estimates of (A) recurrence-free survival and (B) overall survival of esophageal squamous cell carcinoma patients with and without induction chemotherapy who achieved complete pathological response to neoadjuvant chemoradiotherapy and esophagectomy.

[27]. Mokdad et al. found that patients treated with adjuvant chemotherapy had improved overall survival compared with those who did not receive adjuvant treatment. Interestingly, the survival benefit was largest, though not statistically significant, in patients with pCR. To the best our knowledge, there is no research specifically investigate the potential benefits of adjuvant treatment in ESCC patients with pCR. Adjuvant treatment after esophagectomy is associated with increased risk of treatment-related deaths [28]. The consideration to administer any adjuvant treatment after such an aggressive surgery should be based on not only the risk of recurrences but also the response rate to the additional regimen. We regard our finding as a hypothesis generation for adjuvant chemotherapy for pCR patients. The attainment of pCR itself is the presentation of inherent sensitivity to chemotherapy. The distinct response to modest-intensity chemotherapy of neoadjuvant CCRT might be a rationale to administer adjuvant treatment on patients with pCR. This concept undoubtedly should be examined by well-designed adjuvant trials in prospective settings.

This study has several limitations. The most importantly, selection bias should always be carefully examined. Some of patients in the study were selected from two clinical trials at a single institution. The subjects selected for trials might differ from the regular patient population. Variables, including enrollment of trials, ECOG score, surgery year, postoperative complications, and other relevant factors have been incorporated for multivariable analyses. IC remains the only significant factor associated with favorable outcomes after the efforts to correct confounders. Although the present study is a hypothesis-driven investigation, the retrospective nature with small number of patients is still with hidden bias.

Second, immunohistochemical staining was not routinely used for pathological confirmation. In the present study, there were only 5 cases utilizing IHC stain for a confirmation, mainly because of suspicious tiny tumor nests in the fibrotic background. Histological analysis with 5-μm section in thickness systemically was performed in the entire surgical specimen. As micrometastasis (<5 mm) to lymph nodes was reported in 25%–65% of patients undergoing esophagectomy [29], an overestimation of pCR might be suspected. To the best of our knowledge, there is no consensus on standardized immunochemical stain with respect to the antibodies, staining technique, and scoring system for a pCR. In the literature assessing prognosticator among pCR, the lack of standardized immunochemistry stain seems a general limitation [8].

In conclusion, the use of IC before neoadjuvant CCRT was associated with much fewer distant relapses, and favorable outcomes in patients with ESCC achieving pCR. Based on the findings, we propose a hypothesis that adjuvant treatment could be considered for ESCC patients achieving pCR after trimodality treatment. Future prospective studies are warranted.

Table 4
Multivariable analysis by Cox proportional-hazards regression models for the association of prognostic factors with recurrence-free survival (RFS) and overall survival (OS).

Factors	RFS		OS	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Induction chemotherapy	0.18 (0.04–0.77)	0.020	0.18 (0.04–0.81)	0.025
High PET-SUV_{max} before IC/RT	2.21 (0.83–5.91)	0.114	2.46 (0.83–7.24)	0.103
Clinical trial participants	0.85 (0.20–3.56)	0.829	1.37 (0.30–6.15)	0.683
ECOG performance >1	0.56 (0.19–1.64)	0.374	0.82 (0.27–2.49)	0.733
Postoperative complications	1.54 (0.18–13s.09)	0.692	1.64 (0.19–14.39)	0.657
Old age (≥60)	1.75 (0.65–4.66)	0.265	2.53 (0.86–7.48)	0.092
Concurrent taxane	3.17 (0.79–12.71)	0.103	2.90 (0.64–13.04)	0.165
Number of lymph nodes dissected <20	0.90 (0.35–2.33)	0.901	0.74 (0.25–2.19)	0.592
Clinical T stage				
(T3/4 vs. T2)	10.54 (0.02–59.40)	0.964	9.18 (0.11–43.63)	0.963
Clinical N stage				
(N2/3 vs. N0/1)	0.45 (0.15–1.36)	0.223	0.62 (0.21–1.83)	0.386

Abbreviations: HR: Hazard ratio; CI: Confidence interval; PET: positron emission tomography; SUV_{max}: maximum of standardized uptake value; IC: induction chemotherapy; RT: radiotherapy; Postoperative complications: complications of grade 2 or higher.

Conflict of interest notificationss

The author indicated no potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.03.020.

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