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Original Article

The impact of pathological complete response after neoadjuvant chemoradiotherapy in locally advanced squamous cell carcinoma of esophagus

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Abstract

Background: The impact of pathological complete response after neoadjuvant chemoradiotherapy on survival of patients with squamous cell carcinoma of esophagus is still controversial. We retrospectively investigated the survival outcome in this group of patients.
Methods: Ninety-eight patients with locally advanced squamous cell carcinoma of esophagus, who received neoadjuvant chemoradiotherapy were included in this retrospective analysis. Treatment protocols were radiotherapy with standard dose 50.4 Gy/28 fr, and chemotherapy with cisplatin 20 mg/m^2 and 5-FU 800 mg/m^2 for 4 days given on week 1 and 5. After neoadjuvant chemoradiotherapy is completed, patients who were eligible for surgery received surgery within 4−6 weeks. Patients who were not suitable for surgery were shifted to definite chemoradiotherapy. The primary end points were overall survival and progression-free survival.
Results: Sixty-eight patients out of the ninety-eight patients received surgery after neoadjuvant chemoradiotherapy. There were 32 patients who achieved pathological complete response with a pCR rate of 47%. Thirty patients were shifted to definite concurrent chemoradiotherapy. The 2-year overall survival rate was 81.3% in the patients whose tumors showed a pCR and 58.3% in the patients with tumors that had a pathological partial response ($p = 0.025$). The 2-year overall survival in patients who received neoadjuvant chemoradiotherapy followed by surgery and definite chemoradiotherapy were 69.1% and 40.0%, respectively. There are 13 patients experienced grade 3−4 adverse event.
Conclusion: Pathological complete response after neoadjuvant chemoradiotherapy is associated with a significant survival benefit in patients with locally advanced squamous cell carcinoma of esophagus. The toxicities related to neoadjuvant chemoradiotherapy were tolerable.

Keywords: Esophageal cancer; Neoadjuvant chemoradiotherapy; Pathological complete response; Squamous cell carcinoma

1. Introduction

Esophageal cancer is a highly lethal disease with a poor prognosis even under adequate treatments. In contrast to most Western countries, squamous cell carcinoma comprised most of the histology subtype of esophageal cancer in Asia. The incidence rate of squamous cell carcinoma (SCC) in esophageal cancer patients was 90.8% in Taiwan in 2010.[1] The 5-year overall survival rate of patients with esophageal cancer after surgery alone was less than 25%. Neoadjuvant chemoradiotherapy (CCRT) had been demonstrated to improve the survival and local control of locally advanced stage of esophageal cancer in several clinical trials and meta-analyses.[2] The rationale for introducing neoadjuvant CCRT for patients who have locally advanced esophageal cancer is to improve the survival of the patients by eradicating microscopic metastasis before radical surgery, and to improve the local

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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control of the disease by increasing the complete resection rate after downsizing and downstaging of the tumor. There are at least two meta-analyses of randomized trials for neoadjuvant CCRT that showed a clear benefit in survival among patients with adenocarcinoma in the comparison of surgery alone.[3,4] Although the pathologic complete response (pCR) of the tumor was found to be as high as 47% with a median survival of 55 months in a phase II study in patients with adenocarcinoma and squamous cell carcinoma (SCC), the impact of pCR on survival in esophageal SCC after neoadjuvant CCRT is still controversial.[5]

This study retrospectively analyzed the results of patients who achieve pCR and who has less than pCR after neoadjuvant CCRT. The purpose of this study was to determine the impact of pCR rate on survival in locally advanced SCC of the esophagus.

2. Methods

2.1. Patient population

From October 2007 to December 2013, 98 patients with histologically proven SCC of the esophagus, AJCC clinical stage T2-4N0-3M0, who received neoadjuvant CCRT at Taichung Veterans General Hospital, were enrolled in this study. All patients were diagnosed by esophagoscopic biopsy. Complete cancer staging surveys were performed in all patients, including history taking, physical examination, laboratory tests, transesophageal endoscopic ultrasound (EUS), chest and abdominal CT scan, barium esophagogram, bronchoscopy, ultrasound of abdomen, and FDG-PET/CT scan. The staging system in this study utilized the seventh edition of the American Joint Committee on Cancer Tumor-Node-Metastasis (TNM) classification.[6] Patients with distant metastatic disease at diagnosis, incomplete treatment, adenocarcinoma histology, chemotherapy regimen other than cisplatin and 5-FU, radiation dose less than 50 Gy or more than 50.4 Gy were excluded from this study. After neoadjuvant CCRT was complete, tumor re-staging surveys included EUS, chest and abdominal CT scan, and FDG-PET/CT scan were performed again to evaluate the treatment response and multidisciplinary team meeting was conducted. Patients with disease progression, poor performance status or refusal to undergo surgery were shifted to definite concurrent CCRT (Fig. 1). All patients were provided written informed consent. This study was a retrospective analysis of information from patients' medical records, pathology databases, and electronic imaging systems.

2.2. Chemotherapy

Chemotherapy was given concomitantly with cisplatin 20 mg/m^2 iv for 1 h and fluorouracil 800 mg/m^2 iv for 24 h daily on Day 1 to Day 4 (cycle 1), and Day 29 to Day 32 (cycle 2) of radiotherapy. Patients who were not suitable for operation were shifted to definite CCRT and two additional cycles of chemotherapy were given using the same regimen as above. Pre-chemotherapy evaluations were performed every time before chemotherapy, including physical examination, vital sign, white blood count, hemoglobin, platelet, liver function, renal functions, chest X-ray, and urine analysis. Chemotherapy was administered only when the patient was without infection sign, and ANC >1500/μL, Hb >10 g/dL, platelet >100,000/μL, as well as normal liver functions and renal functions.

2.3. Radiotherapy

All patients underwent CT simulation in a supine position with their arms above their heads. A customized vacuum bag was used for immobilization. The CT images were taken at a 5-mm thickness throughout the neck and the thorax for upper and middle thoracic tumor or thorax and abdomen for lower thoracic tumor. The gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV) and organs at risk (OARs) were outlined on the CT image. GTV was defined as gross tumor of the esophagus and enlarged lymph node according to the PET-CT scan. CTV was delineated from the GTV plus margin of 1 cm radially, 5 cm margin cephalic and caudal, and including the lymph nodes over the mediastinum and supraclavicular regions for upper or middle thoracic tumors, or the lymph nodes over the celiac trunk area for lower thoracic tumors. PTV was defined as CTV plus 5 mm margin to overcome the daily setup error and internal organ motion.

The intensity-modulated radiation therapy (IMRT) plan using the multiple field technique was delivered to each patient by a linear accelerator (Varian 2100EX with a 120-leaf Millennium multileaf collimator, Varian Oncology Systems, Palo Alto, CA, USA) using 6 MV photons. Dose calculations were performed using the Varian Eclipse planning system (versions 6.5 to 7.2.24) (Varian Medical Systems Inc., Worldwide Headquarters 3100 Hansen Way, Palo Alto, CA 94304, USA) based on the pencil beam model. A total dose of 50−50.4 Gy was prescribed to the PTV such that 95% of the PTV received 100% of the prescribed dose. The dosage constraints for organs at risk (OARs) were <18 Gy for mean lung dose, <20% for lung volume that received >20 Gy (V20), and <15% for heart volume that received >30 Gy (V30), and <50 Gy for the total spinal cord. Radiotherapy was performed 5 days per week, with a daily dose of 180 cGy for a total course of 5−6 weeks (Fig. 2).

2.4. Surgery

Surgery was performed 4−6 weeks after complete neoadjuvant CCRT. The surgical procedure included thoracoscopic esophagectomy, at least 2-field lymph node dissection and esophagus reconstruction with gastric tube. Extended lymph node dissection including mediastinal lymph nodes (Group 2, Group 4, Group 7, Group 8, and other enlarged lymph nodes suspected to be malignant) and bilateral recurrent laryngeal lymph nodes were removed by the chest surgeon. Further, radical neck lymph nodes dissection was performed

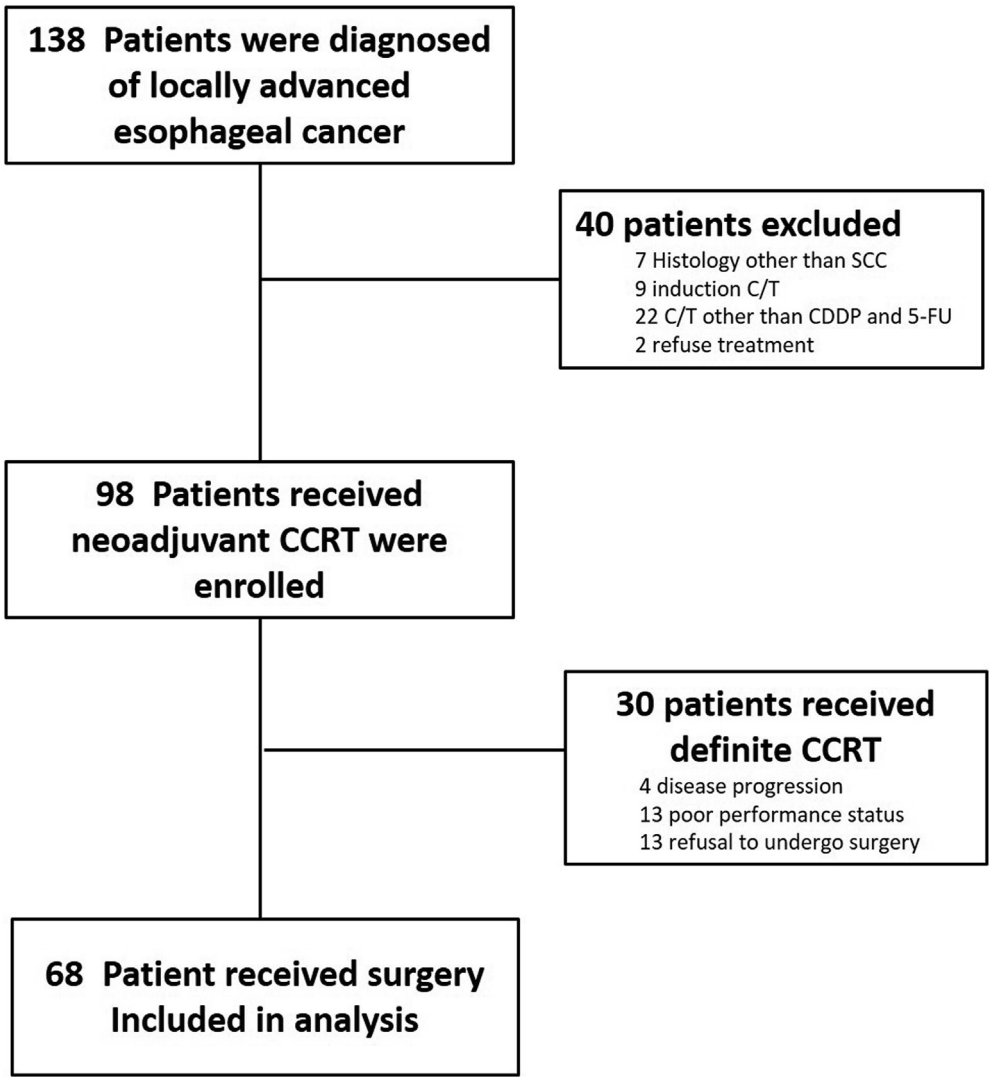

Fig. 1. Trial design.

by an Ear, Nose and Throat (ENT) surgeon if indicated. Reconstruction with gastric tube was pushed through the retrosternal tract in the anatomic plane with the correct axis and was thereafter adequately mobilized. Any abnormal intraoperative finding such as suspected peritoneal seeding or liver metastasis was recorded and removed if possible.

2.5. Pathological analysis

Pathological examination included histology type, tumor extension, lymph node, and resection margin. The treatment response was assessed using the Mandard tumor regression grade (TRG).[7] TRG 1 (complete regression) showed absence of residual cancer; TRG 2 represented rare residual cancer cells; TRG 3 was characterized by an increase in the number of residual cancer cells, but fibrosis still predominated; TRG 4 showed residual cancer outgrowing fibrosis; and TRG 5 showed absence of regressive changes. Pathological complete response (pCR) was defined as TRG 1 plus no positive lymph node, and major response included TRG 1 and TRG 2.

2.6. Follow-up and survival

Patients received follow-up survey including endoscopic examination, chest CT scan, bone scan, liver sonography every 3–4 months in the first 3 years after complete treatment. In the following years, restaging was performed every 6 months till 5 years after treatment. At each visit, the patient was evaluated to assess late toxic effects and disease recurrence. Mortality cases were documented. The severity of toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.3.[8]

2.7. Statistical analysis

The Kaplan–Meier method was used to analyze survival, and comparisons were performed with the log-rank test. The Cox proportional hazards regression model was used to estimate the 95% confidence intervals. The exact χ^2 test was used to compare patient characteristics between pCR and non-pCR group for categorical variables. A p value less than 0.05 was

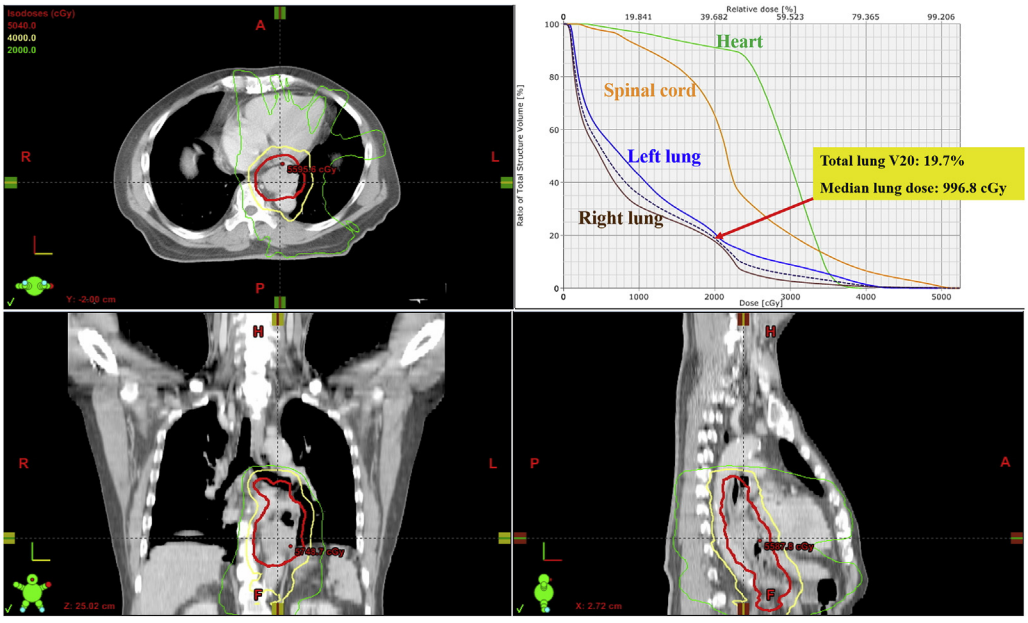

Fig. 2. Example of IMRT dose distribution for esophageal cancer. SCC of esophagus, stage cT3N1M0. Completed neoadjuvant CCRT and received surgery on Aug. 2011, disease free till now.

considered statistically significant. Statistical analysis was performed with the use of SPSS software, version 19.0 (SPSS).

3. Results

3.1. Characteristics of the patients

From October 2007 to December 2013, 98 patients with SCC of the esophagus or gastro-esophageal junction were enrolled in this analysis. For all patients neoadjuvant CCRT followed by surgery was planned. The median follow-up time was 30.0 months (range 3.9–86.2 months). Sixty-eight out of the 98 patients received surgery after neoadjuvant CCRT (resection rate: 69.4%). There were 91.2% of patients received surgery had R0 resection and 8.8% had R1 resection. Thirty patients were shifted to definite concurrent chemoradiotherapy due to disease progression in 4 patients, poor performance status in 13 patients, and refusal to undergo surgery in 13 patients. The median age was 54 years old in the neo-adjuvant CCRT-surgery group, and 55.3 years old in the definite CCRT group. The majority of patients were male (95.5% and 93.3% in each group) and Asian (98.9%). All of the patients (100%) had SCC histology type. Most of the patients had clinical stage III disease (94.9%). The patients' characteristics are shown in Table 1. The overall survival (OS) at 1, 2, 3 and 5 year of patients received CCRT (including patients neoadjuvant CCRT followed by surgery and patients shifted to definite CCRT) were 74.5%, 59.2%, 53.1% and 52.0%. The progression-free survival (PFS) of these patients at 1 and 2 year were 56.1% and 41.8%. The 3-year cumulative incidence rate of local recurrence was 13.3%. The OS at 1, 2, 3 and 5 year of patients who received neoadjuvant CCRT followed by surgery were 79.4%, 69.1%, 61.8% and 60.3%. The PFS of patients who received neoadjuvant CCRT followed by surgery at 1 and 2 year were 67.6% and 52.9%. The 3-year cumulative incidence rate of local recurrence of these patients was 7.4%. The correlation between clinical T stage and overall survival do not showed statistically significant. The OS in cT2, cT3, cT4 were 100%, 79.7%, 66.7% in 1-year; 100%, 68.8%, 66.7% in 2-year and 100%, 60.9%, 33.3% in 3-year. This may

Table 1
Patient characteristics.

Characteristic	Neo-adjuvant CCRT + Surgery (N = 68)			
	Total	pCR (N = 32)	Non-pCR (N = 36)	*P*
Age:				
Median (range)	54 (35–75)	54 (35–75)	55 (35–66)	0.501
Mean (SD)	53.4 (9.1)	54.2 (9.6)	52.7 (8.7)	
Male sex-No. (%)	65 (95.5)	30 (93.8)	35 (97.2)	0.498
Tumor location-No. (%)				0.422
Cervical	1 (1.5)	0	1 (2.8)	
Upper thoracic	8 (11.8)	4 (12.5)	4 (11.1)	
Middle thoracic	32 (47.1)	18 (56.3)	14 (38.9)	
Lower thoracic	24 (35.2)	10 (31.2)	14 (38.9)	
2 site	3 (4.4)	0	3 (8.3)	
Clinical T stage-No. (%)				0.435
T2	1 (1.5)	1 (3.1)	0	
T3	64 (94.1)	29 (90.6)	35 (97.2)	
T4	3 (4.4)	2 (6.3)	1 (2.8)	
Clinical N stage-No. (%)				0.408
N0	3 (4.4)	1 (3.1)	2 (5.6)	
N1	43 (63.2)	18 (56.3)	25 (69.4)	
N2	19 (28.0)	12 (37.5)	7 (19.4)	
N3	3 (4.4)	1 (3.1)	2 (5.6)	
Clinical stage-No. (%)				0.463
IIA	1 (1.5)	1 (3.1)	0	
IIB	3 (4.4)	1 (3.1)	2 (5.6)	
IIIA	40 (58.8)	16 (50.0)	24 (66.7)	
IIIB	18 (26.5)	11 (34.5)	7 (19.4)	
IIIC	6 (8.8)	3 (9.3)	3 (8.3)	

due to small patient number with cT2 (1 patient) and cT4 (3 patient) disease.

3.2. Pathological complete response (pCR)

In the neoadjuvant CCRT plus surgery group, 32 patients achieved pCR, with a pCR rate of 47%. Median OS of patients who achieved pCR and patients who did not achieve pCR were 35.3 months and 22.9 months, respectively ($p = 0.025$). The OS rate at 1, 2, 3 and 5 year was 84.4%, 81.3%, 75.0% and 71.9% in the patients who had a pCR of the tumor, as compare with 75.0%, 58.3%, 50.0%, and 50.0% in the patients who had a pathological partial response. The PFS rate at 1 and 2 year was 81.3% and 75.0% in the patients who had a pCR of the tumor, as compare with 55.6%, and 33.3% in the patients who had a pathological partial response (Fig. 3). The 3-year cumulative incidence rate of local recurrence was 0% in the patients with pCR and 7.4% in the patients who had a pathological partial response.

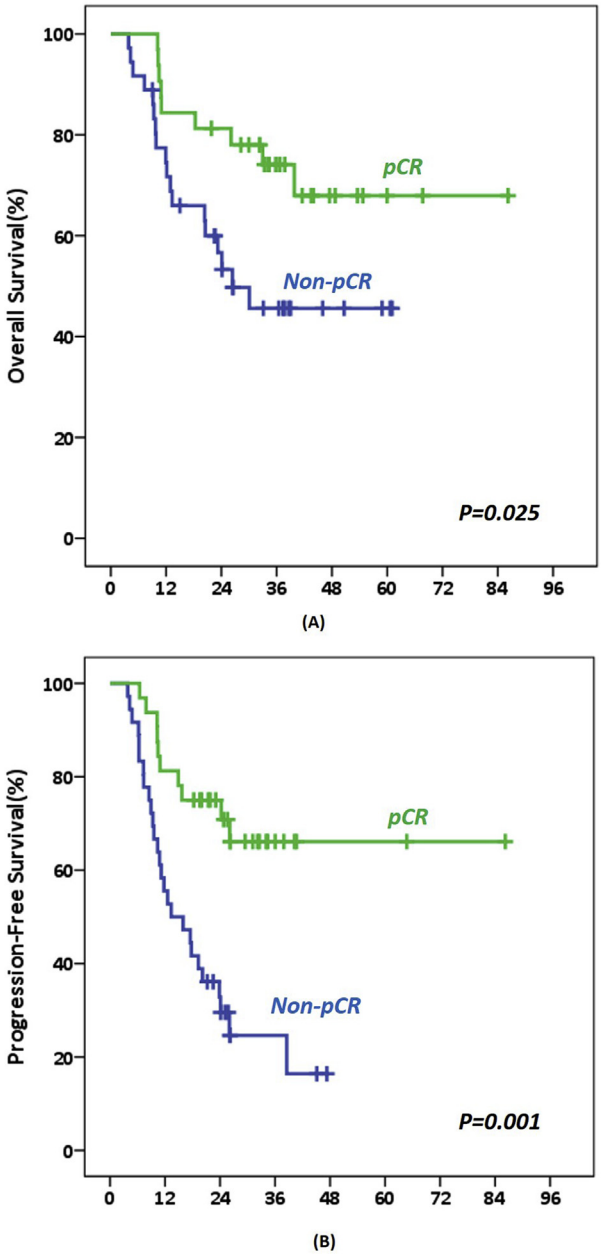

Fig. 3. Survival according to pathological response, PCR and non-PCR. (A) Overall survival; (B) Progression-free survival.

3.3. Toxicity during chemoradiotherapy

Toxicity profile was mild and tolerable, and shown in Table 2. In neoadjuvant CCRT-surgery group, most common grade 3–4 hematologic toxic effects was leucopenia (19.1%), most common grade 3–4 non-hematologic toxic effect was esophagitis (8.8%).

3.4. Post-operative event

The median ICU admission days after surgery was 5 days (2–20 days) in patients received neo-adjuvant CCRT follow by surgery. There is only one patient with stay in ICU for more than 15 days, due to pneumonia and pericardial effusion. There were no post-operative death (<30 days) in patients received surgery, 3 patient developed chylothorax (4.4%), and 12 patient had anastomosis leakage (17%).

4. Discussion

In this study, patients with locally advanced SCC of the esophagus who achieved pCR after neoadjuvant CCRT have significant better overall survival, progression-free survival,

Table 2
Toxicity profile.

Event	Neo-adjuvant CCRT + Surgery (N = 68)
Hematology	
Neutropenia	
Grade 1–2	10
Grade 3	5
Grade 4	7
Anemia	
Grade 1–2	22
Grade 3	–
Grade 4	–
Thrombocytopenia	
Grade 1–2	7
Grade 3	1
Grade 4	–
Non-hematology	
Esophagitis	
Grade 1–2	37
Grade 3	2
Grade 4	–
Lung toxicity	
Grade 1–2	15
Grade 3–4	–
Cardiac toxicity	0
Nausea (all grade)	
Grade 1–2	25
Grade 3–4	–
Vomiting (all grade)	
Grade 1–2	9
Grade 3–4	–

and lower local recurrence rate than those who did not achieve pCR. The two-year overall survival rates of patient achieved pCR and who did not achieve pCR are 81.3% and 61.1% respectively.

The 2-year and 3-year overall survival rate of neoadjuvant CCRT plus surgery group are 70.6% and 63.2% respectively. In our previous study, the 3-year OS of the patient who received post-operative CCRT is 28.1%.[9] When compare with our previous study, neoadjuvant CCRT followed by surgery improve the OS of locally advance esophageal cancer. The two-year overall survival of neoadjuvant CCRT plus surgery group in this study (70.6%) is similar to that of the CROSS trial (neoadjuvant CCRT plus surgery arm: 67%).[10]

In our study, Forty-seven percent of the patients in the neoadjuvant CCRT plus surgery group achieve pCR. The pCR rates in other previous reports with majority histology of adenocarcinoma are around 20%−30%.[10−12] There is a higher pCR rate in this analysis, which may be associated with histological difference (all SCC in this study). In CROSS trial, the pCR rate in adenocarcinoma patients is 23% (28/121), and 49% (18/37) in patient with SCC.[10] A pMR rate upto 60% is reported from a retrospective study analyzed patient with esophageal SCC treated with neoadjuvant CCRT followed by surgery.[13] SCC is considered more radiosensitive and chemosensitive, which also known in other primary site, like SCC of uterine cervix and SCC of head and neck.[14]

In some studies, patients who received neoadjuvant CCRT plus surgery and achieved a pCR had a lower locoregional recurrence rate. In the CROSS trial, the locoregional recurrence rate in the patients who had a pCR of the tumor was 7%, compared with local recurrence rate of 17% for tumors without a pathological complete response.[15] Nevertheless, the superiority of pCR on local control did not reflect the overall survival in some previous studies. In a report by N.K.S. Cheedella et al., the patients with pCR had better recurrence-free survival, but there was no statistically significant difference in overall survival.[11] Our analysis revealed that the patients who had a pCR of the tumor had not only better local control but also better overall survival. The 2-year overall survival rates in patients with pCR and patients without pCR were 81.3% and 61.1%, respectively. This discrepancy may be explained by the difference in the predominant histology type. In the study by Cheedella et al., 91% of patients had adenocarcinoma histology, and 100% of our patients in the present study had SCC.

Clinical tumor responses assessment by PET-CT scan and endoscopic biopsy of esophageal tumor, are routinely performed after neoadjuvant CCRT in our institute. In our previous study, when the difference of standard uptake value (SUV) before and after neoadjuvant CCRT larger than sixty percent indicate better overall survival.[16] According to this finding, surgery should be considered to the patients who have good tumor response (proved by PET-CT scan with ΔSUV >60%).

The chemoradiotherapy-related adverse events in this study were tolerable. A total of thirteen patients experienced grade 3 or grade 4 toxicity, with the most common events being neutropenia and esophagitis. The rate of grade 3−4 neutropenia in the present study was lower compared with the rate reported in the previous study, and the rate of grade 3−4 esophagitis was similar. There is no chemoradiotherapy-related death in this analysis.

There are several limitations in this study including its retrospective design, and single institution. Although there was no statistically significant difference between patient with pCR and non-pCR in baseline characteristics, confounders can still be expected.

In conclusion, neoadjuvant chemoradiotherapy (standard dose of radiotherapy with 50−50.4 Gy in 25−28 fractions, concurrent with a conventional chemotherapy regimen, cisplatin plus 5-FU) followed by surgery have a significant survival benefit in patients with locally advanced SCC of the esophagus. The chemoradiotherapy regimen is associated with an acceptable adverse event rate. Furthermore, the pathological complete response (pCR) is a favorable prognostic factor in patients who received neoadjuvant CCRT followed by surgery.

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