

Survival Between Neoadjuvant and Definitive Chemoradiotherapy In Locally Advanced Esophageal Cancer

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ABSTRACT

BACKGROUND: Most patients with esophageal cancer presented in loco-regional stage and standard treatment involve neoadjuvant chemoradiotherapy (nCRT) followed by surgery. However, when patients have severe medical problems or refuse surgery they will receive definitive chemoradiation (dCRT). Therefore, studies evaluating the necessity of surgery remain of interest.

METHODS: Data were retrospectively collected from locally advanced esophageal squamous cell carcinoma (ESCC) patients at Songklanagarind Hospital from January 2012 to December 2019. All patients received concurrent chemoradiation with platinum and 5-fluorouracil (5FU) based chemotherapy regimens. Then they would be divided into 2 groups (nCRT and dCRT groups). Survival rates in both groups were demonstrated using Kaplan-

Meier curve and factors affecting the log-rank test were compared.

RESULTS: We included 110 patients treated between 2012 and 2019: 22 (20%) with nCRT and 88 (80%) with dCRT. Median OS and DFS were 12 and 7.59 months for nCRT vs. 19.7 and 8.57 months for dCRT (HR 0.7 in OS, 95%CI=0.41-1.22, $p = 0.204$). The prognostic factors included sex, former alcohol consumption and option treatment that were independently associated with OS. **CONCLUSION:** In ESCC patients treated with either nCRT or dCRT showed the similar median OS and DFS in both groups that might cause from more postoperative morbidity or mortality in nCRT patient group. Sex, former alcohol consumption and option treatment were the prognostic factors to the OS in locally advanced ESCC. It responded very well to dCRT which might affect to survival.

Key words: Survival rate; Neoadjuvant chemoradiotherapy; Definitive chemoradiotherapy and locally advanced esophageal squamous cell carcinoma

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INTRODUCTION

Esophageal cancer is a major global health problem, especially in low- and middle-income countries. It constitutes the seventh most common type of cancer and the sixth leading cause of cancer-related death in the world^[1,2]. In Thailand, esophageal cancer is the tenth highest incidence cancer (ASR = 4.1 per 100,000 in male)^[3]. In Asia, esophageal squamous cell carcinoma (ESCC) comprises 80% of esophageal cancer cases^[4] and is associated with smoking and alcohol consumption. Most patients of esophageal cancer who attended the hospital presented loco-regional stage (32%)^[4-7]. In this stage, the standard treatment is neoadjuvant chemoradiotherapy (nCRT) followed by surgery. However, esophagectomy has high morbidity and mortality while the chemoradiotherapy has become

more effective than in the past^[8]. Therefore, studies evaluating the necessity of surgery remain of interest.

In locally advanced cancer, nCRT followed by surgery remains the mainstay of standard treatment among patients at this stage^[9-11]. However, when patients have severe medical problems or refuse surgery, they will receive definitive chemoradiation (dCRT)^[12-14]. Many research studies have reported results among patients receiving nCRT followed by surgery that seem to indicate greater local control and overall survival (OS) than that of patients receiving dCRT^[9,15]. Median OS in the nCRT group is better than that of the dCRT group (3.1 years and 1.0 years)^[16]. Especially, the treatment outcome among patients achieving pathological complete response (pCR) following nCRT will increase 5-year OS when compared with patients without pCR (47.2% and 27.3% respectively, $p = 0.04$)^[17]. Approximately 30 to 50% of these cases reveal no tumor cell in resected specimens, making it doubtful whether the surgery is still needed^[9].

The FFCD 9102 trial showed two-year survival rate was 40% among patients receiving dCRT compared with 34% in the nCRT group^[9]. However, interpreting of these results should be concerned for the presence of potential biases and confounders such as including patients with severe comorbidities or unresectable diseases, differences of radiation dose or studying in adenocarcinomas^[13,14]. Moreover, no appropriate clinical trial has compare nCRT and dCRT among patients with similar baseline characteristics. Therefore, this retrospective study was conducted to compare the survival rate of loco-regional ESCC patients receiving dCRT compared with nCRT. We excluded those patients presenting severe medical problems constituting contraindications of surgery to avoid any selection bias.

MATERIALS AND METHODS

Patients and data

The data were retrospectively collected from locally advanced ESCC patients who received a diagnosis and treatment at Songklanagarind Hospital from January 2012 to December 2019. This study was approved by the Human Research Ethics Committee (HREC), Faculty of Medicine, Prince of Songkla University. We included all patients with a diagnosis of squamous cell carcinoma of the esophagus according to the 7th American Joint Committee on Cancer (AJCC) cancer staging guidelines^[18]. Locally advanced esophagus patients had been defined by T stage 2 to 4 or N positive. Then we excluded patients presenting at least two primary cancers, severe medical problems which contraindicated surgery, unresectable lesions (T4b), lesions at the cervical area and patients not receiving complete treatment protocols. However, our center did not have endoscopic ultrasonography or positron emission tomography to evaluate the staging of esophageal cancer. The patients were determined regarding TNM stages from computed tomography (CT) of the chest and abdomen. Regarding T stages, T1 stage was defined as a normal esophagus and T4b stage was defined in three characteristics from the CT scan. First, the lesion invaded the prevertebral fascia. Second, the lesion encased in the aorta more than 90 degrees. Lastly, the lesion invaded the trachea or main bronchus. The other findings defined T2 to T4a lesions. The N stages were defined as lymph node positive and negative, determined from CT scan.

Treatment protocols

All patients received two cycles of chemotherapy during concurrent chemoradiotherapy (CCRT). In the first cycle, platinum and 5FU chemotherapy were administered on days 1 to 4. In the second cycle, the same regimen was given on days 25 to 28. Total radiation dose of

45-50.4 Gy in 25 to 30 daily fraction was administered. The clinical target volume of the tumor was determined based on the primary site in the esophagus. The irradiation field covers the tumor bed, bilateral supraclavicular fossa, mediastinum, subcarinal area and thoracic paraesophageal lymph nodes area. After treatment, tumor response was evaluated by endoscopy, chest and abdomen CT. Then the patients were asked to choose between two treatment options: surgery or continued chemotherapy without surgery. If the patients decided for surgery, they would be scheduled for operation 4-6 weeks after completing the CCRT (the nCRT group). Secondly, if the patients refused the esophagectomy, they would receive two to four cycles of adjuvant chemotherapy with platinum and 5FU-based regimen with or without salvage esophagectomy (the dCRT group). The pathological results were included tumor size, tumor differentiation, lymphovascular invasion, perineural invasion, circumferential resection margin and margin of resection.

Follow-up

All patients were regularly seen at follow-up examinations. The clinical examinations were recorded each visit at the clinic every three months in the first two years and every six months until three years. Esophagogastroduodenoscopy, chest and abdomen CT scan were performed annually until three years. Biopsy was performed if evidence of recurrence was observed. The local recurrence, distant metastasis data were collected during follow-up. Date of recurrence and recurrent status were retrieved from medical records. All patients' date of death was retrieved from the Cancer Registry of Songklanagarind Hospital.

Statistical analysis

Descriptive data are presented using means and standard deviation in normal distribution data and presented with median and interquartile range in non-normal distribution data. The baseline characteristics in the two groups were compared using the chi-square test, Fisher's exact test or analysis of variance. Disease-free survival (DFS) was calculated from the date of completed treatment in each protocol until the date of local or systemic recurrence. OS was calculated from the date of diagnosis until date of death from any cause or the last follow-up (censor data). DFS and OS were presented using the Kaplan-Meier curve; factors affecting survival were compared using the log-rank test, analyzed using cox regression and presented with hazard ratio and 95% confident interval. All statistical analyses were performed using the R Software with the correlation considered significant at p -value < 0.05 .

RESULTS

From January 2012 to December 2019, 399 patients met the inclusion criteria. Two-hundred and eighty-nine patients were excluded because 107 patients were not fit for the treatment, 54 patients had T4b lesion and incomplete treatment protocol, 40 patients had cervical esophagus cancer and 88 patients had more than two primary cancers (Figure 1). Therefore, 110 patients remained in this study. They were divided in two groups according to treatment protocol. The neoadjuvant chemoradiotherapy group totaled 22 patients and definitive chemoradiotherapy group totaled 88 patients.

Baseline characteristics

Male patients comprised the majority in both groups. Most patients presented dysphagia. Almost one half of the patients in this study could take semisolid but were unable to take any solid food. The

main patients included former smokers and alcohol consumers. Tumor characteristics consisted of greater than T3 lesion and lymph node positive disease. The clinical staging in both groups were similar. The highest number of tumor locations was at the middle and lower thoracic esophagus. All variables in Table 1 did not exhibit any significantly differences excepted age, lymph node and cell differentiation. The mean age in the nCRT group was lower than that in the dCRT group. The dCRT group had N stage higher than the nCRT group. However, the dCRT group had well differentiated cell type more than that of the nCRT group. Baseline characteristics are shown in Table 1.

Tumor response and treatment outcomes

The tumor response and treatment outcomes are illustrated in Table 2. The clinical tumor responses in the nCRT group indicated partial response in all patients in this groups but the majority of patients in the dCRT group had completed and partial responses. Significantly differences were observed in each treatment protocol. One fourth of patients undergoing esophagectomy in the nCRT group and one third of patients undergoing salvage surgery in the dCRT group revealed pathological completed response. However, no significantly difference was found in both groups. Postoperative leakage in the nCRT group was more than the dCRT group of two times (22.7% and 11.1%, respectively). However, nine patients in the dCRT group underwent salvage esophagectomy. Local recurrence and distant metastasis did not indicate any significantly differences. The three-year DFS rates in the nCRT and dCRT groups were 59.1% and 37.5%, respectively. The three-year OS in both groups were equal, exhibiting more than one fourth in both groups. Both DFS and OS did not show any significantly differences.

Survival analysis

The median survival time of DFS in the nCRT group was 7.59 months compared with the dCRT group, of 8.57 months. Nevertheless, during follow-up, the pCR presented not significantly differences in DFS ($p = 0.691$). The 1-, 2- and 3-year DFS were 34, 24, and 18%, respectively in the dCRT group and were 27, 27 and 23%, respectively in the nCRT group, as shown in figure 2. Regarding OS, the median survival time in the nCRT group was 12 months and 19.7 months in the dCRT group which did not exhibit any significantly differences (HR 0.7, 95% CI=0.41-1.22, $p = 0.204$). The 1-, 2- and 3-year OS were 75, 42, and 27%, respectively, in the dCRT group and were 50, 27 and 27%, respectively, in the nCRT group, as shown in figure 3. The analysis of potential prognostic factors demonstrated that former alcohol consumers and circumferential ratio more than 50% significantly differed in both groups. However, the multivariate cox-analysis revealed sex, age and former alcohol consumption were significant factors to predict the survival among these patients. The dCRT group did not indicate any significantly differences for survival (HR 0.57 (95% CI=0.31-1.07), $p = 0.088$) compared with that of the nCRT group.

Results of univariate and multivariate Cox regression analyses are demonstrated in Table 3. All variables in Table 3 were analyzed and dropped out in multivariate cox-analysis. Being male (HR 0.14, $p = 0.047$), former alcohol consumption (HR 7.69, $p = 0.007$) and option treatment (HR 0.52, $p = 0.043$) were significant prognostic factors in locally advanced esophageal cancer.

DISCUSSION

Locally advanced esophagus cancer was the main stage of patients attended the hospital. The nCRT followed by surgery and dCRT were

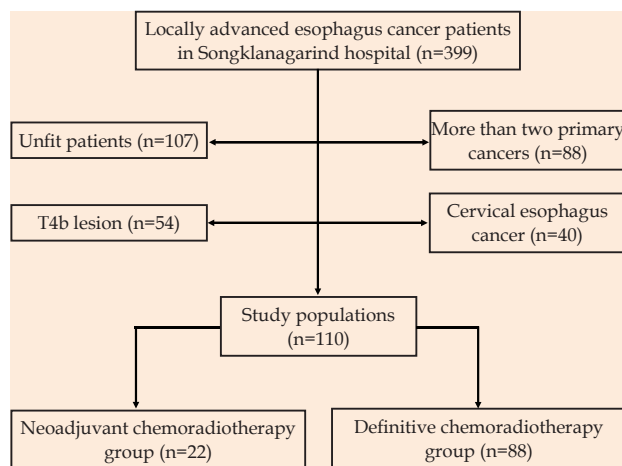


Figure 1 Flow of patients.

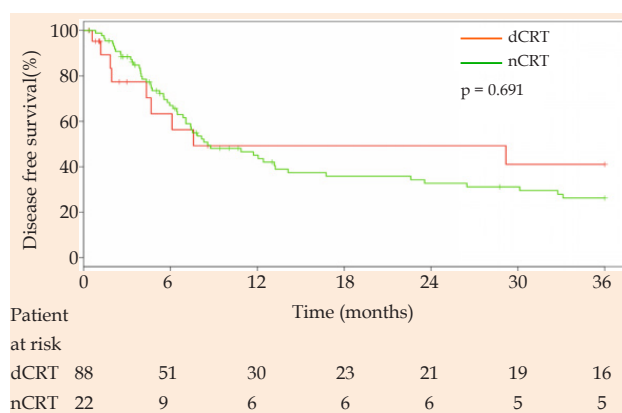


Figure 2 Kaplan-Meier analysis of disease-free survival between nCRT and dCRT groups.

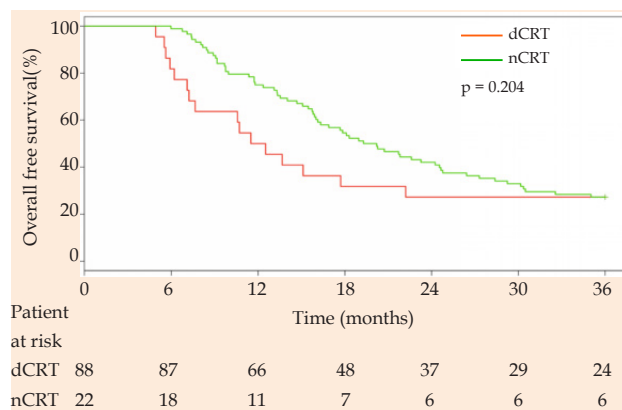


Figure 3 Kaplan-Meier analysis of overall survival rate between nCRT and dCRT groups.

the main treatments in this stage. Our study found that age, clinical N stage and tumor differentiation revealed significant differences between the two treatment groups. The clinical tumor response showed significant differences in both groups. However, local recurrence, distant metastasis, 3-year DFS and OS did not indicate any significant differences in both groups. The multivariate cox analysis showed that sex, former alcohol consumption and option treatment were prognostic factors to survival outcome in locally advanced esophageal cancer. However, age, former smokers and clinical stage did not relate to OS.

Patients' age in the nCRT group was significantly lower than that in the dCRT group. This was similar to a related study^[14]. Younger patients might be healthier than the elderly, so they chose to undergo

Table 1 Baseline characteristics by treatment protocol. (n, %)

Variables	nCRT (n=22)	Dcrt (n=88)	P value
Sex			
Male	21 (95.5)	78 (88.6)	0.69 ^a
Female	1 (4.5)	10 (11.4)	
Age (year, mean (SD))	56.6 (9.6)	63.7 (8.9)	0.001 ^b
Chief complaint			
Dysphagia	20 (90.9)	83 (94.3)	0.143 ^a
GI bleeding	1 (4.5)	1 (1.1)	
Significant weight loss	1 (4.5)	0 (0)	
Dyspepsia	0 (0)	4 (4.5)	
Grade of dysphagia			
Eating normally (I)	2 (9.1)	8 (9.1)	0.395 ^a
Requires liquids with meals (II)	4 (18.2)	6 (6.8)	
Able to take semisolids but unable to take solid food (III)	11 (50)	37 (42)	
Able to take liquids only (IV)	3 (13.6)	27 (30.7)	
Unable to take liquids, but able to swallow saliva (V)	1 (4.5)	6 (6.8)	
Unable to swallow saliva (VI)	1 (4.5)	4 (4.5)	
Former smokers			
Yes	20 (90.9)	78 (88.6)	1.00 ^a
No	2 (9.1)	10 (11.4)	
Former alcohol consumption			
Yes	19 (86.4)	75 (85.2)	1.00 ^a
No	3 (13.6)	13 (14.8)	
Clinical T stage			
2	2 (9.1)	5 (5.7)	0.659 ^a
3	18 (81.8)	70 (79.5)	
4	2 (9.1)	13 (14.8)	
Clinical N stage			
0	8 (36.4)	32 (36.4)	0.024 ^c
1	14 (63.6)	35 (39.8)	
2	0 (0)	21 (23.9)	
Clinical staging			
IB	1 (4.5)	2 (2.3)	0.098 ^a
IIA	2 (9.1)	15 (17)	
IIB	6 (27.3)	14 (15.9)	
IIIA	11 (50)	31 (35.2)	
IIIB	0 (0)	17 (19.3)	
IIIC	2 (9.1)	9 (10.2)	
Circumferential ratio of tumor to esophagus (%)			
26-50	3 (13.6)	18 (20.5)	0.311 ^a
51-75	7 (31.8)	15 (17)	
76-100	12 (54.5)	55 (62.5)	
Tumor location from computed tomography			
Upper thoracic	2 (9.1)	20 (22.7)	0.341 ^a
Middle thoracic	13 (59.1)	37 (42)	
Lower thoracic	6 (27.3)	28 (31.8)	
Esophagogastric junction	1 (4.5)	3 (3.4)	
Tumor differentiation			
Well	1 (4.5)	24 (27.3)	0.013 ^c
Moderate	14 (63.6)	30 (34.1)	
Poor	7 (31.8)	23 (26.1)	
Unknown	0 (0)	11 (12.5)	
RT dose (Gy, median (IQR))	50.2 (50,50.4)	50.4 (50,50.4)	0.248 ^d

Abbreviation: nCRT, neoadjuvant chemoradiotherapy; dCRT, definitive chemoradiotherapy; SD, standard deviation. ^a Fisher's exact test, ^b t-test, IQR, ^c Chi-square test, ^d Rank sum test.

Table 2 Tumor response and treatment outcome by treatment protocol (n, %).

Variables	nCRT (n=22)	dCRT (n=88)	P value
Clinical tumor response			
Complete response	0 (0)	10 (11.4)	0.05 ^a
Partial response	22 (100)	68 (77.3)	
Stable disease	0 (0)	10 (11.4)	
Pathological completed response	6 (27.3)	3 (3.3)*	1.00 ^a
Chemoradiotherapy complications	1 (4.5)	12 (13.6)	0.459 ^a
Postoperative anastomotic leakage	5 (22.7)	1 (1.1)*	0.100 ^a
Local recurrence	7 (31.8)	48 (54.5)	0.095 ^b
Distant metastasis	7 (31.8)	25 (28.4)	0.958 ^b
3-year disease free survival	13 (59.1)	33 (37.5)	0.111 ^b
3-year overall survival	6 (27.3)	24 (27.3)	1.00 ^b

Abbreviation: nCRT, neoadjuvant chemoradiotherapy; dCRT, definitive chemoradiotherapy. ^a Fisher's exact test, ^b Chi-square test. *Patients who underwent salvage esophagectomy = 9 patients.

surgery more than older patients^[19]. The patients presenting more clinical N stage, received dCRT treatment. Elobeidi et al. and Rizk et al. showed that the survival rate of patients with more than four lymph nodes involvement equaled that among patients with M1 disease^[20,21]. The tumor differentiation was a variable which differed in both groups. The majority of tumor differentiation in the nCRT group showed higher grades of tumor differentiation than that in the dCRT group. These tumor differentiations might have exhibited poor response to CCRT when compared with well differentiation^[22]. Therefore, this reason explained that patients with moderate or poor differentiation needed to surgery for treatment^[22].

The clinical tumor showed a complete clinical response of 11.4% in dCRT but 100% of patients in the nCRT group showed a partial response. It could be explained in that patients revealing a clinical complete response would refuse to undergo the surgery. This affected the significant differences between both groups. Nevertheless, the pathologic completed response rates in the nCRT group and among patients in the dCRT group undergoing salvage esophagectomy were 27.3 and 33.3%, respectively. That was similar to related studies^[9,13,23]. The pCR rate was 30 to 50% especially regarding squamous cell carcinoma of the esophagus that was good response to chemoradiation.

The 3-year mortality rate in this study was 72.7% which was equal in both treatment groups. The 3-year DFS was 59.1% in the nCRT and 37.5% in the dCRT group that did not exhibit any significant differences. Moreover, no significant differences were observed in median OS (12 months in nCRT vs. 19.7 months in dCRT) and median DFS (7.59 months in nCRT vs. 8.57 months in dCRT). When compared with the results of the Bedenne et al. study, median survival time was 17.7 and 19.3 months in the nCRT and dCRT groups, respectively, that did not indicate any significant differences in both treatment groups^[9]. From the findings of the Stahl et al. study, no benefit was found among patients receiving surgery after nCRT^[16]. Median survival time of the nCRT group in our study was lower than a related study. It could be explained in that patients in the nCRT group received a higher radiation dose (50 Gy) than standard radiation dose in nCRT treatment (45 Gy). It could have affected the surgery which might have been more difficult and involve more postoperative complications among these patients^[24]. Thus, treatment should be suitably chosen and surgery should be carefully performed especially for those patients receiving a higher radiation dose.

Sex, former alcohol consumption and option treatment were the potential prognostic factors revealed from the cox regression model. The strongest predictor in this study was former alcohol consumption

Table 3 Univariate and multivariate cox regression of potential prognostic factors.

Variables	Univariate		Multivariate	
	Crude HR (95%CI)	P value	Adjust HR (95%CI)	P value
Sex				
Female	1 (ref)		1 (ref)	
Male	1.59 (0.73, 3.45)	0.243	0.14 (0.02, 1.36)	0.047
Age (years)				
< 65	1 (ref)		1 (ref)	
³ 65	1.2 (0.77, 1.87)	0.418	1.46 (0.91, 2.34)	0.116
Grade of dysphagia				
I-III	1 (ref)		-	-
IV-VI	1.07 (0.68, 1.67)	0.783		
Former smokers				
No	1 (ref)		1 (ref)	
Yes	2.2 (0.96, 5.07)	0.063	1.68 (0.44, 6.39)	0.444
Former alcohol consumption				
No	1 (ref)		1 (ref)	
Yes	2.3 (1.14, 4.78)	0.026	7.69 (1.01, 58.38)	0.007
Clinical T stage				
2	1 (ref)		-	-
3,4	1.43 (0.52, 3.91)	0.485		
Clinical N stage				
Negative	1 (ref)		-	-
Positive	1.03 (0.65, 1.63)	0.889		
Clinical stage				
Ib and II	1 (ref)		1 (ref)	
III	1.04 (0.66, 1.64)	0.866	1.13 (0.71, 1.81)	0.61
Circumferential ratio (%)				
≤ 50	1 (ref)		-	-
> 50	1.89 (1.3, 58)	0.05		
Tumor location				
Upper and mid thoracic	1 (ref)		-	-
Lower thoracic	0.9 (0.57, 1.43)	0.669		
Tumor differentiation				
Well	0.67 (0.38, 1.16)	0.153	-	-
Moderate and poor	1 (ref)			
RT dose (Gy)				
< 50	1 (ref)		-	-
³ 50	0.97 (0.45, 2.1)	0.934		
Treatment				
nCRT	1 (ref)		1 (ref)	
dCRT	0.7 (0.41, 1.22)	0.207	0.52 (0.29, 0.95)	0.043

Abbreviation: HR, hazard ratio; ref, reference; RT, radiation; nCRT, neoadjuvant chemoradiotherapy; dCRT, definitive chemoradiotherapy

(HR 8.23, 95%CI 1.07-63.21, $p = 0.006$). From a related study, alcohol was considered a carcinogen of esophagus cancer^[25]. Alcohol causes chronic irritation and inflammation of the esophageal mucosa, and consequently induces a series of molecular changes and causing carcinogenesis^[26]. It produced tumor recurrence and OS of patients^[25]. However, former smokers did not show any significant difference to predict OS in this study. In general, smoking is a strong carcinogen involving many cancers. However, a related study showed that smoking factor was unrelated to survival^[25]. However, smoking affected a systemic response and cell differentiation^[25]. Additionally, sex was a significant prognostic factor in locally advanced esophagus cancer. This result differed that from the Munch *et al.* study which

did not find any relationship between sex and OS^[14]. Our study result might be explained from the confounder among male patients that consumed alcohol. The option treatment constituted the prognostic factor to OS. A related study did not conclude that option treatment affected OS, but affected the local recurrence^[9]. Our study found that nCRT followed by surgery was a poor prognostic factor to OS resulting from surgery. These patients showed postoperative anastomotic leakage resulting in delayed adjuvant treatment or poor survival.

This study was designed to decrease the selection biases and differences between treatment groups according to inclusion and exclusion criteria. All patients presented ESCC of the thoracic and abdominal esophagus. Treatment protocols were similar during the CCRT phase (equal radiation dose in both treatment groups). However, our study encountered many issues. This study involved a single center and enrolled a small sample size especially the nCRT groups. Moreover, this study employed a retrospective design that involved many biases and confounders. Our study included many surgeons which might have affected the oncological outcome based on their surgical experiences. The evaluation after CCRT might have encountered restrictions particularly the endoscopic ultrasonography and positron emission tomography scan was not performed to evaluate the tumor response due to hospital resource limitations. However, our study did not indicate any differences in DFS and OS between nCRT and dCRT groups. The development of radiation techniques and chemotherapy regimens would decrease the complications and produce good treatment outcomes. Therefore, a randomization study should be conducted employing an increased study population to show the necessity of esophagectomy after nCRT in locally advanced esophageal cancer.

CONCLUSION

The ESCC patients treated with either nCRT or dCRT showed the similar median OS and DFS in both groups that might cause from postoperative morbidity or mortality in nCRT group and could influence the OS. The prognostic factors were sex, former alcohol consumption and option treatment to OS in locally advanced esophageal cancer. Especially, squamous cell carcinoma responded very well to definitive chemoradiotherapy which might have affected the survival rate.

Ethical approval

This study was approved by the Human Research Ethics Committee (HREC), Faculty of Medicine, Prince of Songkla University.

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