Original Article

The Outcomes of Multi-Disciplinary Treatment of Esophageal Cancer in Vajira Hospital

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Background: Esophageal cancer is one of the most fatal and difficult-to-treat cancer. Multi-modality management is the key to success of improving outcomes, however, which modality is the most proper is difficult to determine.

Objective: To evaluate the overall survival (OS) of patients with early or locally-advanced (E/LA) esophageal carcinoma treated in Vajira Hospital. The outcomes of the multi-modality management among patients with E/LA diseases were evaluated.

Materials and Methods: The retrospective analyses of esophageal carcinoma patients who attended at Vajira Hospital between January 1, 2012 and December 31, 2016 were performed.

Results: There were 86 patients with complete medical records. The median age was 60.5 years (IQR 52 to 66). Sixty-five patients (75.6%) presented with E/LA diseases. Most of the patients had primary site at thoracic part of esophagus (58 patients, 67.4%) and had squamous cell carcinoma histology (84 patients, 97.7%). Tri-modality treatment including neoadjuvant chemoradiation and esophagectomy for clinically fitted patients without evidence of mediastinal involvement and non-regional lymph node metastasis resulted in the best survival outcome [28.56 months (IQR 10.64 to 46.47)]. The OS of patients with E/LA disease was only 9.15 months (IQR 4.49 to 23.02). Male patients, non-cervical site, and non-surgical treatment were associated with the worse OS.

Conclusion: The outcomes of patients with esophageal carcinoma treated in a real-world practice is still not impressive. Tri-modality management would be the best paradigm; however, it is suitable for well-selected patients.

Keywords: Esophageal cancer, Multi-modality treatment, Real-world practice

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Esophageal carcinoma is the tenth most common cancer in Thailand based on Hospital-based Cancer Registry 2014[1]. It is the world-wide eighth most common cancer and sixth leading cause of death from cancer[2,3]. It is divided histologically into squamous cell carcinoma (SCC) and adenocarcinoma (AC). The SCC is the more commonly diagnosed subtype worldwide, including Thailand. SCC has a greater predilection to occur in the cervical and thoracic part of esophagus, and is associated with tobacco smoking, alcohol consumption, and poor socioeconomic status. On the other hand, AC usually develops in the esophagogastric junction (EGJ) and is more frequently prevalent in the Western countries and associated with obesity, gastroesophageal reflux disease, and the presence of Barrett esophagus[4,5]. Esophageal carcinoma is one of the most difficult-to-treat malignant tumor. Surgery alone leads to the shorter survival among patients with locally advanced (LA) disease (stage II-III). All of the patients need combined modality therapy including preoperative neoadjuvant concurrent chemoradiotherapy (NA-CCRT) to improve survival[6]. Nevertheless, patients with SCC also suffer from smoking-related morbidities that preclude them from curative resection. Definitive concurrent chemoradiotherapy (D-CCRT) is at present the most commonly used, especially in patients with unresectable LA disease and those unfitted to surgery. A meta-analysis performed by Ma and colleagues showed a similar survival outcome between esophagectomy and D-CCRT[7]. The investigators intended to perform a retrospective cohort study of the patients with esophageal cancer treated at Vajira Hospital.

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Objective

The primary outcome was overall survival (OS) of the whole patient cohort. The secondary outcomes included the OS among patients with early or locally-advanced (E/LA) disease and classified based on modality of treatment, the OS of patients with metastatic disease, and the independent risk factors of adverse survival outcome. The OS was calculated as the time from the documented date of the official pathological report of cancer diagnosis to the documented date of death from any causes. It was reported in months and interquartile range (IQR). The exact date of death was determined by requesting the Ministry of Interior's Census database. The present study was approved by the Ethics Committee on Medical Research, Navamindradhiraj University (COA 150/2561) and funded by the Research facilitation Division, Faculty of Medicine Vajira Hospital.

Materials and Methods

The present study was a retrospective cohort study. The participants were the patients with esophageal carcinoma aged 18 years old and older who received medical attention at Vajira Hospital, Navamindradhiraj University between January 1, 2012 and December 31, 2016. The data were retrieved from the hospital's electronic database and written medical records. Any patients with complete official pathological reports and treatment records were eligible for evaluation. The data were censored on December 31, 2016. Staging workup comprised of gastro-esophagoscopy and computer tomography of the thorax and abdomen with contrast study. Bronchoscopy for mid-thoracic tumor was advised, however, it had not been mandatory, until it was recommended in recent years. Tumor staging was determined based solely on the findings from contrast-enhanced computerized topography and classified into E/LA disease and metastatic (M) disease. PET scan and endoscopic ultrasonography with or without fine-needle aspiration biopsy of suspicious malignant lymph nodes were optional and indicated only among patients with potential resectability. The investigators collected demographic data including age, gender, primary site such as cervical, thoracic, or EGJ parts, histopathology as SCC versus AC, stage at presentation, and modality of treatment. Necessity to undergo stenting and gastrostomy as a part of supportive care was also recorded. Pulmonary function testing and cardiologist consultation were obligatory among surgical candidates. The appropriate modality of management was determined by multi-disciplinary cancer care team (MDT) including surgeons, radiation oncologists, and medical oncologists. Among patients with E/LA disease and not amenable to surgery, the definitive chemoradiation as described in the RTOG 85-01[7] protocol was applied. The protocol was radiotherapy, 50 Gy in 25 fractions over five weeks, plus cisplatin intravenously on the first day of weeks 1, 5, 8, and 11, and fluorouracil 1 g/m² per day by continuous infusion on the first four days of weeks 1, 5, 8, and 11. Potential resectability and the necessity of neoadjuvant chemoradiation were decided by the MDT consensus, either concurrent chemo-radiotherapy like the RTOG protocol or the protocol as described in CROSS[8] study was acceptable. The protocol as described in CROSS was weekly administration of carboplatin, the doses titrated to achieve an area under the curve of 2 mg/mL/minute and paclitaxel 50 mg/m² of body-surface area for five weeks and concurrent radiotherapy of 41.4 Gy in 23 fractions, five days per week, followed by surgery. The patients who were candidates for tri-modality management included those who had excellent performance status (ECOG PS 0-1), medically fitted as determined by the pulmonologists and cardiologists as well as no evidence of mediastinal structure invasion and non-regional lymph node metastasis as either evaluated by conventional thoracic CT scan with contrast or PET/CT imaging. The data were censored on December 31, 2019. Dates of death were confirmed with the Ministry of Internal Affair Census Database.

Statistical analysis

The descriptive statistics were reported as percent or median with IQR. Comparing the demographic data between different groups of interest with either Chi-square or t test as appropriate. The survival outcomes were analyzed in intent-to-treat fashion, calculated by using log rank test. Kaplan-Meier method was used to estimate the survival. The OS was the time since the pathological diagnosis was documented to death from any causes and reported in months with IQR and 95% confidence interval (CI). The disease-free survival (DFS) was the time since the pathological diagnosis was documented to the date that recurrence or metastasis was documented or death from any causes, whatever occurred first and reported in months with IQR and 95% CI. Hazard ratio (HR) of DFS, and OS between different groups of interest were calculated using Cox proportional hazard model. According to the study by Teoh et al[9], at least 80 participants were

required for survival analyses. All the statistical data were evaluated using IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA). A p-value of less than 0.05 was considered statistically significant.

Results

Eighty-six patients with complete detailed medical history were analyzed and reported. Baseline patient characteristics including gender, primary site of tumor, histopathology, staging, modality of management, and mode of nutritional support are reported in Table 1.

The median age was 60.5 years (IQR 52 to 66). Seventy-eight patients (90.7%) were male, and eight patients (9.3%) were female. Sixty-five patients (75.6%) presented with E/LA disease. Only six (6.98%) of all participants had ECOG performance status (PS) of 0, 74 (86.5%) had PS 1 to 2, and the rest had PS 3 to 4. The most common sites of metastases were non-regional lymph node, lung, or both. Most of the patients had primary site at thoracic part of esophagus (58 patients, 67.4%). Eighteen (20.9%) and ten (11.6%) had primary site at EGJ and cervical part, respectively. Most of the patients had SCC histology (84 patients, 97.7%). Only two of the eighteen patients with EGJ cancer had AC histology. Either percutaneous endoscopic gastrotomy (PEG) or open gastrostomy was performed for nutritional support. Esophageal stenting was less applied. Definitive chemoradiation (D-CCRT) was the most favorite modality of management in patients with E/LA diseases. Nine, seven, and two patients with E/LA disease underwent neo-adjuvant chemoradiation and esophagectomy (N-CCRT→S), upfront radical esophagectomy, and esophagectomy with salvage chemoradiation (S→S-CCRT) due to positive surgical margins, respectively. Also noted, seven of the 65 patients with E/LA disease received sequential chemotherapy and radiotherapy either due to extreme ages or flail condition. After the median follow-up of five years, the investigators found that D-CCRT led to 8.3 months OS (IQR 4.53 to 12.06). Neoadjuvant chemoradiation and esophagectomy resulted in best OS of 28.56 months (IQR 10.64 to 46.47), however, these were among the highly-selected cases (Table 2, Figure 1). Most of the patients with recurrence or metastasis after treatment with curative intent had more locoregional recurrence (either at primary site or lymph nodes) and occurred within the first year after completed such treatment.

The OS of the whole cohort was only 8.59 months (IQR 4.1 to 17.34). The survival among patients with metastatic disease was quite short [7.9 months (IQR 4.67 to 11.14)]. Such patients received either palliative chemotherapy with either platinum with 5-fluorouracil or a taxane, or sequentially chemotherapy and radiotherapy to relieve the obstructive symptoms. Male patients, non-cervical part of esophagus, AC histology, metastatic disease at presentation, and non-surgical treatment were

Table 1. Baseline demographic data of participants (n=86)

Characteristics	Patients; n (%)
Age (years); median (IQR)	60.5 (52 to 66)
Sex	
Male	78 (90.7)
Female	8 (9.3)
Site	
Cervical	10 (11.6)
Thoracic	58 (67.4)
EGJ	18 (20.9)
Pathology	
Squamous cell carcinoma	84 (97.7)
Adenocarcinoma	2 (2.3)
Stage	
Early/locally advanced	65 (75.6)
Metastatic	21 (24.4)
Stenting	
No	74 (86)
Yes	12 (14)
Gastrostomy	
Not done	20 (23.3)
Done	66 (76.7)
Modality of treatment	
Definitive chemoradiation	40 (46.5)
Neoadjuvant chemoradiation→surgery	9 (10.5)
Surgery only	7 (8.1)
Surgery + salvage CCRT	2 (2.3)
Palliative chemotherapy and RT	10 (11.6)
Palliative chemotherapy only	18 (20.9)
Treatment after recurrent/metastatic disease	4 (4.7)
Palliative chemotherapy	14 (16.3)
Palliative RT	2 (2.3)
BSC	1 (1.2)
Overall survival (months), median (IQR)	8.59 (4.1 to 17.34)
Death	
No	9 (10.5)
Yes	77 (89.5)

EGJ=esophagogastric junction; CCRT=concurrent chemoradiotherapy; RT=radiotherapy; IQR=interquartile range

Table 2. Overall survival outcome stratified based on staging (early/locally advanced vs. metastatic disease) and modalities of management

Modality of treatment	Staging at diagnosis					
	Early/locally advanced disease			Metastatic disease		
	n	Median survival (month)	IQR	n	Median survival (month)	IQR
Definitive chemoradiation	40	8.3	4.07 to 15.31	0	0	0
Neoadjuvant chemoradiation→surgery	9	28.56	13.54 to 78.43	0	0	0
Surgery only	7	7.61	2.49 to 60.82	0	0	0
Surgery and salvage CCRT	2	8.52	8.52 to 10.39	0	0	0
Palliative chemotherapy and RT	3	5.38	3.93 to 6.2	7	6.79	3.41 to 21.02
Palliative chemotherapy only	4	4.69	3.74 to 9.15	14	7.9	5.93 to 10.49
Overall	65	9.15	4.49 to 23.02	21	7.9	4.1 to 14.89

CCRT=concurrent chemoradiotherapy; RT=radiotherapy; IQR=interquartile range

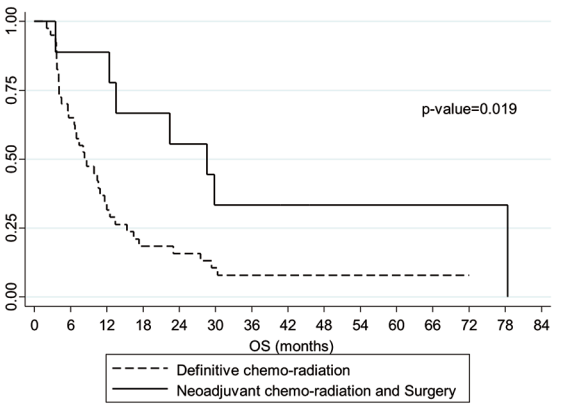

Figure 1. Kaplan-Meier curve of overall survival outcome among patients with early/locally advanced disease who were treated with definitive chemo-radiotherapy compared with those treated with neoadjuvant chemo-radiotherapy and surgery.

associated with adverse OS. However, in multi-variate analysis only male patients, non-cervical part, and non-surgical treatment were associated with worse survival (Table 3).

Serious treatment-related toxicities were paradoxically uncommon, mostly hematologic and electrolyte imbalances (data were not shown), nevertheless, three sudden deaths, presumably because of the mediastinitis from the ruptured esophagus during radiation therapy, were documented. The investigators did not demonstrate the benefit of either an esophageal stenting or aggressive nutritional support by mean of gastrostomy to survival (Table 3). Among patients with metastatic disease, the investigators did not demonstrate the survival benefit of palliative chemotherapy and radiotherapy [OS 6.79 months (IQR 3.41 to 21.02)] over palliative chemotherapy alone [OS 7.9 months (IQR 5.93 to 10.49)], (HR 0.86, p=0.455) (Table 2).

Discussion

In terms of survival, the investigators found that the median OS outcome among the patients with E/LA disease who received definitive chemoradiation (8.3 months) was inferior to the survival among the same patients who received standard radiation dose (50.4 Gy) concurrent with chemotherapy in the landmark Intergroup 0123/RTOG 94-05[10] (18.1 months). The investigators postulated that the flaw of missed pre-operative bronchoscopy for mid-thoracic esophageal cancer would be one of the reasons. Early treatment-related deaths due to mediastinitis, likely from presumed esophageal rupture led to the unexpected worse outcome. Moreover, the investigators assumed that most of the Thai patients were too sick as demonstrated by poor performance and nutritional statuses; however, due to the retrospective design of the present study, the investigators did not collect the baseline data such as albumin level, absolute lymphocyte count, or other surrogate markers of nutritional status determination. Another reason of less impressive outcome would be that most of the participants were under-staged since the re-imbursement policy limited the sophisticated imaging studies like PET scan and trans-esophageal ultrasonography.

The investigators speculated that the tri-modality management including neoadjuvant chemoradiation and then surgery would result in better survival outcome. Among nine patients who underwent tri-modality treatment, the investigators revealed the notable median survival of 28.56 months, even though it did not reach the benchmark survival of the landmark CROSS study of 49.4 months. The better outcome among patients treated with surgery would be as a result of highly-selected patients, or patients with excellent performance status, less

Table 3. Uni-variate and multivariate Cox regression analyses of overall survival

Clinical factors	Uni-variate analysis					Multi-variate analysis		
	n	Median survival (month)	95% CI	IQR	p-value	HR	95% CI	p-value
Sex								
Male	78	8.03	6.38 to 9.68	4.07 to 15.44	0.05	2.86	1.18 to 6.96	0.021*
Female	8	29.34	3.85 to 54.84	9.21 to 33.97		Reference	1	1
Site								
Cervical	10	12.49	0 to 36.57	0 to 10.49	0.029*	Reference	1	1
Thoracic	58	8.95	6.1 to 11.8	4.49 to 17.34		2.28	1 to 5.18	0.049*
EGJ	18	6.3	3.98 to 8.61	3.67 to 9.15		4.92	1.94 to 12.49	0.001*
Pathology								
Squamous	84	8.66	6.28 to 11.03	4.1 to 19.31	0.249			
Adenocarcinoma	2	3.74	0 to 3.74	3.74 to 9.15				
Stage								
E/LA	65	9.15	6.51 to 11.79	4.49 to 23.02	0.156			
Metastatic	21	7.9	4.67 to 11.14	4.1 to 14.89				
Stenting/gastrostomy								
No	15	7.61	3.63 to 11.58	3.51 to 15.44	0.626			
Yes	71	9.15	6.62 to 11.67	4.1 to 19.31				
Paradigm of treatment								
Non-surgical	68	7.9	5.73 to 10.07	4.07 to 14.89	0.017*	2.73	1.48 to 5.03	0.001*
Surgical	18	13.54	0 to 34.4	7.61 to 60.82		Reference	1	1

EGJ=esophagogastric junction; E/LA=early or locally-advanced; IQR=interquartile range; HR=hazard ratio; CI=confidence interval

weight loss, and better pulmonary and cardiac functions. Such highly-selected patients were those who were recruited in the phase 3 clinical trials. The investigators revealed the outcomes of the patients treated in the real-life practices of limited resources. At present, whether the bi-modality definitive concurrent chemoradiation is non-inferior to tri-modality neoadjuvant chemoradiation and surgery is still debatable. The result from FFCD 9102 by Bedenne et al[11] did not demonstrate the benefit of esophagectomy after response to induction chemoradiation compared to continuation to definitive chemoradiation. Ma et al[12] conducted a meta-analysis and revealed that patients with lymph node metastases tended to have a better 5-year overall survival when treated with definitive concurrent chemoradiation than with surgery. Additionally, Western patients who received definitive concurrent chemoradiation had poorer prognoses than patients who underwent surgery. However, the difference between the two methods was not significant. Most of the studies included in this meta-analysis were either not randomized or retrospective ones. The head-to-head comparison between both modalities in a phase 3 randomized study is needed to elucidate this issue.

Regarding the prognostic factors, the investigators unveiled that male patients, non-cervical part, and non-surgical treatment were associated with shorter survival. Venderly et al[13] reviewed the literatures to determine the prognostic factors in patients treated with curative intent. Clinical factors like malnutrition, obesity in non-smoker patients, male gender, extreme aging, poor performance status, multiple co-morbidities, primary site at upper thoracic esophagus, squamous or signet-ring histology, advanced tumor stage, and numbers and sizes of involved nodes were associated with adverse survival. The treatment factors including serious adverse events during neoadjuvant treatment, incomplete resection, anastomotic leakage, or management in low-volume centers were intuitively related to poor survival to multi-modality treatment. Patients with poor socio-economic status or living in rural areas were also among the patients with shorter survival.

The investigators disclosed the extremely short survival among patients with metastatic disease. Combination chemotherapy seemed not to lead to impressive survival compared to other cancers. The investigators suggested the treatment that improve the dysphagia would be the best issue to improve a

patient's quality of life. Esophageal stenting with or without limited field of radiotherapy or endoscopic therapy and palliative chemotherapy would be the best option for such cancer with grave prognosis[14]. However, it is unlikely to be accessible to all patients.

Conclusion

The investigators demonstrated the poor outcome among patients with esophageal cancer treated in a real-life practice. Most of the patients with esophageal cancer have co-morbidities associated with ageing and smoking. The investigators suggest that assessment of associated co-morbidities will guide the physicians to tailor the proper modality of management with tolerable toxicities. The precise imaging techniques accompanied by minimally-invasive biopsy of any suspicious lesions are also advocated prior to multi-modality treatment to exclude a patient with occult metastatic disease from over-treatment.

What is already known on this topic?

Esophageal carcinoma is a difficult-to-treat cancer. Among patients with early or locally advanced disease, the multi-modality treatment leads to improve survival compared to surgery alone.

What this study adds?

The survivals appeared to be less impressive compared to the landmark studies. Tri-modality including neoadjuvant chemoradiation and surgery seemed to be promising, however, it was suitable for well-selected patients. The patients who are candidates for tri-modality management include those who have excellent performance status (ECOG PS 0 to 1), medically fitted as determined by the pulmonologists and cardiologists, as well as no evidence of mediastinal structure invasion and non-regional lymph node metastasis, as either evaluated by conventional thoracic CT scan with contrast or PET/CT imaging. The investigators suggest that any patients amenable to curative surgery need sophisticated functional imaging like PET/CT, trans-esophageal ultrasonography, and fine needle lymph node biopsy to rule out occult non-locoregional disease.

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Conflicts of interest

The authors declare no conflict of interest.

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