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Enteral Access Potentially Endangers Esophageal Carcinoma Patients Under Multi-modality Therapy: A Population-based Study

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Abstract. *Background/Aim: This study aimed to evaluate the clinical outcome of esophageal cancer (EC) patients with enteral access (EA) undergoing multimodality therapy. Patients and Methods: This retrospective study analyzed data between 1997 and 2012 in Taiwan using the National Health Insurance Research Database. Patients with newly-diagnosed EC undergoing multimodality therapy were identified and classified as either EA group or no-EA group. Results: The mortality incidence of EC patients with EA was significantly higher than in no-EA patients. The Cox model revealed the EA group had a higher risk of mortality than the no-EA group. Patients with chronic obstructive pulmonary disease (COPD) were at significantly higher risk of mortality compared to patients without COPD. Conclusion: EA in EC patients undergoing multimodality therapy was associated with an increased risk of mortality.*

Esophageal cancer (EC) is one of the deadliest diseases and is associated with high rates of recurrence and metastasis (1). In Taiwan, it ranked as the ninth most common type of cancer, where squamous cell carcinoma (SCC) accounts for more than 90% of cases (2). After aggressive treatment in EC patients, the 5-year survival rate is rarely higher than 30% (3) and also has the highest risk of malnutrition among different cancer types due to dysphagia (4). Adverse effects and complications of multi-modality therapy can cause or worsen malnutrition in EC patients. As such, many patients are referred for surgically placed feeding tubes or routine enteral access (EA) placement to prevent weight loss and thus reduce the disruption of treatment (5-7).

Research investigating the efficacy of EA in patients with EC has produced inconsistent results (8-13). Despite studies suggesting neoadjuvant therapy has the potential to reduce dysphagia symptoms; the treatment-related adverse events of esophagectomy outcomes were similar for EC patients regardless of EA (8-11). Presently, there is no clinical evidence to infer an association between the use of EA prior to multi-modality therapy and mortality. This population-based retrospective cohort study was conducted to evaluate the efficacy of EA in EC patients treated with multi-modality treatment and its association with mortality.

Materials and Methods

Data sources. Patient data were accessed from The Registry for Catastrophic Illness Patient Database, a subsection of the Taiwanese National Health Insurance Research Database (NHIRD). The NHIRD contains all medical information from the NHI program including (i) outpatient data, (ii) inpatient data, (iii) disease profiles, (iv) drugs prescribed, and (v) intervention procedures. The diagnosis codes are based on the 9th revision of the International Classification of Diseases (ICD-9-CM). To ensure privacy, the individuals' identification is encrypted within the NHI database. This study received approval from the Hualien Tzu Chi Hospital Review Board (IRB number: 102-21).

Study cohort and patient selection. Inclusion criteria consisted of patients who were newly diagnosed with EC (ICD-9 150.1-150.9)

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between January 1, 1997, and December 31, 2012 (Figure 1). Patients were excluded if: (i) they had only received surgical intervention, (ii) only received concurrent chemo-radiotherapy (CRT), and (iii) had previous history of cancer. Eligible patients were classified as either EA insertion (surgery codes 72017C, 73022B, which includes permanent jejunostomy and gastrostomy: EA group) and no EA insertion (No EA group) based on whether or not they received EA insertion undergoing multi-modality therapy for EC. To reasonably compare the two groups, the propensity score (PS) matching (14) at a ratio of 1:1 of EA to no EA patients were employed.

Confounding variables and outcome measures. Potential confounding variables measured included demographic information (gender, age, and monthly income), baseline comorbidities, and treatment modality for EC. Clinical practices for treatment of esophageal squamous cell carcinoma include (i) CRT followed by surgery (S), (ii) surgery followed by CRT (S+CRT), and (iii) CRT followed by surgery and adjuvant CRT (CRT+S+CRT). Baseline comorbidities included: (i) diabetes mellitus, (ii) hypertension, (iii) hyperlipemia, (iv) chronic obstructive pulmonary disease, and (v) Charlson comorbidity index (CCI) score (15). These diseases were determined by at least two outpatient visits or one inpatient visit at least 1 year before enrollment. The study's start and end points are defined as the date of EC diagnosis, to the date of death or December 31, 2012.

Statistical analysis. PS (the predicted probability of EA use) was calculated by logistic regression using; (i) gender, (ii) age, (iii) monthly income, (iv) baseline comorbidity, (v) CCI, and (vi) treatment modality. After PS matching, the balance of covariates was tested through matching procedures using standardized differences (an absolute standardized difference of <20% was considered a negligible imbalance). Survival statistics were calculated using the Kaplan–Meier method, and the log-rank test was used to assess differences in survival between the groups. A Cox proportional hazards model was used to assess the adjusted hazard ratio (HR) and 95% confidence intervals (CI) of mortality. All statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute, Inc., Cary, NC). A p-value of <0.05 indicated statistically significant differences.

Results

A total of 21,471 patients newly diagnosed with EC during 1997-2012 were extracted from the NHIRD. Patients were excluded if: (i) they had a previous history of cancer (ii) received only CRT (iii) received only esophagectomy and supportive care. Among the 3,820 patients treated with multimodal therapy for EC, 2247 were in the EA group and 1,573 in the no EA group. The demographics of the study group are shown in Table I. After PS matching, the differences for each characteristic were found to be low between the groups.

Comparison of the mortality rates between the groups showed that the EA group had a higher mortality rate (44.7 *vs*. 37.0 deaths per 100 person-years, incidence ratio=1.12, 95%CI=1.11-1.32). Kaplan–Meier survival curves showed that the EA group had lower survival than the no EA group (Log-Rank test, p=0.001) (Figure 2). The multivariate Cox proportional analysis of mortality showed that patients undergoing multi-modality treatment with EA were associated with an increased risk of mortality compared to the no EA group (HR=1.13, 95%CI=1.04-1.23) (Table II). Of note, the mortality rate was independently higher in males (HR=1.50, 95%CI=1.20-1.86) and patients with COPD (HR=1.13, 95%CI=1.02-1.26).

Discussion

This study examined the mortality of EC patients with EA undergoing multi-modality therapy based on the NHIRD. After multivariate adjustment, the findings of the study suggested that EC patients undergoing multi-modality therapy with EA showed an increased risk of mortality compared to the no EA patients. In order to prevent treatment-related adverse effects or malnutrition, some centers advocate routine prophylactic pre-treatment EA insertion prior to CRT and surgery (7, 16) The National Comprehensive Cancer Network and European Society for Medical Oncology guidelines recommend EC treatments implement EA for feeding (17, 18). Earlier studies have found improvement in dysphagia post neoadjuvant treatment in patients with EC and the ability to preserve nutritional status without EA (8, 10). One recent study compared changes in nutritional parameters and perioperative complications in EC patients with EA (50/99) and without EA (49/99) after multi-modality treatment (11) and concluded that there were no nutritional or perioperative benefits of EA for EC patients. A prospective study recruited esophageal SCC (ESCC) patients who received an esophageal stent, nasogastric tube, or EA feeding, to compare the changes in nutritional status during CRT. The patients (n=81) were analyzed and all groups showed a similar decrease in mean body weight (BW) with an overall change of –6.41%±5.21% at the end of CRT (19). It must be noted that in these studies, the compared groups showed similar nutritional parameters. The phenomenon reflects the question as to whether patients with normal nutritional status require EA under multi-modality therapy. By contrast, Huerter *et al*. (9) analyzed the nutritional status of 127 patients with EC, with EA (61/127) or no EA (66/127) prior to neoadjuvant therapy. They showed that EA was associated with improved nutrition in patients undergoing CRT who initially presented as malnourished. This finding was supported by our previous retrospective study (13). These findings suggest a potential benefit of EA for malnourished EC patients. Multiple studies investigating EA in EC patients undergoing CRT and its effects on tumor response and patient survival found no positive effect (7-12).

A retrospective cohort study examined EC patients receiving early enteral nutrition (EEN) and total parenteral nutrition (TPN) after esophagectomy and found that EEN reduces postoperative hospital stay and hospital charges of

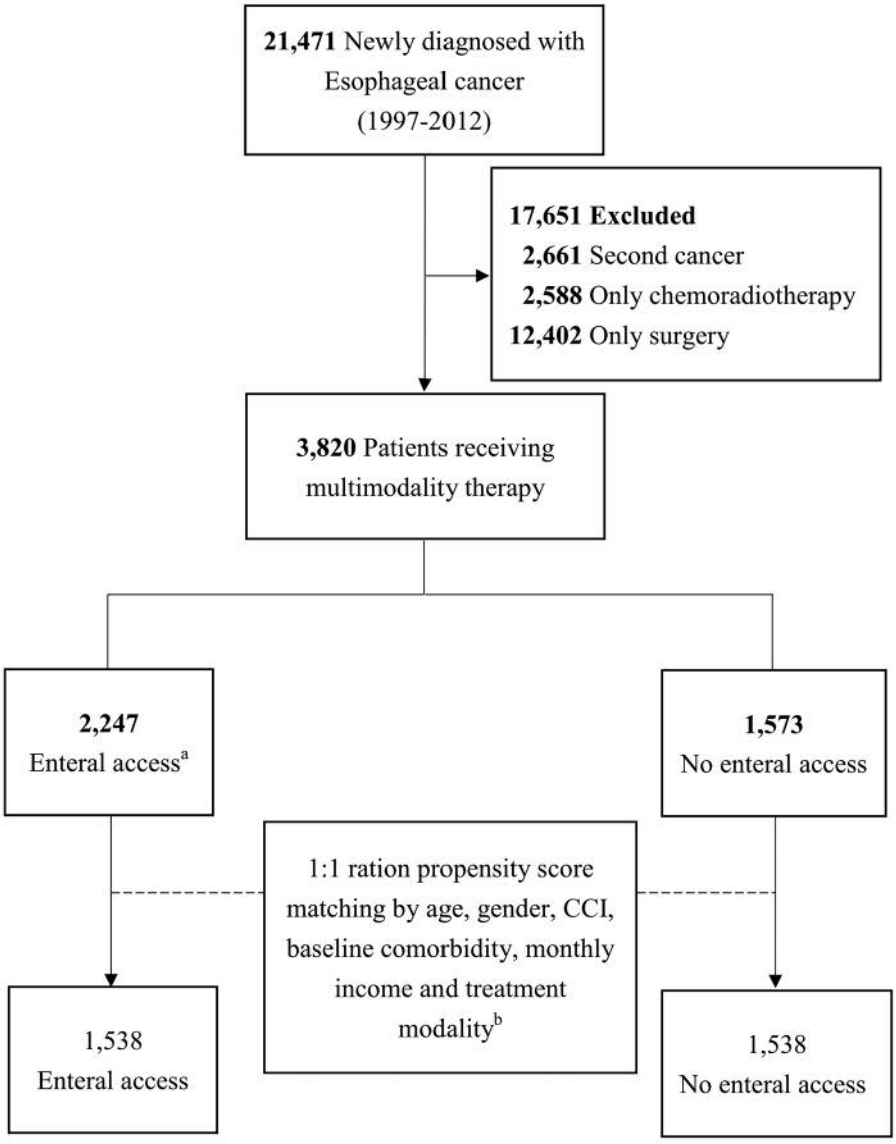

Figure 1. *Patients enrollment flow map. [a]Enteral access (Surgery code): 72017C, 73022B; [b]Treatment modality: chemo-radiotherapy code: 37041B, 36012B; Esophageal surgery including: esophagectomy, simple excision of esophageal cancer with lymphadenectomy, and complicated excision of esophageal cancer with lymphadenectomy.*

EC patients. However, there were no differences between the two groups regarding complications and clinical outcomes post-surgery (20). Timely and optimized nutritional strategies remain crucial. EA-related complications associated with enteral feeding tube infection and/or surgery-related complications have been reported to be as high as 44% (21). Beyond procedure-related morbidity, tube placement delays chemotherapy by 1-2 weeks, to allow for the resolution of local inflammation and contamination that develops at the insertion site in up to 10% of cases (16). Patients also fail to use their EA optimally due to lack of interest, discomfort, leakage and dermal excoriation (8). The survival analysis of this population-based longitudinal cohort indicated that the potential increased risk of mortality among EC patients undergoing multi-modality therapy might be associated with the EA intervention. It may be argued that malignancies of the digestive system significantly impact nutritional status during the acute period. Cancers of the esophagus which present with dysphagia are a clear example. The subjective complaint and experience of dysphagia is often the impetus for EA referral post diagnosis of EC. However, the data are limited concerning the placement of surgical EA in patients

Table I. *Baseline Characteristics of unmatched and matched population.*

	Before match (n=3820)					After PS match (n=3110)				
	EA (n=2247)		No EA (n=1573)			EA (n=1555)		No EA (n=1555)		
	Number	(%)	Number	(%)	SDif	Number	(%)	Number	(%)	SDif
Age (Mean±SD)	55.4±9.9		55.4±10.0		0	55.4±10.0		55.4±10.0		0
Gender										
Female	93	(4.1)	93	(5.9)	0.08	76	(4.9)	87	(5.6)	0.03
Male	2154	(95.9)	1480	(94.1)	0.08	1479	(95.1)	1468	(94.4)	
CCI (Mean±SD)	6.0±3.1		5.8±3.0		0.06	6.0±3.1		5.9±3.0		0.03
<5	900	(40.1)	635	(40.4)	0.01	647	(41.6)	623	(40.1)	-0.03
≥5	1347	(59.9)	938	(59.6)	0.01	908	(58.4)	932	(59.9)	
Diabetes Mellitus	301	(13.4)	179	(11.4)	0.06	171	(11.0)	179	(11.5)	-0.02
Hypertension	640	(28.5)	424	(27.0)	0.03	435	(28.0)	422	(27.1)	0.02
Hyperlipemia	399	(17.8)	272	(17.3)	0.01	265	(17.0)	272	(17.5)	-0.01
COPD	492	(21.9)	323	(20.5)	0.03	346	(22.3)	320	(20.6)	0.04
Treatment modality										
CRT+OP	555	(24.7)	385	(24.5)	0.15	354	(22.8)	384	(24.7)	0.05
OP+CRT	1319	(58.7)	852	(54.2)	0.15	874	(56.2)	852	(54.8)	
CRT+OP+CRT	373	(16.6)	336	(21.4)	0.15	327	(21.0)	319	(20.5)	
Monthly income										
Dependent	417	(18.6)	297	(18.9)	0.09	297	(19.1)	296	(19.0)	0.04
≤19100	526	(23.4)	370	(23.5)	0.09	367	(23.6)	366	(23.5)	
19100-42000	1144	(50.9)	812	(51.6)	0.09	812	(52.2)	799	(51.4)	
>42000	160	(7.1)	94	(6.0)	0.09	79	(5.1)	94	(6.0)	
Media survival time(year)	1.63		1.83			1.61		1.82		

PS: Propensity score; EA: enteral access; SDif: standardize difference; SD: standard deviation; CCI: Charlson comorbidity index; COPD: chronic obstructive pulmonary disease; CRT+OP: concurrent chemo-radiotherapy followed by surgery; OP+CRT: surgery followed by CRT; CRT+OP+CRT: CRT followed by surgery followed by adjuvant CRT.

with EC based on the symptom of dysphagia. Similarly, data on the nutritional status of patient with dysphagia and its' impact are not available from the NHI. Current results support caution in patient selection for EA (11). Improved and appropriate criteria to allow for correct identification of patients in need of EA and a better predictive nutritional status strategy should guide future treatments.

Radiation-induced lung toxicity remains critical in thoracic radiotherapy (22). Despite improved treatment strategies for EC (23), survival remains poor, and serious risks of pulmonary and cardiac toxicity remain. Previous studies on EC undergoing tri-modality therapy, have reported that a radiation dose >7 Gy or 10 Gy, may be a risk factor for compromised pulmonary function (24, 25). Furthermore, COPD is another critical factor for the occurrence of postoperative pulmonary complications in EC patients undergoing esophagectomy. This phenomenon is reflected in the current results where the presence of COPD similarly increased the risk of mortality in patients undergoing multi-modality treatment. EC remains a predominantly male disease. In the United States, the male-to-female ratio of 4.2:1 reflects the presence of EC cancer incidence. Similarly, in Taiwan, the male to female ratio of EC is 15:1 (26). The

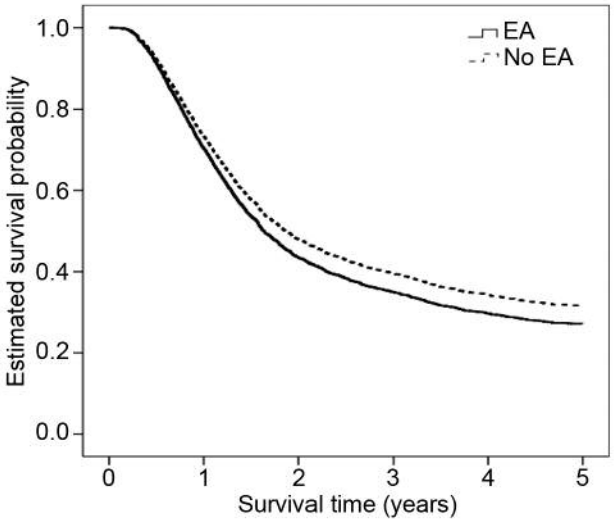

Figure 2. *Kaplan–Meier overall survival (in years). n: Number of patients at events; N: number of patients at risk.*

Table II. *Cox proportional hazards model for identifying the relationship between clinical features and mortality.*

Clinical features	HR (95%CI)	*p*-Value
EA		
No	ref	
Yes	1.13 (1.04, 1.23)	0.006
Age, years	0.98 (0.98, 0.99)	<0.0001
Gender		
Female	ref	
Male	1.50(1.20, 1.86)	<0.001
CCI		
<5	ref	
≥5	1.10(0.99, 1.22)	0.077
Diabetes mellitus	1.13 (0.98, 1.31)	0.102
Hypertension	1.09 (0.98, 1.21)	0.11
Hyperlipemia	0.91 (0.81, 1.04)	0.165
COPD	1.13 (1.02, 1.26)	0.025

EA: Enteral access; CCI: Charlson comorbidity index; COPD: chronic obstructive pulmonary disease. Model adjusted for age, gender, CCI, baseline comorbidity, monthly income and treatment modality.

etiology of the observed gender differences in the incidence of EC is likely multifactorial and remains currently undefined. Higher prevalence of high-risk behavior, such as drinking and smoking, has been demonstrated among male patients (27). These behavioral factors may explain the differences in mortality.

This study has several limitations. First, the NHIRD lacks information on examination results and the NHIRD 'catastrophic illnesses' data set lacks information on the clinical cancer stage and tumor site which might confound our results. Second, this was a retrospective cohort study, where unlike a prospective study, some of the potential risk factors cannot be obtained, such as tobacco, alcohol consumption or nutritional status which are not available in the NHIRD. Finally, only observational results can be provided from the NHIRD.

In conclusion, this analysis of the Taiwan NHI research database indicated that patients undergoing multi-modality therapy in conjunction with EA have a potentially increased risk of mortality. The practice of routine EA placement must be carefully scrutinized and implemented on a case-by-case basis to reduce EC mortality.

Conflicts of Interest

No Authors have any conflict of interest regarding this study.

Authors' Contributions

Huang, Hsieh, and Peng had full access to all the data in the study. Study design: Huang, Hsieh, Wang, and Peng. Statistical analysis of data: Huang, Hsieh, Wu, and Peng. Drafting the article: Huang, Chang and Chang. Revising the article critically for important intellectual content: Huang, Hsieh, and Peng.

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