RESEARCH ARTICLE

Clinical Features of Patients with Esophageal and Second Primary Cancers

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Abstract

Background: The prevalence of esophageal cancer (EC) with second primary cancers (SPC) is increasing worldwide. This study was aimed to understand the clinical features of EC patients with SPC in the Taiwanese population. Materials and Methods: Clinical and laboratory data for 180 EC patients with or without SPC were collected between January 2009 and December 2013. Information on treatment approaches, location of SPCs and ABO blood type were also collected and stratified. Results: The most common SPC in EC patients was hypopharyngeal cancer, followed by laryngeal cancer and hepatocellular carcinoma in our study. Malignancies of colon, prostate and lung were also found. There was a significant higher portion of blood type A in the EC patients with SPC compared with those without (42.4% vs 19.5%, *P*=0.006). Conclusions: The frequency and SPC site distribution and blood type A should be considered in clinical evaluation of EC patients with a high risk of developing SPC in the Taiwanese population.

Keywords: Esophageal cancer - second primary cancer - blood type - Taiwan

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Introduction

Clinical concern of esophageal cancer (EC) had been on the rise worldwide according to its elevating incidence and mortality over the past three decades (Jemal et al., 2009; Mao et al., 2012; Song et al., 2012). In Taiwan, EC was also attributed to the ninth most leading cause of cancer mortality. Most of newly diagnosed EC patients were at advanced tumor stage, implicating a poor prognosis in the overall 5-year survival (Zhang, 2013). Although the preventive strategies of EC had been developed and the treatment such as surgical resection and adjuvant chemoradiotherapy had been improved, the post-therapeutic survival rate remained dismal in clinical practice (Ge et al., 2012; Jingu et al., 2012). What's worse, the development of secondary neoplasms after chemoradiotherapy was observed in several studies recently (Newhauser et al., 2009; Zhu et al., 2012). Hence, the incidence of second primary cancer (SPC) in post-therapeutic EC patients was a public health issue.

As first reported in the 1930s, cases with SPC had been increasingly prevalent since then (Warren and Gates, 1932). The phenomenon could be explained by the improvement in medical technology and the elongation in life span. Some predominant etiological factors were categorized, one of which was chemoradiation-associated (Wood et al., 2012). Also, it was reported that blood type could be a risk factor in the development of SPC in certain cancer (Lawniczak et al., 2014). Previous studies involving SPC had been enormously reported, but a limited number of subjects regarding EC and SPC were announced (Poon et al, 1998; Zhu et al., 2012). Therefore, we conducted this study to analyze the clinicopathological features in EC patients with or without SPC. We believed this investigation would offer physicians an insight into the evaluation and management of EC patients with high risk developing SPC.

Materials and Methods

A total of 263 patients with EC received treatment and regular follow-up at the Far Eastern Memorial Hospital (FEMH) in New Taipei city, Taiwan, were enrolled from January 2009 to December 2013. The clinical data, including age, gender, family history of cancer, history of tobacco and alcohol use, tumor location, TNM stage, sites of second tumor, underlying comorbidities, and treatment types were collected via charts review. Eighty-three patients were excluded due to incomplete chart record and 180 patients were eventually registered in our

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study. All EC and SPC were histopathologically identified. Malignancies from metastasis or recurrence were excluded from SPC. ABO blood types were also obtained during hospital admission or outpatient department follow-up via standard laboratory measurement.

All values were presented as mean±standard deviation or number with percentage (%). The SPSS (version 15.0; SPSS Inc., Chicago, USA) statistical software was used for statistical analyses. Chi-square test was performed for categorical data and student's t test for continuous data. Statistical difference was considered significant at $p<0.05$.

Results

Among the patients enrolled in our study, 146 patients were diagnosed as EC alone and 34 patients were diagnosed as EC with SPC. The prevalence of SPC in EC patients was 18.9% in the present study. The clinical features of the EC patients with or without SPC were shown in Table 1. The mean age of the EC alone patients was similar to those with SPC (59.79±1.77 *vs* 57.64±0.94 years, $p=0.312$). Most EC alone patients or with SPC were male (97.1% *vs* 92.6%, $p=0.392$) and had a history of tobacco use (76.5% *vs* 79.5%, $p=0.701$) and alcohol drinking (79.4% *vs* 77.4%, $p=0.799$). There was about one fifth of patients carrying family history of cancer in both groups (13.7% *vs* 23.5%, $p=0.154$). Among the EC patients with SPC, the upper third esophageal cancer was more common compared with those who had EC alone (32.4% *vs* 15.1%, $p=0.019$). Approximately half of tumor sites were located in the middle portion of esophagus in both group (55.5% *vs* 47.0%, $p=0.375$). The most common TNM stage was stage III (58.2%) in the EC alone patients and stage IV (41.3%) in the EC patients with SPC. Additionally, the portion of the EC patients alone was remarkably higher than those with SPC in the stage III (58.2% *vs* 23.5%, $p<0.001$). EC with SPC group was significantly higher than those without in the early stages of EC (17.6% *vs* 0.7% in stage I, $p<0.001$; 17.6% *vs* 1.4% in stage II, $p<0.001$).

Table 1. Clinical Characteristics of Esophageal Cancer Patients with or without Secondary Primary Cancers

Variables	Total (N=180)	EC (N=146)	EC with SPC (N=34)	P value
Age (y)	58.05±0.83	57.64±0.94	59.79±1.77	0.312
Gender				0.392
Male	169 (93.9)	136 (92.6)	33 (97.1)	
Female	11 (6.1)	10 (7.4)	1 (2.9)	
FHC				0.154
Yes	28 (15.6)	20 (13.7)	8 (23.5)	
No	152 (84.4)	126 (86.3)	26 (76.5)	
Tobacco use	142 (78.9)	116 (79.5)	26 (76.5)	0.701
Alcohol use	140 (77.8)	113 (77.4)	27 (79.4)	0.799
Location				
Upper	33 (18.3)	22 (15.1)	11 (32.4)	0.019
Middle	97 (53.9)	81 (55.5)	16 (47.0)	0.375
Lower	50 (27.8)	43 (29.4)	7 (20.6)	0.299
Stage				
I	7 (3.9)	1 (0.7)	6 (17.6)	<0.001
II	8 (4.4)	2 (1.4)	6 (17.6)	<0.001
III	93 (51.7)	85 (58.2)	8 (23.5)	<0.001
IV	72 (40.0)	58 (39.7)	14 (41.3)	0.876

*EC, esophageal cancer; SPC, secondary primary cancer; FHC, family history of cancer

The types of treatment in EC patients with and without SPC were listed in Table 2. Among these patients, most of them received concurrent chemoradiotherapy (CCRT, 78.8% vs 82.4%, $p=0.641$). Additionally, 22.6% of the EC alone and 38.2% of the EC with SPC patients received surgical resection and reconstruction of esophagus ($p=0.060$). Only few cases received chemotherapy (3.4% *vs* 5.9%, $p=0.504$) or radiotherapy (4.1% *vs* 5.9%, $p=0.651$) alone in consideration of the patient's clinical situation. There was no statistical significance in comparison between both groups.

The frequency and site distribution of SPC in the EC patients was shown in Figure 1. In our data, hypopharyngeal cancer was the most common SPC in the EC patients, followed by laryngeal cancer and hepatocellular carcinoma (HCC). SPCs in colon, prostate, lung, stomach, tongue and acute myeloid leukemia (AML) were also found in our observational results.

Table 2. Treatment Types of Esophageal Cancer Patients with or without Secondary Primary Cancers

Treatment types	Total (N=180)	EC (N=146)	EC with SPC (N=34)	P value
CCRT	143 (79.4)	115 (78.8)	28 (82.4)	0.641
VATS esophagectomy with esophageal reconstruction	46 (25.6)	33 (22.6)	13 (38.2)	0.06
Chemotherapy alone	7 (3.9)	5 (3.4)	2 (5.9)	0.504
Radiotherapy alone	8 (4.4)	6 (4.1)	2 (5.9)	0.651

*EC, esophageal cancer; SPC, secondary primary cancer; CCRT, concurrent chemoradiotherapy; VATS, video-assisted thoracoscopic surgery

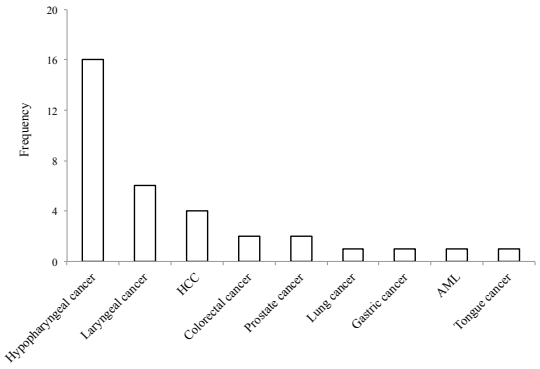

Figure 1. The Site Distribution of Secondary Primary Cancers in Esophageal Cancer Patients. HCC, hepatocellular carcinoma; AML, acute myeloid leukemia

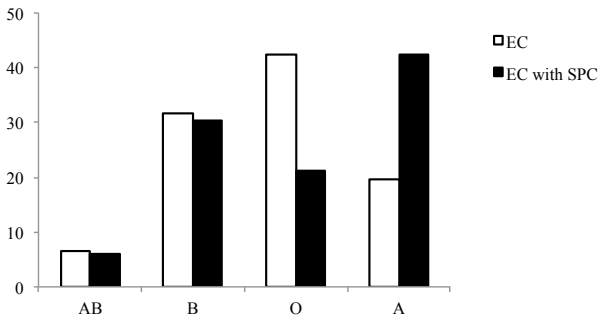

Figure 2. The blood Types in Esophageal Cancer Patients with or without Secondary Primary Cancers. EC, esophageal cancer; SPC, secondary primary cancer

The distribution of ABO blood types was shown in Figure 2. Of these patients with EC alone, 42.3% was blood type O, 31.7% was blood type B, 19.5% was blood type A and 6.5% was blood type AB. Among the patients with EC and SPC, 42.4% was blood type A, 30.3% was blood type B, 21.2% was blood type O and 6.1% was blood type AB. Our results indicated that there was a significant higher portion of blood type A in the EC patients with SPC than in those without (42.4% *vs* 19.5%, p=0.006).

Discussion

The diagnostic criteria of multiple primary cancers should be concurrently satisfied with: *(1)* each neoplasm was anatomically and pathologically distinct from other ones; and *(2)* the subsequent cancer was not a metastasis or recurrence of the primary one (Warren and Gates, 1932). Multiple primary cancers could be separated into synchronous or metachronous according to the time of diagnosis of each primary neoplasm. Although its incidence was low, accumulating cases with SPC has been diagnosed over the past decades. It was estimated that SPC occurred with the prevalence varying from 0.7% to 11.7% of all cancer patients, depending on different primary cancers (Luciani et al., 2009; Gursel et al., 2011). Additionally, the challenges of SPC to physicians had become of increasing concern because the treatment options to SPC could be limited due to its progression. Therefore, it necessitated the investigation of SPC to provide strategy for clinical screening and prevention of secondary ones. There were accumulating evidence demonstrating the association between several specific cancers and subsequent primary neoplasms. To date, a quantity of etiological factors had been proposed and stratified as: *(1)* chemoradiation-asscociated; *(2)* syndromic; *(3)* genetically susceptible; *(4)* environment exposure-related; and *(5)* idiopathic (Wood et al., 2012; Takalkar et al., 2013; Travis et al., 2013). Nevertheless, the detailed interaction of SPCs with certain risk factors required further clarification.

Our main finding in the present study showed the most common SPC in EC patients was hypopharyngeal cancer, followed by laryngeal cancer and HCC. Second primary malignancies were also sporadically found in lung, stomach, colon or prostate. Among these patients, most received CCRT and had the history of tobacco and alcohol use. Previous studies had revealed the most common SPCs were neoplasms of upper aerodigestive organs, lung and thyroid gland in the EC patients (Matsubara et al., 2003; Das et al., 2006). This phenomenon could be interpreted as radiotherapy for esophageal cancers enhanced the risk of developing a second malignancy in nearby organs (Sachs et al., 2007). These results were partially inconsistent with our clinical data because HCC was also shown as one of the most common SPCs in the EC patients in our study. The difference could be attributed to the higher prevalence of HCC in Southeastern Asia. Additionally, Zhu et al. (2012) observed that incidence of SPC in the EC patients was disproportionally higher in male than in female. The reason why SPC occurred in EC patients with male preponderance was not totally clarified yet, but it was generally deemed that tobacco and alcohol consumption played a crucial role in the prevalence of EC with the gender differences (Pandeya et al., 2013; Prabhu et al., 2014). Therefore, lifestyle changes such as restriction of cigarette smoking and alcohol consumption were suggested as one of the preventive strategies of developing SPC in EC patients (Jemal et al., 2011; Tang et al., 2014).

Our results further indicated that EC patients with SPC belonged more commonly to blood type A (42.4%) than other blood types in comparison with the EC alone group. No specific attribution was notified in other blood types. The relationship between risk factor of developing SPC in EC patients and ABO blood types was rarely explored. Caygill et al. (2011) found that individuals carrying blood type O had a high risk of developing esophageal adenocarcinoma with *Helicobacter pylori* infection. Sun et al. (2014) reported that EC patients who had cigarette smoking and blood type O or B had a poorer outcome than those with blood type A or AB. In our study, there was a significant higher portion with blood type A in EC patients with SPC, implying that EC patients who had blood type A should be under surveillance for the development of SPCs. To our knowledge, this is the first report to describe the association of ABO blood types and EC with SPC. Although the bias of blood types distribution in limited case number could not be excluded in the present study, we believed that our results justify for clinical assessment in the EC patients with blood type A due to higher risk of developing SPC.

There were several inherent limitations in the present study. First, the study design was retrospective and the case number was limited in EC patients accompanied with SPC. Second, the bias could not be ruled out according to the geographically regional factors. Furthermore, some clinical data with prognostic significance were unavailable, especially the information regarding details about the amount and time of tobacco and alcohol use, and the dose of chemoradiation, making the survey of a dose-effect association difficult.

In summary, the present study indicated that EC patients seemed to possess a relatively higher risk of developing SPCs, especially cancers in upper aerodigestive tract and liver. Meanwhile, the EC patients carrying blood type A should be followed up carefully for the higher risk of developing SPCs. These should be considered in the risk assessment and clinical management of the EC patients.

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