Original Article

# Clinical features and risk of multiple primary malignancies after endoscopic treatment in patients with early esophageal squamous cell carcinoma: a retrospective cohort study

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**Background:** The incidence of multiple primary malignancies (MPMs) after early esophageal cancer is increasing. This study aimed to explore the clinical features of patients with MPMs and identify independent risk factors for the development of MPMs after endoscopic treatment in early esophageal squamous cell carcinoma (ESCC) patients.

**Methods:** Patients diagnosed as early ESCC at Beijing Friendship Hospital were retrospectively analyzed. Independent factors affecting MPMs were selected by univariate and multivariate Cox regression analyses.

**Results:** Among 299 patients with early ESCC, the mean age was 64.22 years; 219 were male (73.24%). Of these, 32 patients (10.70%) developed MPMs during a follow-up period of 120 months; 10 were metachronous and 22 synchronous. Multivariate Cox analysis showed that alcohol drinking ≥5 standard drinks/day [hazard ratio (HR) =4.21, 95% confidence interval (CI): 1.79–9.90, P<0.001], lower location (HR =2.49, 95% CI: 1.18–5.22, P=0.02), submucosal infiltration depth (HR =3.38, 95% CI: 1.31–8.69, P=0.01), and multiple lesions (HR =2.41, 95% CI: 1.15–5.04, P=0.02) were independent risk factors for developing MPMs in patients with early esophageal cancer.

**Conclusions:** Early ESCC is associated with a high risk of developing MPMs. Monitoring the development of MPMs in patients with early ESCC based on identified risk factors is of great importance.

**Keywords:** Early esophageal squamous cell carcinoma (early ESCC); multiple primary cancer; independent risk factor

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## Introduction

Esophageal cancer ranks as the sixth most prevalent cancer and the fifth leading cause of cancer-related deaths in China, accounting for approximately 252,500 new cases and 193,900 fatalities annually (1). The survival rate for esophageal cancer is meager, with a 5-year survival rate ranging from 10% to 30% in most countries (2). In China, squamous cell carcinoma of the esophagus comprises almost 90% of cases and represents the most prevalent histological type, with an associated 5-year survival rate of less than 30% for advanced esophageal cancer (3,4). Currently, the most effective approach to improve the prognosis of esophageal cancer is

early diagnosis and treatment. The 5-year survival rate of early esophageal squamous cell carcinoma (ESCC) can be significantly improved to over 95% with the widespread implementation of endoscopic screening programs and advancements in minimally invasive endoscopic treatment (5).

It is reported that patients with ESCC have a significantly increased risk of developing multiple primary malignancies (MPMs) compared to the general population, with the highest incidence reaching up to 38.8% (6). MPMs, defined as two or more synchronous or metachronous primary malignancies in the same individual and derived from the same organ, paired organs, different parts of the same system, or different organs of different systems, will have a great impact on patient's prognosis and quality of life (6,7). Additionally, research has found that ESCC is more prone to developing MPMs compared to esophageal adenocarcinoma (8). The diagnosis of early esophageal cancer in China is increasing due to the implementation of esophageal cancer screening projects by the government, with squamous cell carcinoma being the main histological type (3). The prolonged survival time after the treatment in early ESCC can also increase the incidence of developing MPMs (9,10). However, clinicians may focus more on the recurrence and metastasis of the primary cancer, potentially overlooking the development of MPMs. Therefore, it is of great importance to identify the clinical characteristics of patients with early ESCC who are at risk of developing multiple primary cancers, to detect MPMs at an early stage and further improve the prognosis and quality of life for patients with early ESCC.

To our knowledge, there is no specific research on the occurrence of MPMs after early ESCC. In this study, we aimed to identify the clinical characteristics of MPMs particularly through endoscopic and pathological evaluations, and analyze the risk factors for developing MPMs after early ESCC in a retrospective cohort. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-299/rc).

### Highlight box

**Key findings**

- Alcohol consumption ≥5 standard drinks/day, lower location, submucosal infiltration depth, and multiple lesions were independent risk factors for developing multiple primary malignancies (MPMs) in patients with early esophageal squamous cell carcinoma (ESCC).

**What is known and what is new?**

- The incidence of MPMs is increasing after early esophageal cancer with poor prognosis.
- This study investigated a clinical cohort to ascertain the endoscopic characteristics and risk factors of developing MPMs after early ESCC.

**What is the implication, and what should change now?**

- We should monitor the occurrence of MPMs after the endoscopic treatment of early ESCC based on the investigated risk factors, especially in the first 6 months.

## Methods

### *Study population*

The retrospective cohort study received approval from the Beijing Friendship Hospital Ethics Committee (No. 2020-P2-290-01). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was waived due to the study's retrospective design. Our cohort study includes patients who underwent endoscopic treatment and were pathologically diagnosed with early ESCC at Beijing Friendship Hospital from 2013 to 2022. Our pathological criteria for esophageal lesions are based on the diagnostic criteria of the Japan Esophageal Society guideline (11,12). In the latest criteria, high-grade dysplasia is considered carcinoma *in situ* (12). Consequently, the criteria for early ESCC in our study included: (I) confirmation of esophageal lesions as high-grade squamous dysplasia or squamous cell carcinoma; (II) the depth of esophageal lesions not exceeding the submucosal layer. The exclusion criteria were as follows: (I) patients with a history of multiple primary cancers before the occurrence of early esophageal cancer; (II) unavailable in-hospital or out-hospital follow-up information or incomplete medical records; (III) patients treated by surgery. The study patients were primarily followed up through outpatient clinic visits or inpatient medical records before September 30, 2023, until the diagnosis of MPMs or the last follow-up.

### *Primary outcome*

The primary outcome was the diagnosis of MPMs in patients with early ESCC. According to recent research (6), the diagnostic criteria for MPMs proposed by Warren and Gates were as follows: (I) each tumor exhibited clear, malignant histopathological alterations; (II) each tumor had different pathological morphology; and (III) the possibility

 

of metastasis and recurrence must be ruled out. Hence, the MPMs were divided into synchronous MPMs (≤6 months) and metachronous MPMs (>6 months) according to the interval between the diagnosis of two malignancies.

### *Assessment of covariates*

Sociodemographic characteristics, disease history, endoscopy and pathology information for early esophageal cancer at baseline were adjusted as covariates. Potential confounders included patients' age, sex, body mass index (BMI), history of smoking and alcohol drinking, clinical symptoms, marital status, family history of cancer, hypertension, diabetes, cardiovascular and cerebrovascular diseases, other digestive system diseases, lesion location in the esophagus, Paris classification of early esophageal cancer, tumor size (maximum lesion diameter), degree of differentiation, depth of invasion, the situation of surgical margin, whether the lesion site was multifocal, and whether there was lymph node or vascular metastasis at the time of diagnosis of early esophagus cancer.

Alcohol drinking was divided into no or <5 standard drinks, and ≥5 standard drinks. One standard drink was defined as one that contains 14 g of pure alcohol which is equivalent to 120 mL of wine, 360 mL of beer, or 45 mL of liquor according to the criterion of the National Institute of Alcohol Abuse and Alcoholism (13). The clinical symptoms included dysphagia, retrosternal pain, acid reflux, heartburn, nausea, vomiting, abdominal pain, abdominal distension, hematemesis, melena, weight loss, weakness, and anemia. The location of the lesion was divided into the upper (15–20 cm from the incisors) or middle (20–30 cm from the incisors) of the esophagus and the lower (30–40 cm from the incisors) of the esophagus (14). The tumor size was determined based on pathological measurements and was expressed as the maximum diameter of the lesion. Superficial lesions (type 0) were classified as type 0–IIb and others according to the Paris classification criteria (15). Multiple lesions were defined as two or more esophageal lesions (high-grade dysplasia or carcinoma) detected in one endoscopic examination. When there were multiple lesions in the esophagus, the lesion with the deepest infiltration depth was studied as the main lesion. When the infiltration depth of the lesion was the same, the lesion with the longest diameter was studied as the main lesion (11,12). All lesions underwent endoscopic treatment including endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR).

### *Statistical analysis*

The differences in clinical features between groups were analyzed using Chi-square tests, Fisher's exact tests, or Student's *t*-tests. Kaplan-Meier curves and log-rank test were used in univariate survival analysis. The Cox proportional hazards regression analyses were performed to investigate the risk factors for the development of MPMs in patients with early esophageal cancer. Univariate Cox regression analysis was performed on all covariates, and covariates with P values <0.05 were considered significant and were then adjusted by multivariate Cox regression analysis. Statistical analysis was performed using the R statistical software (version 4.2.2). A two-side P<0.05 was considered significant.

## Results

### *Patients' characteristics*

A total of 299 early ESCC patients (mean age 64.22± 8.00 years old, 26.76% females) were enrolled in this cohort. Of whom, 366 lesions were found, with 343 lesions treated by ESD and 23 lesions by EMR. After the follow-up of 120 months, 32 (10.70%) patients developed MPMs, of which 22 (68.75%) synchronous MPMs, and 10 (31.25%) metachronous MPMs. The three leading sites were gastric cancer (n=14), head and neck cancer (n=6), and colon cancer (n=5) in these 32 early ESCC patients with MPMs. Detailed distribution of sites is shown in *Table 1*. The clinical features of early esophageal cancer patients with MPMs were presented in *Table 2*. Compared with single primary tumor group, patients with MPMs were more likely to be current smokers (P=0.01), alcohol drinking especially higher proportion with ≥5 standard drinks per day (P<0.001), lower lesions location (P<0.001) and multiple lesions in esophagus (P=0.001).

### *Independent risk factors for MPMs in patients with early ESCC*

Alcohol drinking [hazard ratio (HR) =4.21, 95% confidence interval (CI): 1.79–9.90, P<0.001], location in esophagus (HR =2.49, 95% CI: 1.18–5.22, P=0.02), infiltration depth (HR =3.38, 95% CI: 1.31–8.69, P=0.01), and multiple lesions (HR =2.41, 95% CI: 1.15–5.04, P=0.02) in esophagus were independent risk factors for the occurrence of MPMs in patients with early ESCC (*Table 3*). The independent risk factors (alcohol consumption, location in

 

**Table 1** Site of MPMs after the diagnosis of early esophageal squamous cell carcinoma

| Site of MPMs | Total (n=32) | Metachronous (n=10) | Synchronous (n=22) |
|---|---|---|---|
| Gastric cancer | 14 | 4 | 10 |
| Colon cancer | 5 | 0 | 5 |
| Head and neck cancer | 6 | 3 | 3 |
| Lung cancer | 3 | 1 | 2 |
| Others | 4 | 2 | 2 |

MPMs, multiple primary malignancies.

esophagus, infiltration depth, and multiple lesions) showed great significance for the impact on the probability of MPMs diagnosis in patients with early ESCC (*Figure 1*).

Furthermore, multivariate analysis revealed that alcohol drinking (HR =7.77, 95% CI: 1.97–30.56, P=0.003) was an independent risk factor for the development of metachronous MPMs in patients with early ESCC. Additionally, alcohol drinking (HR =3.34, 95% CI: 1.33–8.38, P=0.01), location in esophagus (HR =4.40, 95% CI: 1.72–11.29, P=0.002), infiltration depth (HR =4.09, 95% CI: 1.53–10.90, P=0.005), and multiple lesions in esophagus

**Table 2** Demographic and clinicopathological characteristics in patients with esophageal squamous cell carcinoma

| Variables | Total (n=299) | Without MPMs (n=267) | With MPMs (n=32) | P value |
|---|---|---|---|---|
| Age (years) | 64.22±8.00 | 64.28±8.10 | 63.72±7.25 | 0.71 |
| Sex | | | | 0.054 |
| Female | 80 (26.76) | 76 (28.46) | 4 (12.50) | |
| Male | 219 (73.24) | 191 (71.54) | 28 (87.50) | |
| BMI (kg/m$^2$) | 23.94±3.39 | 23.97±3.35 | 23.64±3.71 | 0.60 |
| Smoking | | | | 0.01 |
| No | 207 (69.23) | 191 (71.54) | 16 (50.00) | |
| Yes | 92 (30.77) | 76 (28.46) | 16 (50.00) | |
| Alcohol drinking | | | | <0.001 |
| No or <5 standard drinks/day | 266 (88.96) | 246 (92.13) | 20 (62.50) | |
| ≥5 standard drinks/day | 33 (11.04) | 21 (7.87) | 12 (37.50) | |
| Clinical symptom | | | | 0.23 |
| No | 113 (37.79) | 104 (38.95) | 9 (28.12) | |
| Yes | 186 (62.21) | 163 (61.05) | 23 (71.88) | |
| Marital status | | | | |
| Married | 264 (88.29) | 234 (87.64) | 30 (93.75) | 0.47 |
| Others | 35 (11.71) | 33 (12.36) | 2 (6.25) | |
| Family history of cancer | | | | 0.70 |
| No | 206 (68.90) | 183 (68.54) | 23 (71.88) | |
| Yes | 93 (31.10) | 84 (31.46) | 9 (28.13) | |
| Hypertension | | | | 0.86 |
| No | 182 (60.87) | 163 (61.05) | 19 (59.38) | |
| Yes | 117 (39.13) | 104 (38.95) | 13 (40.63) | |
| Diabetes | | | | 0.28 |
| No | 257 (85.95) | 232 (86.89) | 25 (78.13) | |
| Yes | 42 (14.05) | 35 (13.11) | 7 (21.88) | |

**Table 2** (*continued*)

 

**Table 2** (*continued*)

| Variables | Total (n=299) | Without MPMs (n=267) | With MPMs (n=32) | P value |
|---|---|---|---|---|
| CVD | | | | 0.54 |
| No | 228 (76.25) | 205 (76.78) | 23 (71.88) | |
| Yes | 71 (23.75) | 62 (23.22) | 9 (28.12) | |
| Other digestive system diseases | | | | 0.23 |
| No | 113 (37.79) | 104 (38.95) | 9 (28.13) | |
| Yes | 186 (62.21) | 163 (61.05) | 23 (71.88) | |
| Location in esophagus | | | | <0.001 |
| Middle or upper | 185 (61.87) | 174 (65.17) | 11 (34.38) | |
| Lower | 114 (38.13) | 93 (34.83) | 21 (65.63) | |
| Type | | | | 0.31 |
| 0–IIb | 244 (81.61) | 220 (82.40) | 24 (75.00) | |
| Others | 55 (18.39) | 47 (17.60) | 8 (25.00) | |
| Tumor size (cm) | 3.41±1.70 | 3.45±1.74 | 3.02±1.22 | 0.17 |
| Histology | | | | 0.60 |
| High-grade squamous neoplasia | 109 (36.45) | 96 (35.96) | 13 (40.63) | |
| Squamous cell carcinoma | 190 (63.55) | 171 (64.04) | 19 (59.38) | |
| Infiltration depth | | | | 0.11 |
| Mucosal layer | 271 (90.64) | 245 (91.76) | 26 (81.25) | |
| Submucosal layer | 28 (9.36) | 22 (8.24) | 6 (18.75) | |
| Resection margin | | | | 0.47 |
| Negative | 248 (82.94) | 220 (82.40) | 28 (87.50) | |
| Positive | 51 (17.06) | 47 (17.60) | 4 (12.50) | |
| Multiple lesions in esophagus | | | | 0.001 |
| No | 248 (82.94) | 228 (85.39) | 20 (62.50) | |
| Yes | 51 (17.06) | 39 (14.61) | 12 (37.50) | |
| Lymphatic invasion | | | | |
| No | 294 (98.33) | 262 (98.13) | 32 (100.00) | >0.99 |
| Yes | 5 (1.67) | 5 (1.87) | 0 | |
| Venous invasion | | | | 0.55 |
| No | 292 (97.66) | 261 (97.75) | 31 (96.88) | |
| Yes | 7 (2.34) | 6 (2.25) | 1 (3.13) | |
| Treatment | | | | >0.99 |
| EMR | 10 (3.34) | 9 (3.37) | 1 (3.13) | |
| ESD | 289 (96.66) | 258 (96.63) | 31 (96.88) | |

Data are presented as mean ± SD or n (%). MPMs, multiple primary malignancies; BMI, body mass index; CVD, cardiovascular and cerebrovascular diseases; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; SD, standard deviation.

 

**Table 3** Univariate and multivariate Cox regression analyses of independent risk factors of MPMs

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| Age | 1.00 (0.95, 1.04) | 0.87 | – | – |
| Sex | | | | |
| Female | 1.00 | | – | – |
| Male | 2.52 (0.88, 7.21) | 0.08 | – | – |
| BMI | 0.96 (0.87, 1.06) | 0.45 | – | – |
| Smoking | | | | |
| No | 1.00 | | 1.00 | |
| Yes | 2.38 (1.19, 4.76) | 0.01 | 1.23 (0.54, 2.77) | 0.62 |
| Alcohol drinking | | | | |
| No or <5 standard drinks/day | 1.00 | | 1.00 | |
| ≥5 standard drinks/day | 5.72 (2.78, 11.77) | <0.001 | 4.21 (1.79, 9.90) | <0.001 |
| Clinical symptom | | | | |
| No | 1.00 | | – | – |
| Yes | 1.61 (0.74, 3.47) | 0.23 | – | – |
| Marital status | | | | |
| Married | 1.00 | | – | – |
| Others | 0.64 (0.15, 2.70) | 0.54 | – | – |
| Family history of cancer | | | | |
| No | 1.00 | | – | – |
| Yes | 0.79 (0.36, 1.71) | 0.55 | – | – |
| Hypertension | | | | |
| No | 1.00 | | – | – |
| Yes | 1.07 (0.53, 2.18) | 0.85 | – | – |
| Diabetes | | | | |
| No | 1.00 | | – | – |
| Yes | 1.62 (0.70, 3.75) | 0.26 | – | – |
| CVD | | | | |
| No | 1.00 | | – | – |
| Yes | 1.35 (0.63, 2.92) | 0.44 | – | – |
| Other digestive system diseases | | | | |
| No | 1.00 | | – | – |
| Yes | 1.27 (0.58, 2.77) | 0.55 | – | – |
| Location in esophagus | | | | |
| Middle or upper | 1.00 | | 1.00 | |
| Lower | 2.69 (1.29, 5.60) | 0.008 | 2.49 (1.18, 5.22) | 0.02 |

**Table 3** (*continued*)

 

**Table 3** (*continued*)

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| Type | | | | |
| 0–IIb | 1.00 | | – | – |
| Others | 1.72 (0.77, 3.83) | 0.19 | – | – |
| Tumor size | 0.85 (0.68, 1.07) | 0.18 | – | – |
| Histology | | | | |
| High-grade squamous neoplasia | 1.00 | | – | – |
| Squamous cell carcinoma | 0.88 (0.43, 1.78) | 0.71 | – | – |
| Infiltration depth | | | | |
| Mucosal layer | 1.00 | | 1.00 | |
| Submucosal layer | 3.21 (1.31, 7.91) | 0.01 | 3.38 (1.31, 8.69) | 0.01 |
| Resection margin | | | | |
| Negative | 1.00 | | – | – |
| Positive | 0.74 (0.26, 2.12) | 0.58 | – | – |
| Multiple lesions in esophagus | | | | |
| No | 1.00 | | 1.00 | |
| Yes | 2.59 (1.26, 5.32) | 0.01 | 2.41 (1.15, 5.04) | 0.02 |
| Lymphatic invasion | | | | |
| No | 1.00 | | – | – |
| Yes | NA | NA | – | – |
| Venous invasion | | | | |
| No | 1.00 | | – | – |
| Yes | 1.88 (0.26, 13.84) | 0.54 | – | – |
| Treatment | | | | |
| EMR | 1.00 | | – | – |
| ESD | 1.92 (0.26, 14.30) | 0.52 | – | – |

MPMs, multiple primary malignancies; HR, hazard ratio; CI, confidence interval; BMI, body mass index; CVD, cardiovascular and cerebrovascular diseases; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; NA, not available.

(HR =3.08, 95% CI: 1.27–7.46, P=0.01) were identified as independent risk factors for the development of the synchronous MPMs in patients with early ESCC (*Table 4*).

## Discussion

In this study, we elucidated the clinical, demographic, endoscopic and pathological features of MPMs in patients with early ESCC. We identified several independent risk factors for the development of MPMs after early ESCC including alcohol consumption, tumor infiltration depth, tumor location, and the presence of multiple lesions in the esophagus. To our knowledge, this is the first study investigating the association between early ESCC and MPMs, while incorporating endoscopic characteristics and pathological features for analysis, which has not been previously addressed in the existing literature.

Concurrently, advancements in endoscopic and imaging

 

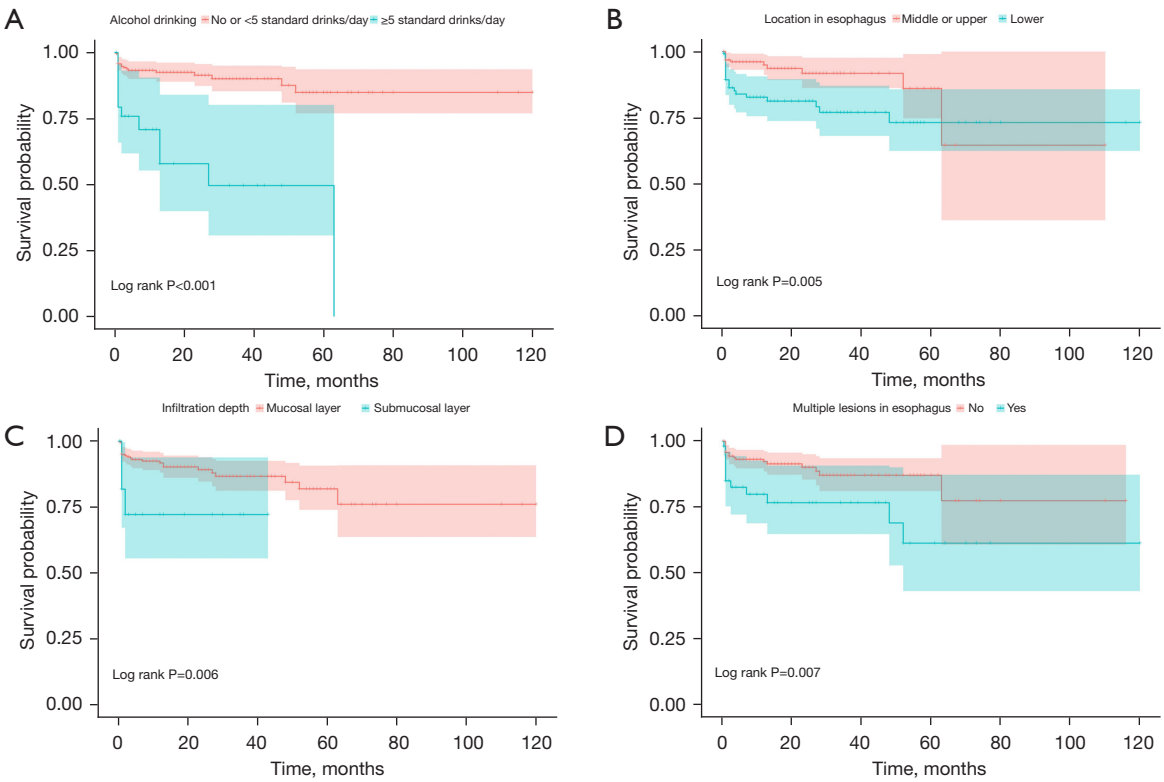


**Figure 1** Kaplan-Meier curves according to MPMs status in patients with early esophageal squamous cell carcinoma by alcohol drinking (A), location (B), tumor infiltration depth (C), and multiple lesions in esophagus (D). MPMs, multiple primary malignancies.

technologies have significantly increased the detection rate of early esophageal cancer (3). Early intervention, either through endoscopic or surgical treatment, has been shown to prolong survival times in patients with early esophageal cancer. However, as survival periods extend, the incidence of multiple primary cancers in these patients also increases (16). Previous studies have documented variations in the incidence of MPMs associated with esophageal cancer (6,16-18). In this study, the occurrence rate of MPMs following the endoscopic treatment of early ESCC was 10.70%. Among these cases, 68.7% were synchronous multiple primary cancers, and 31.3% were metachronous, findings that aligned with prior research (16,18).

Regarding the sites where multiple primary malignant tumors associated with early ESCC occurred, previous studies have predominantly identified the head and neck, gastrointestinal tract, and lungs as common locations (16,17). In our study, the common sites for multiple primary cancers included the gastrointestinal tract, head and neck, and lung, consistent with previous research. We found that early ESCC is more likely to develop synchronous MPMs, particularly synchronous multiple primary gastric cancer. All lesions were located at the cardia. Out of the 10 patients, 8 were initially diagnosed with early esophageal cancer at other hospitals. Upon reevaluation with endoscopy at Beijing Friendship Hospital, cardia lesions were newly identified. In the remaining two patients, the cardia lesions were detected approximately 3 months postoperatively during endoscopic follow-up. Therefore, for patients with early ESCC, especially those with independent risk factors, detailed endoscopic examination of the stomach should be conducted concurrently. Thus, patients with early ESCC might get clinical benefits from close endoscopic and imaging surveillance for MPMs in the first 6 months. Additionally, a further distinction is required between multiple primary cancers and metastases, as distant metastasis often indicates an advanced tumor stage and reduces the likelihood of surgical intervention compared to MPMs. The most common sites of metastasis in esophageal cancer include the liver, distant lymph nodes, and lungs (19), which bear some resemblance to the locations of MPMs (6). The lung is a common site for esophageal cancer metastasis and the

 

**Table 4** Univariate and multivariate Cox regression analyses of independent risk factors of metachronous and synchronous MPMs

| Variables | Metachronous MPMs | | | | Synchronous MPMs | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| Age | 0.95 (0.88, 1.03) | 0.21 | – | – | 1.02 (0.96, 1.07) | 0.56 | – | – |
| Sex | | | | | | | | |
| Female | 1.00 | | – | – | 1.00 | | – | – |
| Male | NA | NA | – | – | 1.84 (0.62, 5.44) | 0.27 | – | – |
| BMI | 1.02 (0.86, 1.20) | 0.86 | – | – | 0.93 (0.82, 1.06) | 0.31 | – | – |
| Smoking | | | | | | | | |
| No | 1.00 | | 1.00 | | 1.00 | | – | – |
| Yes | 5.96 (1.54, 23.11) | 0.01 | 3.21 (0.73, 14.09) | 0.12 | 1.47 (0.62, 3.50) | 0.39 | – | – |
| Alcohol drinking | | | | | | | | |
| No or <5 standard drinks/day | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| ≥5 standard drinks/day | 12.87 (3.66, 45.26) | <0.001 | 7.77 (1.97, 30.56) | 0.003 | 4.78 (1.94, 11.76) | <0.001 | 3.34 (1.33, 8.38) | 0.01 |
| Clinical symptom | | | | | | | | |
| No | 1.00 | | – | – | 1.00 | | – | – |
| Yes | 0.68 (0.20, 2.35) | 0.54 | – | – | 2.66 (0.90, 7.87) | 0.08 | – | – |
| Marital status | | | | | | | | |
| Married | 1.00 | | – | – | 1.00 | | – | – |
| Others | NA | NA | – | – | 0.76 (0.18, 3.27) | 0.72 | – | – |
| Family history of cancer | | | | | | | | |
| No | 1.00 | | – | – | 1.00 | | – | – |
| Yes | 1.21 (0.34, 4.29) | 0.77 | – | – | 0.63 (0.23, 1.72) | 0.37 | – | – |
| Hypertension | | | | | | | | |
| No | 1.00 | | – | – | 1.00 | | – | – |
| Yes | 0.45 (0.10, 2.12) | 0.31 | – | – | 1.42 (0.62, 3.28) | 0.41 | – | – |
| Diabetes | | | | | | | | |
| No | 1.00 | | – | – | 1.00 | | – | – |
| Yes | 0.66 (0.08, 5.26) | 0.70 | – | – | 2.10 (0.82, 5.36) | 0.12 | – | – |
| CVD | | | | | | | | |
| No | 1.0 | | – | – | 1.00 | | – | – |
| Yes | 1.48 (0.38, 5.72) | 0.57 | – | – | 1.32 (0.52, 3.38) | 0.56 | – | – |
| Other digestive system diseases | | | | | | | | |
| No | 1.0 | | – | – | 1.00 | | – | – |
| Yes | 0.71 (0.18, 2.83) | 0.62 | – | – | 1.61 (0.63, 4.13) | 0.32 | – | – |

**Table 4** (*continued*)

 

**Table 4** (*continued*)

| Variables | Metachronous MPMs | | | | Synchronous MPMs | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value | HR (95% CI) | P value |
| Location in esophagus | | | | | | | | |
| Middle or upper | 1.00 | | – | – | 1.00 | | 1.00 | |
| Lower | 1.04 (0.30, 3.67) | 0.95 | – | – | 4.32 (1.69, 11.03) | 0.002 | 4.40 (1.72, 11.29) | 0.002 |
| Type | | | | | | | | |
| 0–IIb | 1.00 | | – | – | 1.0 | | – | – |
| Others | 1.51 (0.32, 7.18) | 0.60 | – | – | 1.82 (0.71, 4.64) | 0.21 | – | – |
| Tumor size | 0.97 (0.69, 1.36) | 0.87 | – | – | 0.79 (0.58, 1.07) | 0.13 | – | – |
| Histology | | | | | | | | |
| High-grade squamous neoplasia | 1.00 | | – | – | 1.00 | | – | – |
| Squamous cell carcinoma | 1.68 (0.43, 6.56) | 0.45 | – | – | 0.67 (0.29, 1.55) | 0.35 | – | – |
| Infiltration depth | | | | | | | | |
| Mucosal layer | 1.00 | | – | – | 1.00 | | 1.0 | |
| Submucosal layer | NA | NA | – | – | 4.13 (1.61,10.56) | 0.003 | 4.09 (1.53, 10.90) | 0.005 |
| Resection margin | | | | | | | | |
| Negative | 1.00 | | – | – | 1.00 | | – | – |
| Positive | 0.60 (0.08, 4.79) | 0.63 | – | – | 0.79 (0.23, 2.67) | 0.71 | – | – |
| Multiple lesions in esophagus | | | | | | | | |
| No | 1.00 | | – | – | 1.00 | | 1.0 | |
| Yes | 2.27 (0.63, 8.13) | 0.21 | – | – | 2.95 (1.24, 7.04) | 0.02 | 3.08 (1.27, 7.46) | 0.01 |
| Lymphatic invasion | | | | | | | | |
| No | 1.00 | | – | – | 1.00 | | – | – |
| Yes | NA | NA | – | – | NA | NA | – | – |
| Venous invasion | | | | | | | | |
| No | 1.00 | | – | – | 1.00 | | – | – |
| Yes | NA | NA | – | – | 2.38 (0.322, 16.67) | 0.40 | – | – |
| Treatment | | | | | | | | |
| EMR | 1.00 | | – | – | 1.00 | | – | – |
| ESD | NA | NA | – | – | 0.93 (0.12, 6.91) | 0.94 | – | – |

MPMs, multiple primary malignancies; HR, hazard ratio; CI, confidence interval; BMI, body mass index; NA, not available; CVD, cardiovascular and cerebrovascular diseases; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

 

occurrence of MPMs. Therefore, in patients with ESCC and concurrent lung tumors, it is crucial to differentiate between metastasis and MPMs. Pathological analysis is the gold standard for differentiating between primary lung tumors and metastatic tumors. If the histological types are identical, further differentiation can be achieved through immunohistochemistry and genetic testing (20). Additionally, distinct radiological characteristics also help differentiate these conditions (21).

Alcohol drinking has been reported as an independent risk factor for the development of multiple primary cancers in esophageal cancer in previous literature (22), and our research is consistent with this finding. Additionally, our findings suggest that long-term heavy alcohol consumption (≥5 standard drinks per day) is strongly associated with an increased incidence of MPMs. This observation supports the "field cancerization" theory in early esophageal cancer (23,24), as alcohol drinking is not only a risk factor for esophageal cancer but also other digestive system cancer and lung cancer (25). Prolonged excessive alcohol consumption may result in the presence of precancerous lesions in other organs at the time of esophageal cancer diagnosis, potentially resulting in subsequent carcinogenesis. At the molecular level, the potential mechanism behind field cancerization and the development of MPMs involves polyclonal mutations in the *P53* gene (26).

For the endoscopic and pathological features of early ESCC combined with MPMs, submucosal invasion, lower location and multiple lesions in esophagus increased the incidence of developing MPMs. Previous studies have demonstrated that multiple Lugol-voiding lesions are associated with an increased incidence of synchronous multiple squamous cell carcinomas in the esophagus, head, and neck, and revealed that *P53* mutations might be the primary mechanism (22,27). Regarding the location of the lesions, we found that lesions located in the lower third of the esophagus are an independent risk factor for the development of MPMs, especially synchronous MPMs. Lower third of the ESCC and adenocarcinoma of the gastric cardia often co-occur, despite their different pathological types (28). This may be due to the fact that these two cancers share common risk factors (such as hot food and smoking) (29) and a common susceptibility locus in *PLCE1* at *10q23* (30). Additionally, the deeper invasion of the tumor was also reported as a risk factor for developing synchronous multiple primary esophageal cancer in esophagus (31), our study further revealed that it was also associated with MPMs of other sites in patients with early ESCC. However, the reason for this is still unclear, and further studies are needed.

There are some limitations in this study. Firstly, this study is retrospective, and the follow-up of cases mainly relied on medical records which may introduce recall bias. Additionally, the smoking and alcohol drinking variables in this study were based on the patient's information at the time they came to Beijing Friendship Hospital, and cancer patients may adopt a healthier lifestyle after treatment. Lastly, our study is a single-center study, and future research may require larger sample sizes or multi-center studies for further validation.

## Conclusions

Our findings indicated that alcohol consumption, lesion location, depth of invasion, and the presence of multiple lesions were significantly associated with the occurrence of MPMs in patients with ESCC. We have also identified the specific locations where MPMs are more likely to occur. These findings will assist clinicians in formulating follow-up strategies, potentially improving the prognosis for patients with early ESCC.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-299/rc

*Data Sharing Statement:* Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-299/dss

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-299/coif). The authors have no conflicts of interest to declare.

*Ethics Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Beijing Friendship Hospital Ethics Committee (No. 2020-P2-290-01), and the informed consent was exempted due to the retrospective design.



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