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Clinical benefits from endoscopy screening of esophageal second primary tumor for head and neck cancer patients: Analysis of a hospital-based registry

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ABSTRACT

Objectives: Esophageal second primary tumors (SPTs) in head and neck cancer (HNC) patients is not uncommon. The impact of image-enhanced endoscopy (IEE) screening for esophageal SPT on the outcome of HNC patients has not been well clarified.

Methods and methods: Patients with malignancies of the head and neck region and esophagus were recruited from a hospital-based cancer registry between July 2000–December 2016. IEE screening included magnifying endoscopy with narrow-band imaging and chromoendoscopy with Lugol's solution. Biopsied specimens with revised Vienna classification categories 1 and 2 were defined as group I, and those with categories 3 to 5 were defined as group II. The Kaplan-Meier estimate and Cox regression model were used for survival analysis.

Results: Totally 1577 HNC and 501 esophageal cancer patients were enrolled. The 5-year overall survival (OS) rates of stage I/II HNC, stage III/IV HNC and esophageal cancer patients were 58%, 29%, and 8%, respectively ($p < 0.01$). The 5-year OS rate of HNC patients with negative IEE results was higher than that of HNC patients without IEE screening, followed by IEE screening groups I, II and esophageal cancer patients (44% *vs.* 39% *vs.* 35% *vs.* 11% *vs.* 8%, respectively, p for trend < 0.01). Among advanced HNC patients, those who received IEE screening had a trend of better prognosis than those without screening (5-year OS rate of 31% *vs.* 28%, $p = 0.17$).

Conclusions: IEE screening for esophageal SPTs is helpful in risk stratification and prognosis prediction for HNC patients. Routine IEE screening is recommended in HNC patients.

Introduction

The occurrence of synchronous second primary tumors (SPTs), which is associated with a higher mortality rate, is not uncommon in head and neck cancer (HNC) patients, where the incidence of SPTs ranges between 7–36% [1–5]. The most common sites of SPTs are the esophagus, the head/neck region and the lungs, and they can develop synchronously or metachronously with the index primary malignancies

Abbreviations: AJCC, the American Joint Committee on Cancer; CI, confidence interval; CIS, carcinoma in situ; DSS, disease-specific survival; ESD, endoscopic submucosal dissection; ESCN, esophageal squamous cell neoplasia; FEMH, Far Eastern Memorial Hospital; HR, hazard ratio; HNC, head and neck cancer; HGIN, high-grade intraepithelial neoplasia; IEE, image-enhanced endoscopy; IPCL, intraepithelial papillary capillary loop; LGIN, low-grade intraepithelial neoplasia; ME, magnifying endoscopy; NBI, narrow-band imaging; OS, overall survival; SPT, second primary tumor; WLI, white-light imaging

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with a cumulative incidence rate of up to 36% at 20 years after diagnosis of primary malignancies [3,6,7]. The sites of SPT formation, which belong to the upper aerodigestive tract, are exposed to common carcinogens leading to tumorigenesis in high-risk populations, especially those with genetic polymorphisms of alcohol-metabolizing enzymes, so-called "field cancerization" [8,9]. The screening or management of SPTs in diverse areas remains challenging in HNC patients, particularly for asymptomatic SPTs that are easily overlooked.

Esophageal squamous cell neoplasia (ESCN) is the most common SPT in HNC patients; the overall survival of those with synchronous or metachronous ESCN has been demonstrated to be worse than those without SPTs [1,3,6,10,11]. Given that superficial ESCNs have a lower nodal metastasis rate with excellent survival and that surgical esophagectomy has considerably high mortality and morbidity rates, endoscopic resection techniques such as endoscopic submucosal dissection (ESD) have replaced surgery as a minimally invasive procedure that can provide comparable long-term outcomes and better patient quality of life [12,13]. Hence, through endoscopic screening of ESCNs in HNC patients, especially using image-enhanced endoscopy (IEE) techniques, early ESCNs can be identified and resected endoscopically before late stage-related obstructive symptoms. It has been theorized that with screening and endoscopic resection of early ESCNs before the management of index primary tumors, the outcome of HNC patients could be improved. However, direct benefits from IEE screening of ESCNs in HNC patients have not been demonstrated, and the long-term outcome of those who underwent IEE screening remains undetermined [14,15]. In this study, we aimed to evaluate the survival benefits from IEE screening of ESCNs in HNC patients according to large hospital-based registry data.

Materials and methods

Study design

This study protocol was approved by the intuitional ethical review board (IRB No: 106090-E) of Far Eastern Memorial Hospital (FEMH). Between July 2000 and December 2016, patients with registered malignancies of the head and neck region in the Cancer Center of FEMH were recruited; we excluded patients with a diagnosis of cancers of the nasopharynx, salivary glands, ear, and trachea (Fig. 1). Another group of esophageal cancer patients who were registered in the same period was recruited for comparison. The cancer staging was recorded according to the AJCC 7th edition system. The medical records, including demographic data, treatment course and endoscopic reports, were reviewed. The treatment strategy of HNC patients with esophageal SPTs was made by expert opinions from tumor board meetings composed of gastroenterologists, radio-oncologists, and surgical and medical oncologists. After a complete review and discussion of each patient's condition, the final treatment options of index primary cancers and esophageal SPTs were made. Concomitant treatment of index primary HNC and esophageal SPTs was given, including ESD for superficial ESCNs and concurrent chemoradiotherapy of both primary and secondary tumors.

IEE screening of esophagus and histopathological examination

HNC patients who had undergone endoscopic screening of the esophagus received magnifying endoscopy (ME) screening, which has a powerful 80-fold optical magnification with a narrow-band imaging (NBI) system (Evis Lucera CLV-260NBI, GIF-H260Z endoscopy, Olympus Medical Systems Corp, Tokyo, Japan), and chromoendoscopy with 2% Lugol's solution (Sigma-Aldrich, St. Louis, Missouri, USA). Those without endoscopy within one year of index tumor diagnosis were defined as those without screening for synchronous esophageal neoplasms. All endoscopists in this study had experience of at least 60 NBI endoscopy screening procedures per month. Endoscopic, suspicious esophageal neoplasia was defined as a hyperemic change, uneven or nodularity of mucosa under a white-light (WLI) system, brownish discoloration of mucosa with abnormal intraepithelial papillary capillary loops (IPCLs) under the ME-NBI system, a well-demarcated Lugol-unstained area with a diameter ≧5 mm or Lugol-voiding lesions of any size accompanied with a pink color change [16–18]. Endoscopic biopsies were performed for all suspicious lesions fulfilling the criteria mentioned above.

The biopsied specimens were examined by experienced pathologists and reported using the definition of revised Vienna classification for gastrointestinal epithelial neoplasia [19]. Specimens that were negative for neoplasia/dysplasia were classified as category 1, chronic inflammation and squamous hyperplasia belonging to the diagnosis of indefinite for neoplasia were classified as category 2, noninvasive, low-grade intraepithelial neoplasia (LGIN) were classified as category 3, high-grade intraepithelial neoplasia (HGIN) and carcinoma-in situ (CIS) were classified as category 4, and intramucosal or submucosa invasive carcinomas were classified as category 5 [19]. Dysplastic mucosa is associated with an increased risk for ESCNs; thus, we defined categories 1 and 2 as benign conditions (group I) and categories 3 to 5 as premalignant and malignant conditions (group II) [20].

Statistical analysis

The outcome assessment was connected to the national cancer registry and death registry databases, and we assessed both overall survival (OS) and disease-specific survival (DSS). The endpoint OS was defined as the time from initial diagnosis to any cause of death or to the last follow-up. DSS was defined as the time from diagnosis to cancer-related death or to the last follow-up. We used the Kaplan-Meier method with the log-rank test to test different variables with OS and DSS. Univariate and multivariate Cox-regression analyses were used to assess the hazard of risk factors, and statistical analyses were performed using STATA software, version 12.0 (Stata Statistical Software: Release 12. College Station, TX: Stata Corp LP).

Results

Demographic data, endoscopic findings and treatment of SPTs

In total, 3352 patients were diagnosed with HNC during the study period (Fig. 1). Among them, 91 patients had repeated registration. A total of 868 patients with cancers of the nasopharynx, salivary glands, ear, and trachea were excluded. During the study period, 790 patients were registered as having esophageal cancer. We excluded data from 315 HNC and 289 esophageal cancer patients with uncertain staging. Finally, 1577 HNC and 501 esophageal cancer patients were enrolled for analysis (Table 1). The designations of index primary tumors were oral cancer (1206, 76.5%), oropharyngeal cancer (180, 11.4%), hypopharyngeal cancer (111, 7.0%), and laryngeal cancer (80, 5.1%). The mean (± SD) age and the percentage of male patients within the HNC and esophageal cancer groups were 54.95 ± 11.52 years and 91.82% and 57.58 ± 10.99 years and 93.01%, respectively. The TNM stage I/II/III/IV of HNC and esophageal cancer patients were 324 (20.55%)/252 (15.98%)/227 (14.39%)/774 (49.08%) and 24 (4.79%)/62 (12.38%)/235 (46.91%)/180 (35.93%) patients, respectively. Among HNC patients, 501 (31.77%) had undergone IEE screening for synchronous ESCNs. There was a higher proportion of advanced stage (III/VI) HNC patients (68.26% *vs.* 61.25%, $p < 0.01$) and hypopharyngeal cancer patients (57.66% *vs.* 42.34%, $p < 0.01$) in the IEE screening group. Compared with HNC patients, more esophageal cancer patients were diagnosed at advanced stage (III/IV, 82.84% *vs.* 63.47%).

Among 501 H&N cancer patients with IEE screening (Fig. 1), 413 (82.4%) patients underwent endoscopy within 3 months of index tumor diagnosis. A total of 109 endoscopic biopsies were performed. There were 49 (44.95%) benign pathologies, 12 (11.01%) LGIN, 26 (23.85%)

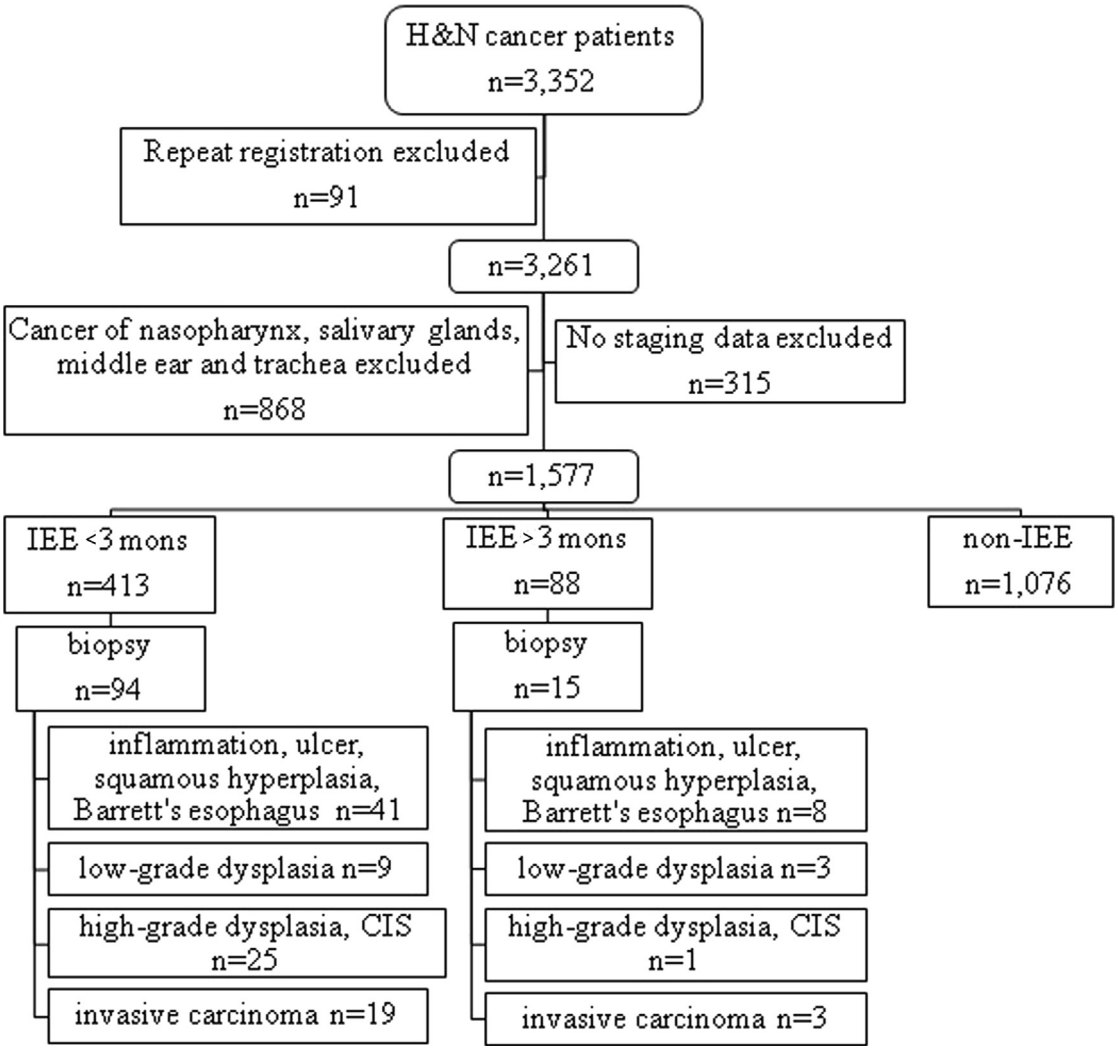

Fig. 1. Study flow diagram. H&N- head and neck; IEE- image-enhanced endoscopy; CIS- carcinoma in situ.

HGIN or CIS, and 22 (20.18%) invasive carcinoma lesions of the esophagus screened by IEE. Among invasive lesions, there were one patient at IIA, one at IIIA, six at IIIC, and 2 at IV stage. Ten patients did not complete staging work-up for esophageal SPTs because of advanced primary HNC. Two patients with LGIN were treated by endoscopic radiofrequency ablation, 10 LGIN and 26 HGIN lesions were treated by endoscopic submucosal dissection. CCRT were administered for 22 patients with invasive esophageal SPTs and six of them received esophagectomy. Three patients developed lung cancer at 18, 45, and 59 months after treatment of primary tumors, respectively.

Survival analysis

The survival analysis is shown in Fig. 2 and Table 2. The 5-year OS/DSS rates for stage I/II HNC, stage III/IV HNC and esophageal cancer patients were 58%/58%, 29%/29%, and 8%/8%, respectively ($p < 0.01$, Fig. 2A & B). The 5-year rate of OS/DSS for HNC patients with negative IEE results was higher than for HNC patients without IEE

Table 1
Demographic characteristics of recruited patients.

	H&N cancer (n = 1577) No. of patients (%)				Esophageal cancer (n = 501) No. of patients (%)
	IEE	Without IEE	p	Total	Total
	n = 501	n = 1076		n = 1577	n = 501
Age (mean ± SD), years	55.18 ± 10.29	54.84 ± 12.05	0.59	54.95 ± 11.52	57.58 ± 10.99
AJCC stage			0.01		
I/II	159 (27.6)	417 (72.4)		576 (37)	24 (4.8)/62 (12.4)
III/VI	342 (34.2)	659 (65.8)		1001 (63)	235 (46.9)/180 (35.9)
Gender, female:male	41 (8.2): 460 (91.8)	88 (8.2): 988 (91.8)	1.00	129 (8.18): 1448 (91.82)	35 (7): 466 (93)
Location of H&N cancer		< 0.01			
Oral cavity	339 (28.11)	867 (71.89)		1206 (76.47)	
Oropharynx	64 (35.56)	116 (64.44)		180 (11.42)	
Hypopharynx	64 (57.66)	47 (42.34)		111 (7.04)	
Larynx	34 (42.5)	46 (57.5)		80 (5.07)	

Abbreviation: AJCC, the American Joint Committee on Cancer; H&N, head and neck; IEE, image-enhanced endoscopy.

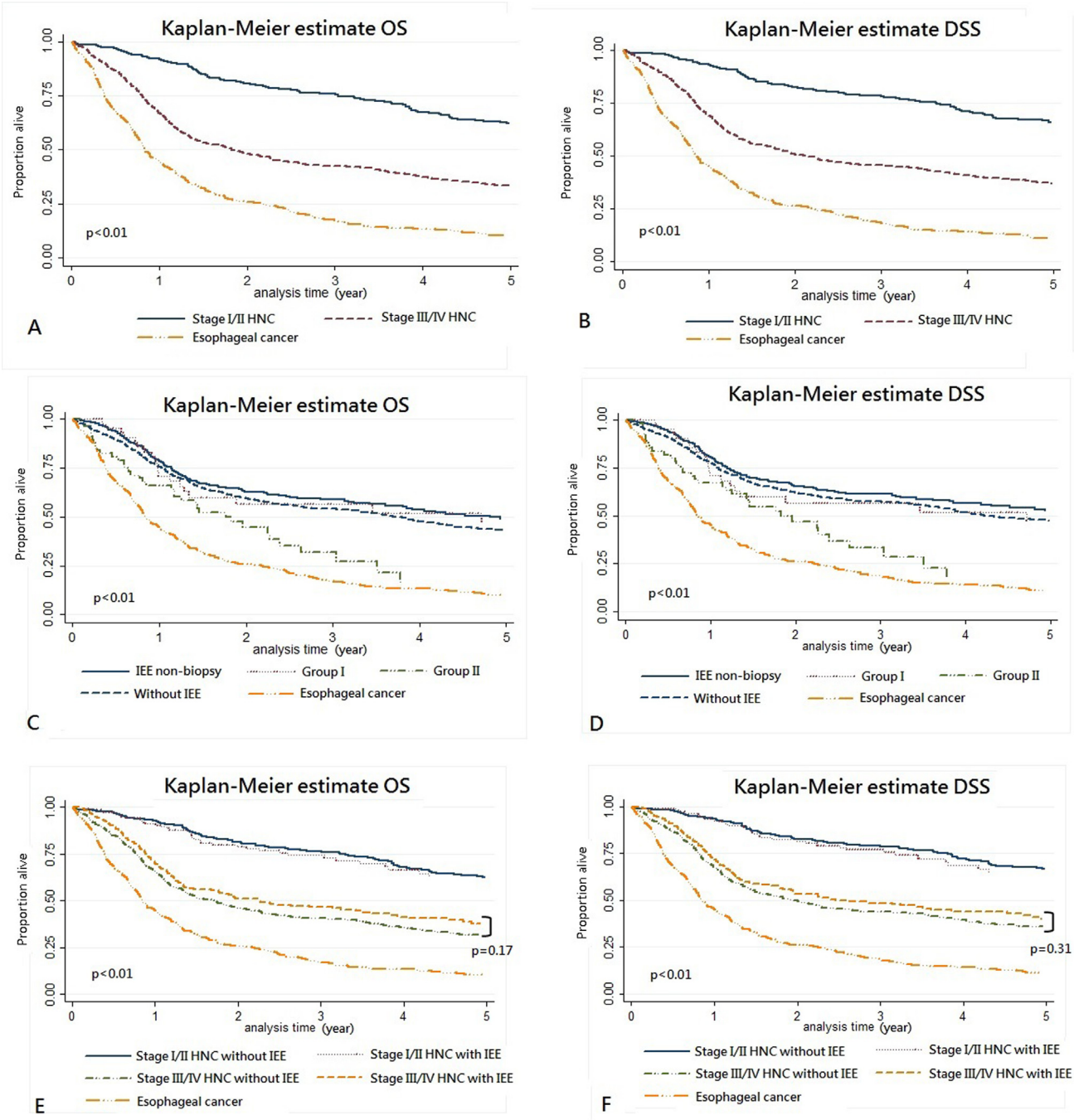

Fig. 2. Kaplan-Meier estimate for survival analysis. OS-overall survival; DSS-disease-specific survival. (A) & (B) Comparison between head and neck cancer (HNC) and esophageal cancer patients. (C) & (D) Comparison between HNC patients with negative findings on IEE screening, benign condition (group I), premalignant and malignant condition (group II), without IEE screening, and esophageal cancer patients. (E) & (F) Comparison between HNC patients with and without IEE screening and esophageal cancer patients.

screening (44%/44% *vs.* 39%/39%), while group II HNC patients (11%/11%) and esophageal cancer patients (8%/8%) had worse outcomes than group I HNC patients (35%/35%) ($p < 0.01$, Fig. 2C & D). Stage I/II HNC patients with and without IEE screening of the esophagus had similar survival, while advanced HNC patients who received IEE screening had a trend of better prognosis than those without IEE screening of esophagus (OS/DSS 31%/31% *vs.* 28%/28%, $p = 0.17/0.31$, Fig. 2E & F).

Cox regression analysis is shown in Table 3. In univariate analysis, age (OS/DSS, HR 1.01/1.01, p for both < 0.01) and cancer of the oropharynx (HR 1.55/3.75, $p = 0.05/ < 0.01$, respectively) and hypopharynx (HR 1.90/4.50, p for both < 0.01) were associated with worse prognosis. In multivariate analysis, age (HR 1.01/1.01, p for both < 0.01) and cancer of the oropharynx (HR 1.43/1.50, $p = 0.01/ < 0.01$, respectively) were associated with poor survival. Compared with stage I/II HNC patients who received IEE screening of the esophagus, stage III/IV patients with IEE (HR 2.48/2.70, p for both < 0.001 in univariate analysis, HR 2.33/2.42, p for both < 0.01 in multivariate analysis) and without IEE (HR 2.81/2.99, p for both < 0.01 in univariate analysis, HR 2.77/2.84, p for both < 0.01 in multivariate analysis) screening had worse survival.

Table 2
Median time analysis and five-year survival rate analysis for overall survival and disease specific survival.

		Overall survival		Disease specific survival	
		Median time (95%CI), years	5 years survival (95%CI), %	Median time (95%CI), years	5 years survival (95%CI), %
H&N cancer					
Stage I/II	Total	8.12 (6.43–9.81)	58 (53–64)	10.45 (8.12–NA)	58 (53–64)
	Without IEE	7.87 (5.90–9.85)	58 (52–64)	NA (5.79–NA)	59 (47–69)
	With IEE	9.57 (5.16–13.98)	59 (47–69)	10.45 (7.33–NA)	58 (52–64)
Stage III/IV	Total	1.83 (1.50–2.26)	29 (25–33)	2.14 (1.77–2.65)	29 (25–33)
	Without IEE	1.69 (1.40–2.05)	28 (23–32)	1.94 (1.52–2.45)	31 (24–38)
	With IEE	2.26 (1.58–3.61)	31 (24–38)	2.46 (1.83–4.52)	28 (23–32)
Overall					
Without IEE		3.78 (1.29–5.79)	39 (35–43)	4.31 (3.81–5.19)	39 (35–43)
IEE with negative findings		4.82 (3.61–6.77)	44 (37–51)	5.45 (4.19–NA)	44 (37–51)
IEE group I		4.71 (0.69–8.74)	35 (17–54)	4.71 (0.69–8.74)	35 (17–54)
IEE group II		1.77 (1.18–2.39)	11 (2–30)	1.83 (1.18–2.63)	11 (2–30)
Esophageal cancer		0.84 (0.78–0.97)	8 (6–12)	0.84 (0.79–0.99)	8 (6–12)

Abbreviation: CI, confidence interval; H&N, head and neck; IEE, image-enhanced endoscopy; NA-Not available due to data without convergence.

Discussion

Currently, no well-established evidence and recommendations are available to define the screening and treatment protocol for SPTs in HNC patients. Given that the development of SPTs associated with poor prognosis is not uncommon in HNC patients, it is of paramount importance to investigate the impact of screening programs on the survival of HNC patients [1–5]. In this study, utilizing a large hospital-based cancer registry database for analysis, we found that the survivals of HNC patients are better than those of esophageal cancer patients. Additionally, the 5-year OS and DSS rates of HNC patients with negative findings on IEE screening of esophagus are the best, followed, in decreasing order, by those of patients without IEE screening, those with benign conditions, and those with premalignant and malignant conditions by IEE screening (44%, 39%, 35%, and 11%, Table 2). In advanced (stage III/IV) HNC patients, those with IEE screening of the esophagus tended to be associated with a better outcome than those without screening (Table 3 and Fig. 2E & F). Therefore, the application of IEE screening for esophageal SPTs is helpful in risk stratification and prognosis prediction for HNC patients.

HNC and esophageal cancers are among the most common malignancies, with poor overall survival rates worldwide [21]. Delayed diagnosis and neglect of synchronous or metachronous SPTs are important reasons for poor prognosis, whereby HNC patients with second primary esophageal cancer have poor prognosis with 5-year OS of only 6% [11,22]. In a Turkish study of 1112 HNC patients, Erkal et al. demonstrated that 7–9% of patients presented with SPTs of head and neck regions different from the index primary site [2]. Of note, 1% and 7% of patients developed metachronous esophageal and lung SPTs, respectively [2]. Another long-term (follow-up of at least 10 years) prospective study of 2063 HNC patients showed an incidence of 17% for metachronous SPTs with a median survival of only 12 months [23]. Moreover, the longer survival of HNC patients is associated with a higher incidence of developing SPTs. A Korean study of 937 HNC patients revealed a cumulative incidence of 7.2% within 6 months (synchronously), 17.9% at 5 years, and 23.1% at 10 years to develop SPTs after index primary tumor diagnosis [3]. These large cohort studies without routine endoscopic screening for esophageal SPTs shed light on the importance of screening and surveillance of SPTs in HNC patients.

The screening of SPTs in HNC patients has become one of the most important aspects of treatment strategies. Among SPTs of different sites, the incidence of synchronous SPTs in the esophagus ranges from 3.2–28% in HNC patients through IEE screening [1–5,14,15,18]. Previous studies on screening ESCN in HNC patients reported that approximately 15.5%～23.3% of patients had modified treatment plans after detection of esophageal SPTs [1,5,14,15,18]. Meanwhile, several retrospective case-control studies demonstrated that HNC patients may benefit from routine IEE screening of esophagus, but prospective studies are inconclusive [15,24,25]. The contribution of index primary tumors to survivals might be larger than SPTs, especially SPTs at superficial status, and the treatment plan for primary and secondary tumors should be determined by the staging of both sites, patients' condition and

Table 3
Overall survival and disease specific survival analysis with Cox regression.

	Univariate analysis				Multivariate analysis			
	Overall survival		Disease specific survival		Overall survival		Disease specific survival	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.01 (1.01–1.02)	< 0.01	1.01 (1.00–1.01)	0.002	1.01 (1.00–1.02)	0.001	1.01 (1.00–1.01)	0.167
Gender (male:female)	1.21 (0.96–1.51)	0.111	1.23 (0.96–1.56)	0.097	1.16 (0.84–1.55)	0.327	1.15 (0.84–1.57)	0.389
Location of H&N cancer								
Larynx	1		1		1		1	
Oral cavity	1.13 (0.75–1.69)	0.559	2.57 (1.37–4.81)	0.003	1.19 (0.95–1.49)	0.122	1.28 (1.02–1.61)	0.035
Oropharynx	1.55 (0.99–2.42)	0.054	3.75 (1.95–7.22)	< 0.01	1.43 (1.10–1.86)	0.007	1.50 (1.15–1.96)	0.003
Hypopharynx	1.90 (1.19–3.02)	0.007	4.50 (2.30–8.80)	< 0.01	0.96 (0.66–1.40)	0.841	0.48 (0.28–0.84)	0.01
Screening of synchronous esophageal neoplasm								
Stage I/II with IEE	1		1		1		1	
Stage I/II without IEE	1.07 (0.75–1.52)	0.712	1.07 (0.73–1.57)	0.735	1.08 (0.76–1.54)	0.672	1.05 (0.72–1.55)	0.786
Stage III/IV with IEE	2.48 (1.76–3.49)	< 0.01	2.70 (1.87–3.90)	< 0.01	2.33 (1.65–3.29)	< 0.01	2.42 (1.67–3.51)	< 0.01
Stage III/IV without IEE	2.81 (2.03–3.87)	< 0.01	2.99 (2.11–4.24)	< 0.01	2.77 (2.00–3.83)	< 0.01	2.82 (1.99–4.00)	< 0.01

Abbreviation: CI, confidence interval; DSS, disease specific survival; HR, hazard ratio; IEE, image-enhanced endoscopy.

preference to receive aggressive management of both primary and second primary malignancies. According to the results of our previous and current studies, most ESCNs detected by IEE are at premalignant or superficial malignant states, which could be curatively treated by ESD [1,10,24]. By IEE screening, there were more patients with esophageal SPTs at premalignant conditions or early stages when compared with symptomatic esophageal cancer cohort in this study. We also demonstrated that HNC patients with negative findings on IEE screening had better survival than those without IEE screening (Table 2), and there is a trend of slightly better survivals in advanced HNC patients who received IEE screening of esophageal SPTs and treatment of both primary and secondary tumors simultaneously than in patients who were not screened for SPTs, although this difference was not statistically significant (Table 3 and Fig. 2E & F). Thus, by using esophageal SPT detection and management accordingly, the prognosis of HNC patients could be predicted, and the overall outcome could be improved.

Regarding the screening tools for ESCNs, endoscopic examination remains the gold standard. Compared with conventional WLI, advances in IEE technology using optical- and dye-based techniques have improved diagnostic performance for the detection of esophageal precancers or early cancers [10,26]. Among various IEE techniques, the NBI system has been demonstrated as the most highly accurate screening tool for SPTs by a meta-analysis of 4918 patients from 16 prospective and randomized trials with an area under the receiver-operating characteristic curve of 97%, which is higher than that for WLI (66%) and Lugol's chromoendoscopy (82%) [10]. Through IEE screening of the esophagus in HNC patients, superficial synchronous ESCNs could be identified before late-stage obstructive symptoms occur [1,5,14,16]. These superficial ESCNs can be treated by ESD with a complete resection rate of 78–100% and a low recurrence rate of 0–2.6% [27]. Because of high morbidities and mortalities from surgical esophagectomy, patients with early ESCNs benefit from ESD with comparable long-term survival and better quality of life. Nevertheless, no established evidence has shown survival benefits from the management of SPTs simultaneously in HNC patients, and it has remained debated whether early esophageal SPTs in advanced HNC patients should be treated or not. In our study, advanced HNC patients who received IEE screening of esophageal SPTs and treatment of both primary and secondary tumors simultaneously (multivariate analysis, HR 2.33, 95% CI 1.65–3.29) had better survival than those without IEE screening of esophageal SPTs (HR 2.77, 95% CI 2.00–3.83), although the differences were not statistically significant (Table 3 and Fig. 2E & F). Given that the survival of advanced HNC patients has been improved by advancements in multidisciplinary treatment modalities, we believe that the treatment of superficial esophageal SPTs should still be considered as long as the general conditions of HNC patients allow ESD or concurrent chemoradiotherapy intervention for esophageal SPTs [28].

There were some limitations in this study. Firstly, it was conducted in a single tertiary center, not in multicenter or nationwide fashions. However, the number of patients was large, and diagnosis or treatment strategies were standardized in this hospital-based study. Secondly, the surveillance of IEE screening for metachronous esophageal SPTs was not standardized. Only HNC patients in group II received regular IEE surveillance every 6–12 months, and the impact of metachronous esophageal SPTs was not analyzed. Thirdly, because of small number of HNC patients with synchronous esophageal SPTs, we did not perform subgroup analysis according to different site of primary index tumors.

Conclusion

IEE screening could not only identify early stage, esophageal SPTs that have a chance to be curatively resected by ESD but also help in risk stratification and prognosis prediction for HNC patients. We recommend routine IEE screening of the esophagus in newly diagnosed HNC patients. However, further studies are warranted to evaluate the surveillance program for metachronous esophageal SPTs for HNC patients.

Declaration of Competing Interest

None declared.

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