ORIGINAL ARTICLE

Image-enhanced endoscopy for detection of second primary esophageal neoplasms in patients with hypopharyngeal cancer: Prevalence, risk factors, and characteristics

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Abstract

Background: Esophageal second primary neoplasms (ESPNs) are common in hypopharyngeal squamous cell carcinoma (HPSCC) patients and are associated with poor prognoses. The effectiveness of image-enhanced endoscopy (IEE) has not been well established.

Methods: We reviewed the patients between April 2016 and April 2018 with HPSCC receiving ESPNs screening via white-light imaging, narrow-band imaging, and Lugol chromoendoscopy.

Results: Of 99 eligible patients, ESPNs prevalence was 31%. Of the 69 patients assigned to the follow-up group, 23 with positive findings showed significantly increased previous histories of second primary malignancies in the upper aerodigestive tract. Among them, patients without symptoms at the time of IEE screening showed less advanced T stages and higher percentages of receiving minimal invasive therapy.

Conclusion: The present study represented the clinical utility of routine IEE screening in HPSCC patients and proposed routine surveillance may help identify and properly manage early-stage ESPN.

Keywords: Esophageal neoplasms; Head and neck cancer; Hypopharyngeal squamous cell carcinoma; Image-enhanced endoscopy; Second primary neoplasms

1. INTRODUCTION

Hypopharyngeal squamous cell carcinoma (HPSCC) accounts for approximately 3%–5% of all head and neck cancers[1] and has the poorest prognosis in primary head and neck cancers due to delayed diagnosis and the high frequency of regional neck lymph node metastasis and distant metastasis. Furthermore, the prognosis of these patients is influenced by the occurrence of second primary malignancies (SPMs).[2]

The theory of "field cancerization," explained by Slaughter et al[3] in 1953, states that repeated exposure of carcinogens can result in the development of multiple tumors throughout the upper aerodigestive tract (UADT). In patients with HPSCC, SPMs are common, with an incidence of 10%–50%,[2,4–6] and the esophagus is the most common site. In our previous report,[7] 16% of the patients with HPSCC developed SPMs and esophagus is the most common site of SPMs (43%). The SPMs that occurred in the nonhead and neck area had poorer survival than those in the head and neck area (30% vs 58% at 3 years, $p = 0.002$).

In the past, esophageal squamous cell neoplasms were often diagnosed late and required highly invasive treatment.[8] Recently, the improvement of endoscopy technology helps with the early detection and treatment of esophageal second primary neoplasms (ESPNs).[9] Several published studies have investigated the efficacy of endoscopy screening for patients with newly diagnosed head and neck cancer;[9,10] however, it is interesting and important to put more effort into understanding the incidence of ESPNs and to determine the risk factors for developing metachronous ESPNs in patients with treated HPSCC.

The aim of our study was to evaluate the clinical utility of image-enhanced endoscopy (IEE) for the detection of ESPNs in patients with newly diagnosed and treated HPSCC.

2. METHODS

2.1. Study population

We retrospectively reviewed the medical charts of patients who were diagnosed with HPSCC at Taipei Veterans General Hospital, Taiwan, between April 2016 and April 2018. The enrolled patients were referred to the endoscopy center for

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diagnosis in Taipei Veterans General Hospital, where they underwent IEE screening of the upper gastrointestinal tract. The exclusion criteria for our study were as follows: Other head and neck cancers, hypopharyngeal cancer but not squamous cell carcinoma (SCC), recurrent or metastatic HPSCC cases, and patients who did not receive IEE due to compromised airways, tumor bleeding, or refusal. Patients who were newly diagnosed with HPSCC and underwent IEE screening during a primary staging work-up were defined as the newly diagnosed (ND) group, and patients who had previously been treated for HPSCC and underwent IEE screening during their follow-up (FU) period were defined as the FU group. All patients provided written informed consent and the study design was approved by the hospital' s institutional review board (Number of IRB: 2020-03-002CC).

2.2. Primary tumor survey/follow-up

All patients routinely received a standard work-up, including medical history submission, comprehensive physical examination, and endoscopic examinations of the pharynx and larynx during initial staging and FU after treatment. Patients underwent FU every month during the first year, every 2 months in the second year, every 3 months in the third year, and every 6 months thereafter. Computed tomography or magnetic resonance imaging of the head and neck was carried out every 6 to 12 months up to the second year and every 2 years thereafter.

2.3. Esophageal screening

Since 2016, patients with head and neck cancer in our hospital have received routine IEE screening of the esophagus. Patients who were newly diagnosed with head and neck cancer received IEE screening before treatment of the index primary tumor. For patients with a history of head and neck cancer, IEE was also arranged annually during their FU outpatient visits. IEE was performed by three experienced endoscopists for diagnosis and treatment at the endoscopy center of our hospital using high-resolution zoom endoscopy and narrow-band imaging using the Evis Lucera CV-290 Endoscopy Processer System (GIF-H260Z or GIF-H290Z; Olympus Medical System Corp, Tokyo, Japan). A soft black hood (MAJ-1989, Olympus Medical System Corp, Tokyo, Japan) was attached to the tip of the endoscope to obtain an optimal image of up to 80× magnification. For patients with trismus, a 5.5-mm diameter endoscope (XP-260N or XP-290N, Olympus Medical System Corp, Tokyo, Japan; Evis Lucera CLV-290) was used for examination. For detection of any suspicious mucosal lesions in the upper gastrointestinal tract, white-light endoscopy (WLE), and narrow-band imaging with magnification (NBI-M) were used for initial endoscopic evaluation. Then Lugol chromoendoscopy was performed by steadily spraying approximately 10–20 mL of iodine staining (Lugol's solution) over the entire esophagus via dye-spraying catheter (PW-5L-1, Olympus Medical System Corp, Tokyo, Japan). Endoscopic biopsies were performed on all suspected ESCNs as follows: (1) hyperemic changes, ulcerations, uneven, or nodular mucosa under WLE (Fig. 1), (2) brownish discoloration of mucosa with abnormal intraepithelial capillary loop pattern according to Japanese Esophageal Society (JES) classification Type B1-B3 under NBI-M (Fig. 2),[11] (3) demarcated Lugol-voiding lesions of diameter >0.5cm (Fig. 3), (4) Lugol-voiding lesions with pink-color sign (Fig. 4).

The biopsied tissues were sent for pathological studies. The ESCNs in this study included high-grade dysplasia, carcinoma in situ, and SCC. The 7th edition of the American Joint Committee on Cancer were used for tumor staging.[12]

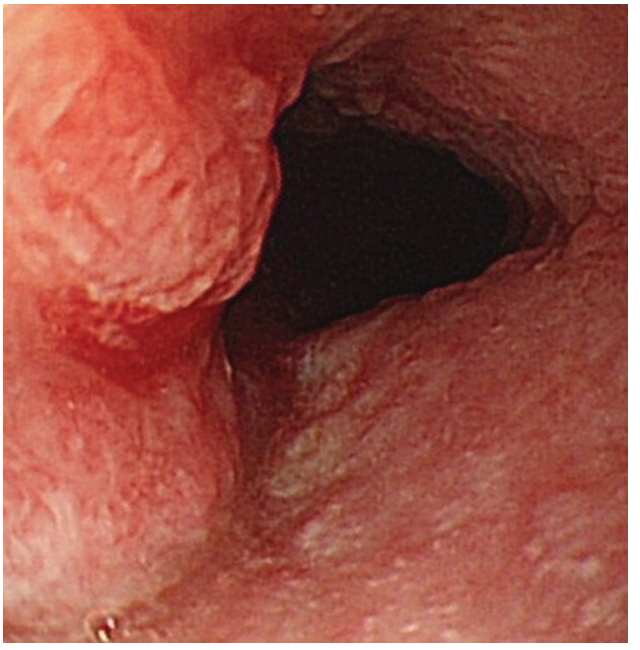

Fig. 1 Uneven mucosa with nodularity.

Second primary ESCN was defined based on the criteria established by Warren and Gate in 1932 as follows: (1) both tumors are malignant on histological examination, (2) the tumor must be anatomically separated by normal mucosa, and (3) the possibility that one tumor represents metastasis from the other must be excluded.[13]

2.4. Statistical analysis

Statistical analyses were performed using commercially available computer software (SPSS v 21.0, Chicago, IL). Descriptive statistical analyses were undertaken on patient characteristics and the results of IEE. Nonparametric qualitative and quantitative comparisons were performed using Pearson chi-square or Fisher's exact test. For all analysis, a two-sided p value of 0.05 or less was considered statistically significant.

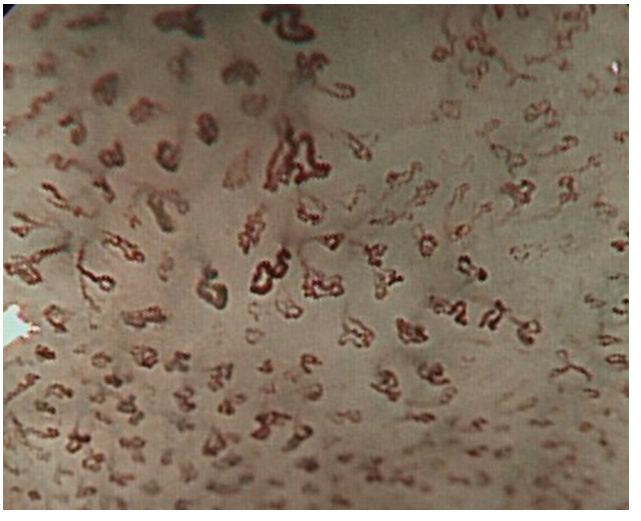

Fig. 2 Brownish discoloration with abnormal intraepithelial capillary loop, JES Type B1.

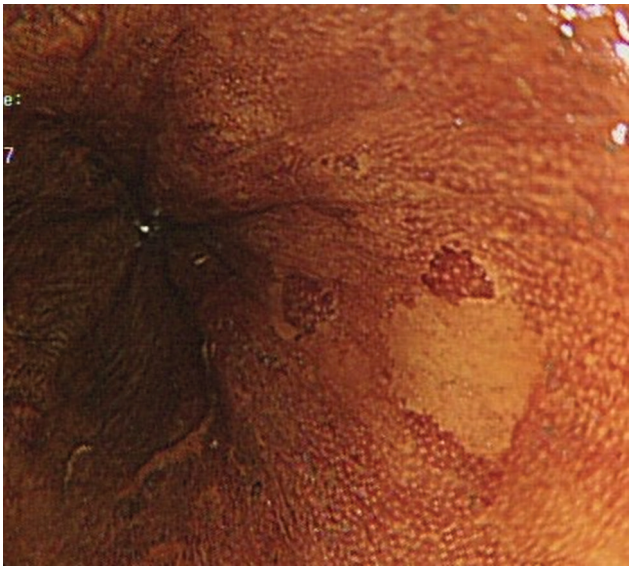

Fig. 3 Demarcated Lugol-voiding lesions.

3. RESULTS

A total of 99 patients were enrolled in this study. The demographic data of the patients are listed in Table 1. Age ranged from 35 to 79 years, with a mean age of 57 years. Most patients had a history of carcinogen exposure, including tobacco consumption, alcohol consumption, and betel quid chewing. In accordance with the American Joint Committee on Cancer (7th Edition),[12] 15 patients (15%) were stage I or II, 15 (15%) were stage III, and 69 (70%) were stage IV. Forty-one patients (41%) had received radiation therapy or chemoradiation therapy as primary treatment. Nineteen patients (19%) had a history of SPMs.

The results of IEE examination are summarized in Table 2. A positive finding of ESPN was detected in 31 patients (31%). The prevalence of ESPN in the ND group and the FU group were 27% (8 patients) and 33% (23 patients), respectively.

Among the eight patients with ESPN in the ND group, a total of 10 lesions were found, and the pathologic examinations showed that the lesions included severe dysplasia, carcinoma in situ, SCC, and non-SCC. The locations of the ESPN included the upper third, middle third, and lower third segments of the esophagus, and one patient had multiple-site ESPNs.

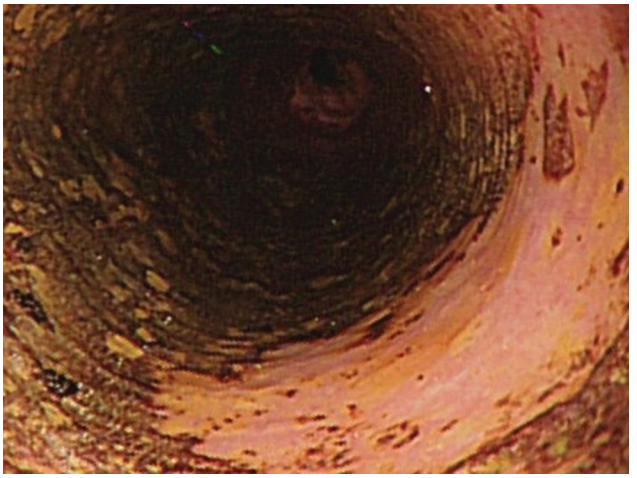

Fig. 4 Lugol-voiding lesions with pink—color sign.

Table 1

Demographic data of the patients

Factor	No. (%)
Age, y	
Median (range)	57 (35–79)
Sex	
Male	98 (99)
Female	1 (1)
Tobacco consumption	
Yes	97 (98)
No	2 (2)
Alcohol consumption	
Yes	92 (93)
No	7 (7)
Betel quid chewing	
Yes	70 (71)
No	29 (29)
Clinical T stage	
T1	10 (10)
T2	34 (34)
T3	13 (13)
T4	42 (43)
Clinical N stage	
N0	24 (24)
N+	75 (76)
Clinical TNM stage	
Stage I	5 (5)
Stage II	10 (10)
Stage III	15 (15)
Stage IV	69 (70)
Primary treatment	
RT/CRT	41 (41)
Surgery ± adjuvant therapy	58 (59)
Previous second primary malignancy	
Yes	19 (19)
No	80 (81)

RT = radiation therapy; CRT = chemoradiation therapy.

In the FU group, ESPNs were detected in 23 patients, and 26 lesions were found. The histology of ESPNs included severe dysplasia, carcinoma in situ, and SCC. The sites of lesions involved upper third, middle third, and lower third segments of the esophagus.

The staging of ESPNs in the ND and FU groups are presented in Table 2. All ESPNs in the ND group and 74% of ESPNs in the FU group were determined as early-stage (from stage 0–II) lesions.

Table 3 shows the results of the comparison of patient characteristics and the indices of primary tumors between patients in the FU group with and without positive lesions. The patient characteristics and the indices of primary tumors were similar between these two groups, including carcinogen exposure, TNM classification of the primary tumor, treatment modality, and presence/absence of symptoms at UGI exam. Only the history of previous UADT SPMs showed significantly differences.

Subgroup analysis was conducted on the FU group with ESPNs (Table 4). Seven patients had symptoms (dysphagia, foreign body sensation) at the time they received IEE. There were significant differences between the two subgroups in clinical T-classification and treatment modality of ESPNs. Nearly half of the ESPNs were classified as Tis lesions (44%) in patients without symptoms in the FU group compared with 0% in those with symptoms (p = 0.04). The number of patients who were able to

Table 2

Results of image-enhanced endoscopy

Factor	All (n = 99)	ND group (n = 30)	FU group (n = 69)
Positive exam	31 (31%)	8 (27%)	23 (33%)
Number of positive lesion			
One	27	6	21
Two	3	2	1
Three	1	0	1
Histology of ESPN			
Severe dysplasia	7	3	4
Carcinoma in situ	8	2	6
Squamous cell carcinoma	19	3	16
Non-SCC	2	2	0
Location of ESPN			
Upper third	9	2	7
Middle third	12	1	11
Lower third	8	3	5
Multiple sites	1	1	0
Clinical T classification			
Tis	11	4	7
T1	14	3	11
T2	2	0	2
T3	4	1	3
T4	0	0	0
Clinical N classification			
N0	26	7	19
N+	5	1	4
Clinical M classification			
M0	28	8	20
M1	0	0	0
Clinical TNM stage			
Stage 0	11	4	7
Stage I	12	3	9
Stage II	2	1	1
Stage III	3	0	3
Stage IV	3	0	3

ND = newly-diagnosis; FU = follow-up; ESPN = esophageal second primary neoplasm.

be treated with minimal invasive therapy (defined as endoscopic submucosal dissection, endoscopic mucosal resection) was significantly higher among patients without symptoms than those with symptoms. (75% vs 0%, $p = 0.0013$).

The overall malignant and nonmalignant findings in IEE examinations are shown in Table 5. In the 99 patients of hypopharyngeal cancer with IEE, 31 (31%) were found to have malignant lesions; while 46 (46%) had no malignant findings, including reflux esophagitis in 42 (42%), low-grade dysplasia in 2 (2%), and moderate-grade dysplasia in 2 (2%).

4. DISCUSSION

The occurrence of SPMs is a crucial issue in the treatment of HPSCC. Previous observations have shown that the frequency of SPMs vary from 7% to 36%, according to the anatomical site of original primary. In particular, ESPNs are more frequently found in patients with HPSCC. This phenomenon is supported by the concept of field cancerization.[4–6,9,14–17] The average prevalence of ESPNs in patients with HPSCC in a recent systemic review was 15.2% (413 of 3386, 95% confidence intervals [CI]: 11.4%-19.0%).[18] In terms of sublocation, the average prevalence of esophageal lesions screened both synchronously and metachronously in patients with hypopharyngeal tumors of seven studies was 28.0% (161 of 574, 95% CI: 22.5%-33.5%).

Table 3

Factors affect to develop ESPN in follow-up group

Factor	Positive lesions in IEE		p
	Yes (n = 23)	No (n = 46)	
Persistent exposure in			
Alcohol	3 (13%)	2 (4%)	0.32
Betel nut	0 (0%)	0 (0%)	1
Cigarette	2 (9%)	5 (11%)	1
Primary T stage			
T1	4 (17%)	3 (7%)	0.33
T2	10 (43%)	16 (35%)	
T3	3 (13%)	7 (15%)	
T4	6 (26%)	20 (43%)	
Primary N stage			
N0	2 (8%)	17 (37%)	0.05
N1	6 (26%)	8 (18%)	
N2	15 (65%)	19 (41%)	
N3	0 (0%)	2 (4%)	
Primary M stage			
M0	23 (100%)	46 (100%)	
M1			
Primary TNM stage			
Stage I	1 (4%)	3 (7%)	
Stage II	2 (8%)	6(13%)	0.33
Stage III	5 (22%)	6 (13%)	
Stage IV	15 (65%)	31 (67%)	
Treatment of primary tumor			
Surgery ± adjuvant therapy	5 (22%)	28 (61%)	0.18
RT/CRT	18 (78%)	18 (39%)	
History of previous SPM-UADT	8 (35%)	6 (13%)	0.03
Symptoms at examination	10 (43%)	14 (30%)	0.28

ESPN = esophageal second primary neoplasm; SPM = second primary malignancy; UADT = upper aerodigestive tract.

Our study analyzed 99 patients with HPSCC who received IEE screening of the upper gastrointestinal tract. We used the triple endoscopy combination of conventional WLE, NBI-M, and Lugol chromoendoscopy to detect suspicious ESPNs. The prevalence of ESPNs in the ND group was 27%, and 33% in the FU group. Our results were similar to those obtained studies using the same endoscopic screening techniques.

Table 4

Comparison of the stage, treatment, and tumor control in ESPN patients of follow-up group with or without symptoms

	With symptoms (n = 7)	Without symptoms (n = 16)	p
Clinical T classification			
Tis	0 (0%)	7 (44%)	0.04
T1-3	7 (100%)	9 (56%)	
Clinical N classification			
N0	5 (71%)	14 (88%)	0.29
N+	2 (29%)	2 (12%)	
Clinical TNM classification			
Stage 0	0 (0%)	7 (44%)	0.06
Stage I–IV	7 (100%)	9 (56%)	
Treatment			
Minimal invasive therapy	0 (0%)	12 (75%)	0.01
Nonminimal invasive therapy	7 (100%)	4 (25%)	
Tumor control			
Yes	3 (43%)	13 (81%)	0.14
No	4 (57%)	3 (19%)	

ESPN = esophageal second primary neoplasm.

Table 5

Overall malignant and nonmalignant findings in IEE examination

	Number	%
Malignant lesions	31/99	31
Adenocarcinoma	1	1
Squamous cell carcinoma	19	19
Carcinoma in situ	7	7
Severe dysplasia	4	4
Other nonmalignant lesions	46/99	46
Reflux	42	42
Low-grade dysplasia	2	2
Moderate-grade dysplasia	2	2

IEE = image-enhanced endoscopy.

In the ND group, 8 of the 30 patients (27%) was found ESPNs in the IEE screening with varies histology, including severe dysplasia, carcinoma in situ, and SCC. It is essential to evaluate the UADT before definitive treatments and may change the treatment planning.[17]

SPMs have a significant effect on the survival of patients with primary head and neck cancers and are a major threat to the morbidity and mortality of patients with HPSCC after treatment. ESPNs, especially, is known to be associated with a poor prognosis.[19,20] Patients with ESPNs have significantly lower survival rates (hazard ratios 2.75/2.79, 95% CI: 1.11%-6.82%/1.15%-6.80%, p = 0.03/0.02 in multivariate analyses) than those without second primary ESCNs.[21]

In the FU group, 23 of the 69 patients (33%) had ESPNs in the IEE examination. According to previous studies,[22,23] the risk analysis of clinical parameters revealed that alcohol exposure and N3 disease of HPSCC were the most important independent risk predictors for simultaneous esophageal lesions. Some studies showed that an age of under 50 years was also a risk predictor on univariate analysis as well.[24,25] Our study shows only those with previous history of SPMs-UADT had higher incidence of ESPNs than those without the history (35% vs 13%, p=0.0343). Therefore, routine IEE screening of the esophagus is recommended for HPSCC patients, especially at those with previous history of SPMs in the UADT.

Most oncologists agree that early diagnosis and treatment are the best way to manage SPMs in head and neck cancer. Imaged-enhanced endoscopy has become a useful screening tool for precancerous or early cancerous lesions in the esophagus by means of dye- or optical-based techniques.[26] When using the combination of chromoendoscopy with Lugol solution and NBI system with high-resolution ME, the margin and invasiveness of the neoplasia can be well delineated and predicted.[26–28]

Recently, several studies have reported Lugol-based detection methods to aid the early diagnosis of esophageal second primary malignancies in the head and neck cancers, therefore, more and more researchers have suggested that routine screening of ESPNs in patients with head and neck cancer is recommended. In clinical practice, however, a comprehensive UGI endoscopy may not be possible in treated HPSCC patients because of local tumor obstruction or structural changes after surgery or irradiation. It is important to find out the characteristics of high-risk ESPNs occurrence groups for more detailed surveillance arrangement. Also, it is important to know the role of endoscopy in patients without dysphagia or other GI symptoms. Our study is the first article which reported the relationship between the T stage of ESPNs and the presence of symptoms. In our study of the FU group, there was significant difference in clinical T-classification and treatment modalities of ESCNs between patients with symptoms and those without symptoms; patients without symptoms at the time of UGI screening had less advanced T stages (44% vs 0%, p = 0.04), and had a higher percentage of nonminimal invasive therapy (75% vs 0%, p = 0.01).

We did not make the further survey of quality of life in patients with ESPNs after treatment, however, based on the literature's report, patients underwent minimal invasive therapy did have the good quality of life.[17,29]

In addition to the diagnosis of the malignant neoplasms of the esophagus, our study also reported that 46 patients (46%) had found the nonmalignant problems, which was not reported in the previous studies. Among them, reflux esophagitis was the most common (42%) nonmalignant problem at the IEE examination. Reflux esophagitis, an esophageal mucosal injury that occurs secondary to retrograde flux of gastric contents into the esophagus, could cause a variety of symptoms that included dysphagia, odynophagia, or heartburn sensation. Although thought of as 2 separate disease entities, reflux esophagitis and hypopharyngeal cancer possess various similarities, including a number of similar risk factors (smoking, alcohol consumption). To our best knowledge, although there is no study investigating the association between reflux esophagitis and the risk for laryngeal or pharyngeal cancer, a number of studies have evaluated the relation between heartburn or gastroesophageal reflux disease and laryngeal or pharyngeal cancer, with mixed results. Herein, more research is needed regarding the possible correlation between reflux esophagitis and hypopharyngeal cancer.

Our study has some limitations. First, although most patients with HPSCC were referred for IEE screening from the Department of Otolaryngology, the referral rate was not 100%. Some patients were referred from other physicians when experienced the symptom of dysphagia. This bias may increase the incidence of ESPNs in patients with HPSCC. Second, this was a retrospective study with a relatively small sample size. Larger prospective studies are necessary to confirm the effectiveness of IEE for early detection and treatment of ESPNs in patients with treated HPSCC. Finally, in our study, since we used WLE, narrow-band imaging with magnification and lugol chromoendoscopy as our endoscopic screening method in all inclusion cases, the effectiveness of routine endoscopic screening in our patients was not available because there was no ideal control group. Herein, we dedicated on the clinical utility of endoscopic screening by analyzing the characteristics of patients in newly diagnosed group and FU group.

In conclusion, our study represented the clinical utility of IEE screening in patients with HPSCC. Higher incidence of ESPNs was found in those patients. Routine esophageal screening with IEE was recommended in both newly diagnosed and FU treated HPSCC. Furthermore, the IEE surveillance can improve the detection rate and identify ESPNs in early stage.

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