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ORIGINAL ARTICLE

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두경부 암 환자에서 이차암 발견을 위해 수술 전 위장내시경 검사가 필요한가? 10년 등록자료 분석

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Is a Preoperative Gastrointestinal Endoscopy for Second Primary Cancer Detection in Head and Neck Cancer Necessary? Ten-year Registry Data

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Background/Aims: In head and neck squamous cell carcinoma, second primary gastrointestinal tumors are not uncommon. However, it is unclear whether a screening endoscopy is needed for detecting gastrointestinal neoplasm in patients with head and neck cancer. Therefore, we analyzed the prevalence and independent risk factors for second primary gastrointestinal neoplasm in head and neck squamous cell carcinoma.
Methods: A consecutive series of 328 patients with primary head and neck squamous cell carcinoma that underwent esophagogastroduodenoscopy or colonoscopy were included using our registry. An age- and sex-matched group of 328 control subjects was enrolled. We assessed risk factors of synchronous gastrointestinal cancer.
Results: The prevalence of esophageal cancer with head and neck squamous cell carcinoma was significantly higher than that of the control group (1.5% *vs.* 0.0%, p=0.011). An age of 54 years or more (OR, 1.033; 95% CI, 1.008-1.059; p=0.009) and male gender (OR, 4.974; 95% CI, 1.648-15.013; p=0.004) were risk factors for concomitant colorectal cancer or adenomas in the head and neck squamous cell carcinoma patients.
Conclusions: Preoperative colonoscopy can be recommended for detecting synchronous second primary colorectal lesions in head and neck squamous cell carcinoma patients with male sex regardless of age, and esophagogastroduodenoscopy is necessary in all head and neck squamous cell carcinoma patients for detecting esophageal cancer. **(Korean J Gastroenterol 2016;68:23-28)**

Key Words: Head and neck neoplasms; Esophagogastroduodenoscopy; Colonoscopy; Diagnosis

INTRODUCTION

Second primary tumors (SPTs) are common in head and neck squamous cell carcinoma (HNSCC) patients. Most cases of HNSCC are linked with esophageal cancer or lung cancer.[1] Gastrointestinal malignancies in particular, such as gastric cancer and colorectal cancer, are often found.[1-6] SPT of the respiratory and upper digestive tract is the main cause of death after treatment in early-stage HNSCC patients.[7] In the first five years after treatment of the primary tumor, the rates for metachronous SPT reach approximately 15% to 25%.[8] Therefore, SPT constitutes a major challenge in the field of head and neck oncology, and preoperative work-up for synchronous cancer is very important.

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According to the cancer statistics of Korea in 2011, the age-standardized incidence rate of head and neck cancer was 4.0 (men, 6.3 and women, 2.1) per 100,000 persons per year, and the mortality rates were 2.2 per 100,000 men per year and 0.5 per 100,000 women per year. The 5-year survival rates have improved over the past two decades from 41.1% to 61.6% because of advances in surgery and chemoradiation treatments in Korea.[9] However, the overall survival rate for HNSCC remains low (～55% after five years).[10] The poor outcome of HNSCC affects patient quality of life because of its functional anatomic location.[11]

The role of routine esophagogastroduodenoscopy (EGD) and colonoscopy as screening tools for SPT assessment in patients with HNSCC has been controversial until now. Several studies on routine preoperative evaluation of upper gastrointestinal tract were discrepant over cost effectiveness and efficiency.[12-15] Furthermore, there are few studies assessing the value of colonoscopy for the preoperative work-up in HNSCC patients.[5,6]

We hypothesized that colorectal tumor prevalence may be higher in HNSCC patients than in the control group because of shared risk factors, such as smoking, alcohol consumption, and old age, for both HNSCC and colorectal cancer. The present study assesses the prevalence and independent risk factors for gastrointestinal neoplasm in HNSCC patients using the HNSCC registry.

SUBJECTS AND METHODS

1. Study population

We included consecutive patients diagnosed with primary HNSCC from January 2005 to December 2014 using the head and neck cancer registry at the center at Hallym University Kangdong Sacred Heart Hospital (Seoul, Korea). This registry included the patients' demographics, risk factors (e.g., smoking and alcohol consumption), underlying diseases (e.g., hypertension and diabetes mellitus), laboratory findings, staging work-up results (e.g., computed tomography and endoscopy), histological results, cancer location, and cancer stage. Inclusion criteria were the patients who had a cancer located in the oral cavity, oropharynx, hypopharynx, or larynx. We excluded cancers of the salivary glands and the thyroid gland. All enrolled 328 HNSCC patients had undergone preoperative EGD, whereas 224 HNSCC patients had undergone preoperative colonoscopy.

The age- and sex-matched controls visited the gastroenterology center for various gastrointestinal symptoms, and underwent successful EGD and colonoscopy on the same endoscopy day of enrolled HNSCC patients with a seven day window from January 2005 to December 2014.

2. Study design

The data of this cross-sectional study was collected retrospectively. The study subjects were divided into an HNSCC and control group to assess the prevalence of synchronous gastrointestinal malignancies such as esophageal, gastric and colorectal cancer. The frequencies of colonic adenoma or adenocarcinoma in the HNSCC group were compared with those of the control group. We assessed risk factors of synchronous gastrointestinal cancer using various parameters, such as 1) pathological type of synchronous gastrointestinal malignancies and pre-cancerous lesions, 2) sex, 3) age, 4) lifestyle factors (e.g., smoking and alcohol), 5) underlying diseases (e.g., hypertension and diabetes mellitus), and 6) cancer location. Staging of HNSCC was performed using the seventh TNM classification of malignant tumors of the American Joint Committee on Cancer (AJCC).

This study was approved by the institutional review boards of Hallym University Kangdong Sacred Heart Hospital (IRB No: 11-040). Informed consent for this research project, not for treatment and procedures, was waived.

3. Statistical analysis

The variables associated with risk factors were initially identified using the independent sample t-test for continuous variables and the chi-squared test for categorical variables. Additionally, we used multivariate logistic regression analysis to detect independent risk factors for synchronous gastrointestinal cancer. All analyses were performed with SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Null hypotheses of no difference were rejected if p-values were less than 0.05, or, equivalently, if the 95% CIs of risk point estimates excluded 1.

RESULTS

Baseline characteristics for study subjects are in Table 1. By design there were 281 men and 47 women in both groups.

Table 1. Clinicopathological Data for Patients with HNSCC and the Control Group

Variable	HNSCC group (n=328)	Control group (n=328)	p-value
Sex			1.000
Male	281 (85.7)	281 (85.7)	
Female	47 (14.3)	47 (14.3)	
Age (yr)	60.18 (19-89)	60.23 (19-89)	0.998
Alcohol			
Heavy drinking (>60 g/daily)	149 (45.4)	67 (20.4)	<0.0001
Moderate drinking	94 (28.7)	92 (28.0)	
None	85 (25.9)	169 (51.5)	
Smoking			
Current smoking	220 (67.1)	46 (14.0)	<0.0001
Ex smoking	21 (6.4)	60 (18.3)	
None	87 (26.5)	222 (67.7)	
Underlying disease			
Hypertension	74 (22.6)	77 (23.5)	0.858
Diabetes mellitus	27 (8.2)	37 (11.3)	0.654
Head and neck cancer location			
Supraglottic cancer	36 (11.0)		
Glottic cancer	71 (21.6)		
Hypopharynx cancer	46 (14.0)		
Nasopharynx cancer	11 (3.4)		
Tonsil cancer	51 (15.5)		
Tongue cancer	54 (16.5)		
Palate cancer	11 (3.4)		
Maxillar cancer	12 (3.7)		
Others	36 (11.0)		
Stage			
I	87 (26.5)		
II	126 (38.4)		
III	59 (18.0)		
IV	56 (17.1)		

Values are presented as n (%) or mean (range).
HNSCC, head and neck squamous cell carcinoma.

The mean age was 60.18 years for men and 60.23 years for women. The HNSCC group had a greater proportion of heavy drinkers (>60 g/daily) (45.4% *vs.* 20.4%, $p < 0.0001$) and current smokers (67.1% *vs.* 14.0%, $p < 0.001$). In terms of underlying disease, hypertension and diabetes mellitus were not significantly different between the two groups. Based on the seventh TNM classification of malignant tumors of AJCC, 126 were stage II, the most common staging, with 38.4% of patients. Further, 87 were stage I (26.5%), 59 were stage III (18.0%), and 56 were stage IV (17.1%) (Table 1).

Of the patients with primary head and neck cancer, synchronous esophageal cancer was diagnosed in 5/328 (1.5%), gastric in 4/328 (1.2%), and colorectal cancer in 7/224 patients (3.1%). Of the 328 controls, there was no esophageal, 6 (1.8%) gastric, and 17 (5.2%) colorectal cancers diagnosed. Only the prevalence of esophageal cancer with HNSCC was significantly higher than that of the control group (1.5% *vs.* 0.0%, p=0.01) (Table 2).

Table 2. Characteristics of Synchronous Gastrointestinal Neoplasm with HNSCC and the Control Group

Gastrointestinal neoplasm	HNSCC group	Control group	p-value
Esophageal cancer	5/328 (1.5)	0/328 (0.0)	0.011
Gastric cancer	4/328 (1.2)	6/328 (1.8)	1.000
Gastric adenoma	3/328 (0.9)	2/328 (0.6)	0.400
Colon cancer	7/224 (3.1)	17/328 (5.2)	0.292
Colon adenoma	83/224 (37.1)	117/328 (35.7)	0.787

Values are presented as n (%).
HNSCC, head and neck squamous cell carcinoma.

The HNSCC patients with colorectal cancer were older than HNSCC patients without colorectal cancer (mean age of 71.29 years *vs.* 59.00 years, $p < 0.0001$). There was no significant difference for sex between the HNSCC patients with colorectal cancer and those without colorectal cancer

Table 3. Univariate Analysis of Risk Factors in HNSCC Patients with or without Colon Cancer *vs.* with or without Colon Cancer or Adenoma

Variable	With colon cancer (n=7)	Without colon cancer (n=217)	p-value	With colon cancer or adenoma (n=90)	Without colon cancer or adenoma (n=134)	p-value
Age (yr)	71.29±5.16	59.00±11.93	<0.0001	62.01±10.03	57.62±12.85	0.003
Sex			0.37			0.001
Male	7 (100.0)	188 (86.6)		86 (95.6)	109 (81.3)	
Female	0 (0.0)	29 (13.4)		4 (4.4)	25 (18.7)	
Location of lesion			0.44			0.03
Supraglottic	2 (28.6)	19 (8.8)		11 (12.2)	10 (7.5)	
Glottis	1 (14.3)	38 (17.5)		19 (21.1)	20 (14.9)	
Hypopharynx	3 (42.9)	32 (14.7)		18 (20.0)	17 (12.7)	
Nasopharynx	0 (0.0)	8 (3.7)		2 (2.2)	6 (4.5)	
Tonsil	0 (0.0)	35 (16.1)		14 (15.6)	21 (15.7)	
Tongue	1 (14.3)	39 (18.0)		7 (7.8)	33 (24.6)	
Palate	0 (0.0)	9 (4.1)		2 (2.2)	7 (5.2)	
Maxillar	0 (0.0)	12 (5.5)		4 (4.4)	8 (6.0)	
Others	0 (0.0)	25 (11.5)		13 (14.4)	12 (9.0)	
Alcohol			1.00			0.08
Heavy drinking (>60 g/daily)	3 (42.9)	100 (46.1)		48 (53.3)	55 (41.0)	
Moderate drinking	2 (28.6)	66 (30.4)		22 (24.4)	46 (34.3)	
None	2 (28.6)	51 (23.5)		20 (22.2)	33 (24.6)	
Smoking			0.26			0.007
Current smoking	7 (100.0)	141 (65.0)		69 (76.7)	79 (59.0)	
Ex smoking	0 (0.0)	16 (7.4)		6 (6.7)	10 (7.5)	
None	0 (0.0)	60 (27.6)		15 (16.7)	45 (33.6)	
Diabetes mellitus			0.53			0.33
Present	0 (0.0)	19 (8.8)		19 (21.1)	33 (24.6)	
Absent	7 (100.0)	198 (91.2)		71 (78.9)	101 (75.4)	
Hypertension			0.21			0.48
Present	3 (42.9)	49 (22.6)		7 (7.8)	12 (9.0)	
Absent	4 (57.1)	168 (77.4)		83 (92.2)	122 (91.0)	

Values are presented as mean±SD or n (%).

Table 4. Multivariate Logistic Regression Analysis of Risk Factors for Colon Cancer and Colon Cancer or Adenoma among the HNSCC Patients

	Risk factor	Adjusted OR	95% CI	p-value
Colon cancer	Age (≥65 yr)	1.126	1.028-1.234	0.01
Colon cancer or adenoma	Age (≥54 yr)	1.033	1.008-1.059	0.009
	Sex (male)	4.974	1.648-15.013	0.004

HNSCC, head and neck squamous cell carcinoma.
Including variables for adjustment: age, sex, location of lesion, smoking.

(p=0.37). There was no significant difference in alcohol consumption, smoking, hypertension, and diabetes mellitus between groups (Table 3). The HNSCC patients with colorectal cancer or adenoma were older than those without colonic neoplasm (mean age of 62.01 years *vs.* 57.62 years, p=0.003). The HNSCC subjects with colonic neoplasm had a greater proportion of men (95.6% *vs.* 81.3%, p=0.001). The location of HNSCC was different between the HNSCC patients with colonic neoplasm and those without colonic neoplasm (p=0.03). Current smokers were more prevalent in the HNSCC with colonic neoplasm than the non-colonic neoplasm group (76.7% *vs.* 59.0%, p=0.007). There was no significant difference in terms of alcohol consumption, diabetes mellitus, and hypertension between groups (Table 3).

In the multivariate logistic regression analysis, old age (≥65 years) was an independent risk factor for concomitant colorectal cancer in the HNSCC patients (OR, 1.126; 95% CI, 1.028-1.234; p=0.01). In addition, an age of 54 years or more (OR, 1.033; 95% CI, 1.008-1.059; p=0.009) and male gender (OR, 4.974; 95% CI, 1.648-15.013; p=0.004) were risk factors for concomitant colorectal cancer or adenomas in the HNSCC patients (Table 4).

Table 5. Positive and Negative Predictive Value of the Risk Factors for Colon Cancer and Colon Cancer or Adenoma among the HNSCC Patients

Risk factor		n/n	PPV (%)	n/n	NPV (%)
For colon cancer	Age (≥65 yr)	7/78	9.0	146/146	100.0
For colon cancer or adenoma	Age (≥54 yr)	68/145	46.9	57/79	72.2
	Sex (male)	86/195	44.1	25/29	86.2

HNSCC, head and neck squamous cell carcinoma; PPV, positive predictive value; NPV, negative predictive value.

The risk factor of old age (≥65 years) had a positive predictive value (PPV) of 9.0% and a negative predictive value (NPV) of 100.0% for colorectal cancer in the HNSCC patients. An age of 54 years or more had a PPV of 46.9% and an NPV of 72.2% for predicting colorectal cancer or adenoma in the HNSCC patients. Male sex had a PPV of 44.1% and an NPV of 86.2% for predicting colorectal cancer or adenoma in the HNSCC patients (Table 5).

DISCUSSION

The independent risk factors for concomitant colorectal neoplasm (cancer or adenoma) in HNSCC patients were an age of 54 years or more (OR, 1.033; 95% CI, 1.008-1.059; p=0.009) and the male sex (OR, 4.974; 95% CI, 1.648-15.013; p=0.004). Although the overall prevalence of colorectal neoplasm was not higher in the HNSCC group than the control group in this study, the same result as an earlier report,[6] this association between HNSCC and colorectal neoplasm can be explained by the shared carcinogens of cigarette smoking and alcohol drinking.[1,5] Advances in the prevention, treatment, and surveillance of HNSCC await a more complete understanding of the mechanism of the multifocality of this tumor. According to the field carcinogenesis concept, multiple cell groups independently undergo neoplastic transformation under the stress of regional carcinogenic activity.[16]

Considering that NPV of age and sex was higher than PPV (72.2% *vs.* 46.9%; 86.2% *vs.* 44.1%, respectively), preoperative colonoscopy for detecting colonic neoplasm may not be recommended in patients less than 54 years of age and women. However, screening colonoscopy is strongly recommended for early detection of colorectal cancer in average-risk persons aged 50 years and older in Korean guidelines.[17] The colorectal cancer incidence decreased by 76-90% in a cohort that underwent colonoscopy and polypectomy compared to reference populations.[18] Moreover, increased colonoscopy use was related to colorectal mortality reduction.[19] Thus, in combination with our results and colorectal cancer screening guidelines, preoperative colonoscopy could be beneficial in all HNSCC men regardless of age or ≥50 years HNSCC women for detecting concomitant colorectal neoplasm.

Esophageal cancer was the most common malignant gastrointestinal SPT with a significantly higher prevalence in the HNSCC group in this study (2.2% *vs.* none in the control group, p=0.01). Several studies provide evidence for this result.[1,3,20-23] The previous prospective study reported that the rate of second esophageal primary tumors was 1.9% in the 268 HNSCC patients.[23] One recent study reported that esophageal surveillance was recommended because early detection of esophageal cancer in HNSCC patients led to a good prognosis.[24] The co-existence of either a colorectal malignancy or adenoma with esophageal cancer is also not uncommon (1.5%).[25] Therefore, EGD and colonoscopy as a screening tool for detecting SPT in HNSCC is crucial in diagnosis and treatment.

Our study has several strengths. First, to the best of our knowledge, this is the first study assessing the risk factors for colorectal neoplasm as SPTs in HNSCC. Second, we analyzed detailed clinical parameters for each patient using our registry. This enabled our study to adjust for potential confounders. There are some limitations in this study. First, this study has possible selection bias in our exposed (HNSCC) and control group. In fact, the prevalence of colorectal cancer in our control group was too high (5.2%). Our control group who visited the gastroenterology center for various gastrointestinal symptoms was not a general population. However, this bias might be trivial because we used our HNSCC registry in which the HNSCC patients were enrolled consecutively. Second, the prevalence of colorectal cancer as an SPT is likely to be underestimated because we did not conduct a colonoscopy in all patients due to patient refusal.

In conclusion, preoperative colonoscopy can be recommended for detecting synchronous second primary color-

ectal lesions in HNSCC patients with male sex regardless of age, and EGD is necessary in all HNSCC patients for detecting esophageal cancer.

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