Effect of Routine Esophageal Screening in Patients With Head and Neck Cancer

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Importance: Transnasal esophagoscopy or pandoscopy to conduct a tumor survey is routinely recommended for patients with head and neck squamous cell carcinoma (HNSCC). Despite this recommendation, the effect of routine esophageal screening remains unclear.

Objective: To investigate the effect of routine esophageal screening on the detection of second primary esophageal squamous cell carcinoma (ESCC) among patients with HNSCC.

Design and Setting: Retrospective study at the Academic Institute of Otolaryngology, Kaohsiung, Taiwan.

Participants: Medical records between January 1, 2004, and December 30, 2010, from 3053 patients with HNSCC were retrospectively reviewed.

Intervention: Patients were divided into 2 groups based on whether or not they had received routine esophageal screening, and the 2 groups were compared.

Main Outcome Measures: Univariate logistic regression analysis was performed to investigate the odds ratios (ORs) for developing second primary ESCC at different sites. The prevalence and cancer stage of second primary ESCC among these 2 groups were compared using the χ² test.

Results: The prevalences and ORs of second primary ESCC at different tumor sites were 0.8% (reference) for the oral cavity, 6.2% (OR, 8.35) for the oropharynx, 6.6% (OR, 8.89) for the supraglottis, 8.3% (OR, 11.43) for the transglottis, and 14.2% (OR, 20.83) for the hypopharynx. The prevalence of second primary ESCC among the routine screening group (71 of 1592 [4.5%]) was significantly higher than that among the non–routine screening group (44 of 1461 [3.0%]) (P = .04). Among 115 second primary ESCC cases, patients in the routine screening group were diagnosed at an earlier cancer stage than patients in the non–routine screening group.

Conclusions and Relevance: Routine esophageal screening is recommended for patients with HNSCC, especially those with oropharyngeal, supraglottic, transglottic, and hypopharyngeal cancers. Routine esophageal screening can increase the early detection of second primary ESCC.

METHODS

PATIENTS AND STUDY DESIGN

This study was approved by the institutional review board. All patients with newly diagnosed HNSCC registered in a database be-
between January 1, 2004, and December 30, 2010, at the Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, were retrospectively enrolled in this study. In January 2007, following the introduction of TNE in the Department of Otolaryngology, the treatment guidelines for HNSCC were changed. The new guidelines stipulated that all patients with HNSCC would undergo esophageal screening by TNE or pandoscopy. Since the new guidelines were instituted, more than 90% of patients have undergone TNE. However, rigid esophagoscopy was excluded from the routine screening procedure. If there is concern about a lesion surrounding the esophageal inlet before treatment, rigid esophagoscopy is performed for tumor mapping. During TNE, this endoscope is routinely passed into the stomach, rigid esophagoscopy is performed for tumor mapping. Then, slow withdrawal of the endoscope is performed to reevaluate the esophagus.

Regardless of the time of study enrollment, all patients with HNSCC underwent esophageal survey as part of their tumor workup before treatment. Before the introduction of TNE, patients with HNSCC underwent esophageal survey by esophagogastroscopy, pandoscopy, or questionnaire only. Following completion of treatment, all patients with HNSCC were advised to undergo regular esophageal follow-up assessment at least every 6 months for 3 years.

The patients included in the study were divided into 5 categories based on tumor location (nasal cavity, oral cavity, oropharynx, larynx, or hypopharynx). The prevalences and odds ratios (ORs) of second primary ESCC were analyzed based on HNSCC location. In addition, the patients were divided into 2 groups based on whether or not they had received routine esophageal screening (ie, whether patients were included in the study before or after January 2007). The prevalence and cancer stage of second primary ESCC among these 2 groups were compared.

### STATISTICAL ANALYSIS

Univariate logistic regression analysis was performed to investigate the ORs for developing second primary ESCC at different sites. The prevalence and cancer stage of second primary ESCC were compared between the routine screening group (those enrolled between 2004 and 2006) and the non–routine screening group (those enrolled between 2007 and 2010) using the χ² test. Significance was set at P < .05.

### RESULTS

From the HNSCC database, 3053 consecutive patients between January 1, 2004, and December 30, 2010, were enrolled in the study. All included patients were divided into 5 categories based on cancer site (Table 1). These comprised 67 patients (2.2%) with nasal cavity cancer, 1774 patients (58.1%) with oral cavity cancer, 514 patients (16.8%) with oropharyngeal cancer, 297 patients (9.7%) with laryngeal cancer, and 401 patients (13.1%) with hypopharyngeal cancer. No adenocarcinomas of the esophagus were identified in any patient. The overall prevalences of second primary ESCC were 0.8% for the oral cavity, 6.2% for the oropharynx, 4.0% for the larynx, and 14.2% for the hypopharynx. Among 297 laryngeal cancer cases, there were 106 in the supraglottis, 138 in the glottis, 5 in the subglottis, and 48 in the transglottis; the prevalences were 6.6%, 0.7%, 0.0%, and 8.3%, respectively.

Results of a logistic regression model to analyze the risk of developing second primary ESCC are summarized in Table 2. Using oral cavity cancer as the reference, univariate analysis revealed that patients with oropharyngeal cancer (OR, 8.35), supraglottic cancer (OR, 8.89), transglottic cancer (OR, 11.43), and hypopharyngeal cancer (OR, 20.83) (P < .001 for all) had a much higher risk of developing second primary ESCC.

In total, 1592 patients underwent routine esophageal screening (ie, patients enrolled between 2007 and 2010), and 1461 patients did not undergo routine esophageal screening (ie, patients enrolled between 2004 and 2006) (Table 3). The prevalence of second primary ESCC among the routine screening group (4.5%) was significantly higher than that among the non–routine screening group (3.0%) (P = .04). Furthermore, the prevalence of second primary ESCC associated with oral cavity cancer cases among the routine screening group (1.2%) was significantly higher than that among the non–routine screening group (0.3%) (P = .03). Although there were no significant differences at other sites of HNSCC between the 2 groups, a trend toward a higher prevalence of second primary ESCC among the routine screening group was observed in the patients with laryngeal cancer (4.2% vs 3.8%), oropharyngeal cancer (6.5% vs 5.9%), and hypopharyngeal cancer (15.9% vs 12.3%).

There were 115 second primary ESCC cases. Of those, 44 were diagnosed in the non–routine screening group, and 71 were diagnosed in the routine screening group. The differences in cancer stage between the 2 groups are summarized in Table 4. Second primary ESCC was di-

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
</tr>
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<tbody>
<tr>
<td>Oral cavity</td>
<td>1774</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>514</td>
</tr>
<tr>
<td>Larynx</td>
<td>297</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>106</td>
</tr>
<tr>
<td>Glottis</td>
<td>138</td>
</tr>
<tr>
<td>Subglottis</td>
<td>5</td>
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<tr>
<td>Transglottis</td>
<td>48</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Variable</th>
<th>Prevalence of Second Primary ESCC, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>0.8</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>6.2</td>
</tr>
<tr>
<td>Larynx</td>
<td>4.0</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>8.3</td>
</tr>
<tr>
<td>Glottis</td>
<td>0.7</td>
</tr>
<tr>
<td>Subglottis</td>
<td>0.0</td>
</tr>
<tr>
<td>Transglottis</td>
<td>14.2</td>
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Patients with HNSCC are at risk of developing second primary neoplasms, particularly in the head and neck, lung, and esophagus. The occurrence of these multiple malignant neoplasms has been attributed to field cancerization in the mucous membranes of these regions, which probably results from the common exposure of these areas to tobacco, alcohol, and betel nut. In this study, the overall prevalence of second primary ESCC among the patient population with HNSCC was 115 of 3053 (3.8%). In recent years, studies assessing the prevalence of ESCC among patients with HNSCC have reported a higher prevalence of ESCC. This is probably because of differences in distribution at HNSCC sites, as summarized in Table 5.

The number of second primary tumors identified in Taiwan is far greater than that reported in the United States or Europe. Morris et al showed that the incidence of a second esophageal cancer was 14.2 per 10,000 patients per year in a cohort of 70,000 patients with head and neck cancer from the Surveillance, Epidemiology, and End Results database, meaning that 702 patients with HNSCC need to be followed up for 1 year to identify 1 case of esophageal cancer. Clearly, this shows that the occurrence of esophageal cancer as a second primary cancer is much less common in that database compared with a Taiwanese population. The origin of esophageal cancer differs between Taiwan and the United States or Europe. Most of our patients were accustomed to betel nut chewing, alcohol consumption, or smoking. Betel nut chewing is considered a risk factor for the development of esophageal cancer in Taiwan. A multicenter case-control study in Taiwan revealed independent and combined effects of alcohol intake, smoking, and betel nut chewing on the risk of developing esophageal cancer. The strongest risk factor for the development of esophageal cancer was alcohol intake, with the highest OR (13.9) among those who consumed more than 900 g/d. Combined exposure to any 2 of the 3 substances raised the risk 8.8-fold to 19.7-fold, and combined exposure to all 3 substances raised the risk 41.2-fold.

The results of this study showed that patients with glottic cancer had the same probability of developing second primary ESCC as patients with oral cavity cancer; however, patients having supraglottic and transglottic cancer were about 10 times more likely to develop second primary ESCC compared with patients having oral cavity cancer. Similarly, patients with oropharyngeal cancer were 8 times more likely to develop second primary ESCC than patients with oral cavity cancer. Therefore, patients with oropharyngeal, supraglottic, transglottic, and hypopharyngeal cancers should be aware of the possibility of esophageal lesions.
Before January 2007, our hospital’s treatment guidelines did not include routine esophageal screening for patients with HNSCC. It was optional because large tumors in the laryngopharynx cause patient discomfort and airway problems, such as severe cough, choking, and airway obstruction, during conventional esophagoscopy. Many patients underwent esophageal survey only after symptoms of esophageal cancer developed. With improved comfort owing to the small size of TNE equipment and because patients can remain in a seated position during the examination, the aforementioned disadvantages have been minimized. Therefore, in January 2007, the treatment guidelines for patients with HNSCC were changed to stipulate that all patients newly diagnosed with HNSCC should undergo esophageal TNE as part of their tumor workup and follow-up assessment.

According to a previous study, the risk of developing a second primary esophageal cancer was extraordinarily high for patients with a follow-up interval of less than 1 year. In the present study, after completion of treatment, all patients with HNSCC received regular esophageal follow-up evaluation at least once every 6 months for 3 years. In general, the prevalence of second primary ESCC among the routine screening group was significantly higher than that among the non–routine screening group.

Early detection of second primary ESCC among individuals with HNSCC may improve patient survival. In this study, 115 patients with second primary ESCC were further analyzed. In the routine screening group, approximately 41% had an early T classification of ESCC, but in the non–routine screening group, only about 20% had an early T classification; the difference between the groups was significant (P = .02). This result confirms that routine esophageal screening can help with the early detection of second primary ESCC. However, many patients in the routine screening group had advanced ESCC, with the primary survey identifying tumor invasion of other adjacent structures or regional lymph node metastases (and even distant metastases). The introduction of techniques such as narrow band imaging and Lugol dye spray chromoendoscopy or shortening the interval between examinations to 3 months may be helpful in these patients to diagnose earlier ESCC.

In conclusion, routine esophageal screening by TNE or pandoscopy is recommended for patients with HNSCC, especially those with oropharyngeal, supraglottic, transglottic, and hypopharyngeal cancers, because of the higher prevalence of second primary ESCC. Routine esophageal screening can increase the early detection of second primary ESCC and may improve survival in this cohort.

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Author Contributions: Drs Su, Chen, Chuang, Guo, Lin, Luo, Fang, and Chien had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Su and Chen contributed equally to this work. Study concept and design: Chien. Acquisition of data: Chuang, Guo, Lin, and Luo. Analysis and interpretation of data: Su, Chen, and Fang. Drafting of the manuscript: Chen, Chuang, Guo, Lin, Luo, and Fang. Critical revision of the manuscript for important intellectual content: Su and Chien. Statistical analysis: Chen, Chuang, Guo, Luo, and Fang. Obtained funding: Su, Guo, and Luo. Administrative, technical, and material support: Su, Chen, Lin, and Chien. Study supervision: Chuang and Chien.

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