Symptom-Directed Selective Endoscopy

Long-term Efficacy

Michael S. Benninger, MD; Afser Shariff, MD; Kathleen Blazoff, RN, CNP

Background: Synchronous primary neoplasms have been encountered in some patients with mucosal squamous cell carcinoma of the head and neck. Routine panendoscopy along with various radiological tests have been advocated to identify these potential tumors. In 1993, we originally described symptom-directed, selective endoscopy as an efficient and cost-effective means to evaluate patients to identify synchronous primary neoplasms.

Objective: To review the ultimate success rate of symptom-directed, selective endoscopy in that initial cohort of patients and the success of the program longitudinally in clinical practice over the intervening 6 years.

Patients and Methods: The status of the original 100 patients who participated in the selective endoscopy study were reviewed at least 6 months after the original procedure. A statistically significant random sample of 101 subsequent patients who had at least 6 months’ follow-up or until their death were reviewed.

Results: No additional primary, mucosal head and neck, esophageal, or pulmonary cancers were identified in the surviving original cohort of patients suggesting that the selective endoscopy identified all synchronous tumors. Sixteen metachronous primary cancers were identified between 12 and 70 months after the initial evaluation. Eight synchronous primary cancers were identified in the new cohort using symptom-directed evaluation, direct laryngopharyngoscopy, and chest x-ray films. No additional tumors were detected within 6 months.

Conclusion: Symptom-directed, selective endoscopy seems to be an effective alternative to routine panendoscopy in identifying synchronous primary cancers.


PATIENTS WITH squamous cell carcinomas (SCCs) of the head and neck have been found to have an associated synchronous primary upper aerodigestive tract malignant neoplasm in many cases with synchronous tumors being identified in 1% to 17% of these patients. It is believed that these tumors occur because of the chronic irritant exposure of the mucosa of the pharynx, larynx, esophagus, and tracheobronchial tree. In an effort to identify these neoplasms, routine endoscopic assessment including direct laryngoscopy, esophagoscopy, and bronchoscopy (triple endoscopy) has been recommended by many authors. Additional evaluations such as a barium swallow esophagogram, bronchial washings, and various laboratory tests have also been recommended. These recommendations are based on the desire to identify and manage these synchronous neoplasms with a goal of improving outcome and survival.

In 1993, we suggested that symptoms could be used to direct the subsequent endoscopic evaluations, decrease potential morbidity, and reduce the costs of the evaluations. Esophagoscopy was recommended if patients had symptoms of true dysphagia (not just a globus sensation), odynophagia, or noncardiac chest pain. Bronchoscopy was recommended for symptoms of chronic cough, hemoptysis, shortness of breath, or stridor. That study showed that symptom-directed esophagoscopy and bronchoscopy along with direct or indirect laryngopharyngoscopy and a chest x-ray film could identify second primary tumors without the need for mandatory triple endoscopy. Because some patients are initially seen with silent pharyngeal tumors, direct laryngopharyngoscopy was recommended in all patients, although the potential for office-based videolaryngopharyngoscopy was considered. Bronchial washings were not valuable and, therefore, were not recommended. That study also suggested that further research and long-term evaluations may be needed to strengthen the recommendations.

This study evaluated the long-term results and survival of the original cohort of patients to identify if there was any evidence of missed second primary tumors, assessed the frequency of metachronous neoplasms, and analyzed the success of the selective endoscopic recommendations in the intervening years to determine if this approach failed to identify any subsequent second primary tumors.
PATIENTS, MATERIALS, AND METHODS

The medical records of the original cohort of 100 patients were retrospectively reviewed. Variables evaluated included the following: disease status, ultimate survival and outcome, potential missed second primary tumors, recurrences, and metachronous cancers. A separate cohort of 101 randomly sampled, statistically significant patients were also retrospectively evaluated. These patients were drawn from an average of 150 new head and neck cancer evaluations per year. One hundred one patients were originally assessed to determine the success of identification of second primary cancers. A minimum follow-up of 6 months or death from disease before 6 months was required to have the success of the evaluations determined. The medical records of these 101 patients were evaluated for original evaluations performed, disease status, ultimate survival and outcome, length of follow-up, potentially missed second primary tumors, recurrences, and metachronous tumors.

RESULTS

No new laryngopharyngeal, pulmonary, or esophageal tumors were identified in the original group of patients within 6 months of the original endoscopies and evaluations. This would suggest that the endoscopic assessment and chest x-ray films identified all second primary tumors. These patients have had an average follow-up of 38 months (follow-up range, 2-131 months). The average follow-up for the 52 patients who were alive at the last office visit or contact was 53 months (range, 5-131 months). Only 1 of these patients were followed up for less than 6 months and only 5 for less than 12 months. Overall, 10 patients were followed up for less than 6 months—8 either died of disease (6 patients) or died of unrelated causes (2 patients). One patient never returned for treatment after the original assessment and 1 was lost to follow-up after 4 months.

Thirty-one patients developed a recurrence; 16 were local recurrences, 8 were locoregional, 1 was regional only, 2 were local metastatic, and 3 developed locoregional metastatic recurrences. Six patients had persistence of their disease after the initial treatment. Fourteen patients were subsequently found to have developed a metachronous cancer, with 11 being in the upper aerodigestive tract (Table 1). The average time to the identification of a metachronous primary tumor was 29.9 months (range, 12-70 months). None was identified in the first year after the initial evaluation.

Fifty-two patients were alive with no evidence of disease; 1 was alive with disease; 32 had died of their primary, secondary, or metachronous cancer; 12 died with no evidence of disease; and 3 had less than 1 year follow-up where final status could not be assessed. Of the 11 patients who were originally identified with a second primary cancer, 3 were alive with no evidence of disease, 4 had died of disease, and 4 died with no evidence of disease.

Table 1. Metachronous Cancers in Original 100 Patients

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of Patients</th>
<th>Time to Presentation, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Tongue</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Pyriform sinus</td>
<td>1</td>
<td>18, 70</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>2</td>
<td>18-48</td>
</tr>
<tr>
<td>Lung</td>
<td>7</td>
<td>18-48</td>
</tr>
<tr>
<td>Brain</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Colon (adenocarcinoma)</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1</td>
<td>36</td>
</tr>
</tbody>
</table>

Table 2. Primary Tumor, Nodal Status, and Stage at Presentation of Second Cohort of 101 Patients

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>35</td>
</tr>
<tr>
<td>T2</td>
<td>28</td>
</tr>
<tr>
<td>T3</td>
<td>21</td>
</tr>
<tr>
<td>T4</td>
<td>14</td>
</tr>
<tr>
<td>Tx</td>
<td>3</td>
</tr>
<tr>
<td>N0</td>
<td>61</td>
</tr>
<tr>
<td>N1</td>
<td>14</td>
</tr>
<tr>
<td>N2</td>
<td>22</td>
</tr>
<tr>
<td>N3</td>
<td>4</td>
</tr>
<tr>
<td>I</td>
<td>31</td>
</tr>
<tr>
<td>II</td>
<td>17</td>
</tr>
<tr>
<td>III</td>
<td>19</td>
</tr>
<tr>
<td>IV</td>
<td>34</td>
</tr>
</tbody>
</table>

Following the original study, 101 patients from an average of 150 new head and neck cancer evaluations per year were randomly sampled from patients undergoing selective endoscopic evaluations. Qualifying patients had at least 6 months of follow-up evaluation or had died of disease. The sites of tumors for the 101 patients were larynx, 56 patients; oropharynx, 19; hypopharynx, 11; oral cavity, 9; nasopharynx, 3; and unknown primary with neck metastases, 3. The tumor stage, nodal status, and disease stage at presentation are noted in Table 2. All patients underwent direct laryngopharyngoscopies and chest x-ray films as part of their initial evaluation. Eight of the chest x-ray films had an abnormality that might suggest cancer. Three pulmonary second primary tumors were identified. No esophagrams were performed. Twenty symptom-directed esophagoscopies were performed; no esophageal cancers were identified. Seven symptom-directed bronchoscopies were performed with 1 being positive for cancer. The positive result was in a patient who had already been identified as having a mass by chest x-ray film.

Six synchronous second primary cancers were identified in the upper aerodigestive tract; 2 epiglottic tumors that were symptomatic, 1 asymptomatic hypopharynx cancer; and 3 lung cancers (1 that was symptomatic). In addition, an adenocarcinoma of the colon and a non-Hodgkin lymphoma were discovered. A total of 19 synchronous cancers were discovered in 18 patients (9.5%) from a total of 201 patients from the prior and present studies. The sites of the total synchronous primary tu-
Synchronous primary cancers are identified in the upper aerodigestive tract in 1% to 17% of the patients with SCCs of the head and neck. Our present studies suggest that this occurs in 8% to 9% of individuals. It can be suggested that this occurs because of the field cancerization effect from chronic exposure to cancer-causing agents, principally tobacco and alcohol exposure, and perhaps in individuals with a genetic predisposition. The development of second primary cancers in 201 patients showed that 75 are alive with no evidence at an average follow-up of 33.8 months (follow-up range, 3-75 months). Sixteen patients have died of disease at an average of 14.7 months and 7 patients have died with no evidence of disease at an average of 10.3 months.

**COMMENT**

Synchronous primary cancers are identified in the upper aerodigestive tract in 1% to 17% of the patients with SCCs of the head and neck. Our present studies suggest that this occurs in 8% to 9% of individuals. It can be suggested that this occurs because of the field cancerization effect from chronic exposure to cancer-causing agents, principally tobacco and alcohol exposure, and perhaps in individuals with a genetic predisposition. The development of second primary cancers is frequent enough to warrant further investigation. Traditional teaching has suggested that a thorough search for these secondary tumors should include a chest x-ray film, bronchoscopy, esophagoscopy, and laryngoscopy (triple endoscopy). Other studies such as a barium swallow esophagogram and various laboratory tests have also been recommended. The principles of these approaches are to attempt to identify early tumors, some of which may be asymptomatic to treat promptly and perhaps affect the ultimate outcome.

Some studies indicate that asymptomatic tumors can be identified through routine endoscopy. Whether this is the case has not been made clear. The definition of asymptomatic is not always firmly established, or has there been established diagnostic protocols for defining the subsequent evaluations. Our studies indicate that there are asymptomatic pharyngeal and pulmonary tumors. Although no asymptomatic esophageal tumors were identified, the numbers were small. Anecdotally, we are unaware of any unidentified esophageal tumors since we have initiated our selective evaluations. The clinical influence of identifying asymptomatic tumors has also been undetermined. No study has yet examined whether patients with synchronous pulmonary or esophageal tumors have increased survival if their tumors are detected with routine endoscopy when asymptomatic instead of later, when symptomatic.

The 101 patients have been followed up for an average of 27 months (follow-up range, 3-75 months). Patients who were alive at their last encounter were followed up for an average of 32.9 months (follow-up range, 7-72 months) while those who died were followed up for an average of 13.5 months (follow-up range, 2-39 months). There have been no missed second primary tumors identified. Two patients had a history of adenocarcinoma of the lungs. Two patients developed metachronous upper aerodigestive tract malignant neoplasms during the follow-up period; a nasopharyngeal carcinoma at 38 months, and an SCC of the lip at 43 months. Seven patients developed metastatic SCCs. Five of these were in the lungs at an average of 27 months after initial evaluation and 2 in the liver at an average of 23 months. For the 201 patients evaluated, a total of 16 metachronous upper aerodigestive tract cancers (7.9%) and 3 other tumors were identified. Because many of these patients have had a short follow-up, it can be expected that this rate would likely increase over time.

The status of the 101 patients from the most recent cohort of patients showed that 75 are alive with no evidence of disease at an average follow-up of 33.8 months and 3 patients are alive with disease at an average of 11 months. Sixteen patients have died of disease at an average of 14.7 months and 7 patients have died with no evidence of disease at an average of 10.3 months.

### Table 3. Synchronous Primary Cancers in 201 Patients

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>9</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>4</td>
</tr>
<tr>
<td>Epiglottis</td>
<td>2</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>2</td>
</tr>
<tr>
<td>Tonsil</td>
<td>1</td>
</tr>
<tr>
<td>Lung</td>
<td>5</td>
</tr>
<tr>
<td>Esophagus</td>
<td>3</td>
</tr>
<tr>
<td>Upper aerodigestive tract*</td>
<td>17</td>
</tr>
<tr>
<td>Colon (adenocarcinoma)</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
</tr>
</tbody>
</table>

*The percentage of patients with upper aerodigestive tract cancer was 8.5%.

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goscopy in an office potentially obviating the need for op-
erative direct laryngoscopy,10 the routine performance of
esophagoscopy would be more costly and associated with
greater risks. The bottom line is that there is a lack of ade-
quately data.9 Given the findings of our study and the fail-
ure to show increased survival benefit in the large Na-
tional Cancer Institute’s Surveillance, Epidemiology, and
End Results Program study,8 we believe that symptom-
directed selective endoscopy is a reasonable option for
screening for secondary esophageal cancers.

The role of bronchoscopy is more speculative. Since
many pulmonary and tracheobronchial tree tumors are
likely to be either asymptomatic or associated with non-
specific symptoms, some pulmonary evaluation is war-
ranted. In our initial study, bronchial washings were not
found to be valuable having both low sensitivity and speci-
fic.5 In neither of our studies was bronchoscopy found
to be of valuable. Only 1 patient with pulmonary cancer
had an abnormal bronchoscopy, and that tumor was sus-
pected after identification on a chest x-ray film. On the
premise that true tracheal neoplasms are rare, in addition
with most secondary respiratory primary cancers being
found in the lungs or bronchial tree and because we ad-
vocate routine chest x-ray film, bronchoscopic assessment
would seem to add little value in ruling out second pri-
mary tumors. To perform bronchoscopy on symptomatic
patients still seems reasonable despite the expected low yield,
but routine bronchoscopy in asymptomatic patients is prob-
ably unnecessary. The questions regarding the roles of other
imaging techniques such as computed tomographic or mag-
netic resonance imaging scans was not addressed in this
study, although this may be found to be important in the
future.

We do believe that a thorough evaluation of the la-
ryngopharynx should be accomplished in all patients,
since secondary primary tumors are most common in these
areas and may on occasion be asymptomatic. This could
be performed in the following setting: (1) when accu-
rate staging is desired, (2) when difficult to obtain bi-
opsy specimens are needed such as from the larynx or
hypopharynx, (3) during planned excision of the primary,
or (4) when symptom-directed esophagȯscopy or bronchoscopy is planned. In skilled hands, a com-
plete evaluation can be performed with office-based
videolaryngopharyngoscopy.10 Our initial study sug-
gested the cost-effectiveness of symptom-directed eval-
uations and is consistent with the findings of others.5,11

Given the results of this long-term follow-up study, the
consideration of performing symptom-directed esophagȯscopy and bronchoscopy along with a complete eval-
uation of the laryngopharynx and a chest x-ray film seems
justified. Two unanswered questions remain: whether a
few select patients will have asymptomatic cancers that
are missed by these selective evaluations, and if so, will
their ultimate outcome be affected? Further study is nec-
essary to provide the data needed to definitely answer
these questions.

Our studies revealed that metachronous primary tu-
mors occurred in 7.9% of patients, despite a short fol-
low-up in some patients. Ultimate metachronous can-
cer rates would be expected to be higher, consistent with
other reports.12 Metachronous cancers likely occur sec-
ondary to the field cancerization effect suggested with
synchronous tumors. With these frequent occurrences of
metachronous cancers, long-term observation and screen-
ing is important and is recommended. Although the eval-
uation of metachronous cancers was not ex-
 plored in these studies, a selective approach with rou-
tine evaluation of the laryngopharynx with periodic chest
x-ray films and symptom-directed selective broncho-
copies and esophagoscopy would seem to be an appro-
riate surveillance method.

CONCLUSIONS

Symptom-directed selective endoscopy along with chest
x-ray films and a complete examination of the laryn-
pharynx by direct or indirect laryngopharyngoscopy is a
reasonable alternative to mandatory triple endoscopy
in identifying second primary tumors in patients with head
and neck SCCs. The role of bronchoscopy in the pres-
ence of advancing appropriate radiological evaluation of
the chest and lungs is questioned.

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