Role of Chest Computed Tomography in Head and Neck Cancer

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Objectives: To evaluate the role of chest computed tomography (CT) in patients with head and neck squamous cell carcinoma (HNSCC) and to determine the optimal timing and predictive factors for positive findings.

Design: Retrospective analysis.

Setting: Tertiary referral center.

Patients: Two hundred seventy screening chest CT scans performed in 192 patients with HNSCC during a 42-month period were reviewed.

Main Outcome Measures: The scans were categorized as new cases, follow-up cases, or recurrent cases. The results were classified as abnormal or normal. Scans of patients having a radiologic diagnosis of a malignant neoplasm of the lung or an indeterminate lesion were considered abnormal. Factors correlating with an abnormal chest CT scan or development of malignant neoplasm of the lung were analyzed, including the timing of imaging and the patients’ clinicopathologic data.

Results: Seventy-nine scans (29.3%) were considered abnormal. The rate of an abnormal scan was significantly higher in the follow-up case group (44.2%) than in the new case group (14.2%) (P < .001). Ten of 15 indeterminate scans (66.7%) with small (<1 cm) solitary pulmonary nodules showed disease progression on subsequent follow-up scans, changing the patients’ diagnoses to a malignant neoplasm of the lung. The predictive factors for development of a malignant neoplasm of the lung were initial N2 or N3 disease, stage IV disease, recurrent disease, and distant metastasis to another site.

Conclusions: Chest CT is recommended for high-risk patients, especially during the follow-up period. Intensified evaluation and management are mandatory for indeterminate small solitary pulmonary nodules because of the high rate of malignant neoplasms.


The development of a malignant neoplasm of the lung, including distant metastasis and second primary cancer, is an important factor that limits the survival of patients with head and neck squamous cell carcinoma (HNSCC). The most common site of distant metastasis is the lungs, with an incidence of 8% to 15% in clinical studies. Primary lung cancers account for 23% of second primary tumors in patients with HNSCC. Because the presence of a malignant neoplasm of the lung may alter the case management, evaluation of the chest condition is important for patients with HNSCC at the initial diagnosis and during the follow-up period.

Chest radiography is the most common screening tool for many patients with HNSCC, but its sensitivity for early chest lesions is far from satisfactory. Chest computed tomography (CT) is a sensitive tool for the detection of pulmonary lesions. However, routine screening by chest CT in patients with HNSCC is controversial, and the cost-effectiveness and optimal timing for this imaging are not clearly defined. The objective of this study was to review the results of a screening chest CT in patients with HNSCC at Taipei Veterans General Hospital during a 42-month period. The rates of an abnormal chest CT scan at different times of imaging were analyzed. Possible predictive factors for the development of a malignant neoplasm of the lung were also explored to guide appropriate use of chest CT in the future.

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were advanced cases (stage III or IV) according to the 2002
American Joint Committee on Cancer staging system.12 All pa-
ents underwent detailed history taking, physical examination,
and comprehensive tumor surveys, including chest radi-
ography, abdominal ultrasonography, and bone scintigraphy.
Further investigation and consultation were arranged as nec-
essary to ensure that patients had no other primary malignant
neoplasms that had metastasized to the lungs. Medical rec-
ords and radiology and pathology reports were reviewed, and
the characteristics of 192 patients with HNSCC are summa-
ized in Table 2.

**DATA ANALYSIS**

Statistical analyses were performed to determine the associa-
tion between variables and an abnormal chest CT scan or de-
development of malignant neoplasm of the lung. χ² Test or Fisher
exact test was used for univariate analysis. Variables analyzed
included timing of imaging, history of cigarette smoking, pri-
mary tumor location, T and N classifications, locoregional re-
currence, and distant metastasis to another site. For patients
with primary tumor treated by surgery, pathologic variables of
the primary tumor or neck metastasis were analyzed where ap-
propriate, including perineural invasion, lymphovascular per-
meation, surgical margin, and extracapsular spread (ECS) of
neck metastasis. Multivariate analysis was performed using a
logistic regression model and inclusion of the significant fac-
tors on univariate analysis. All analyses were performed using
commercially available statistical software (SPSS version 12.0;

**RESULTS**

**CHEST CT**

According to the radiologic criteria, 79 of 270 chest CT
scans (29.3%) were initially considered abnormal, in-
cluding 54 manifesting a malignant neoplasm of the lung
(20.0%) and 25 manifesting indeterminate lesions (9.3%).
All malignant neoplasms occurred within the lungs, and
no isolated mediastinal lymph node metastasis was found.
Besides chest lesions, additional findings were noted on 7 chest CT scans, including 4 liver, 2 adrenal gland, and 1 peripancreatic lymph node metastases. Seventy-five abnormal chest CT scans had antecedent chest radiography, but only 21 (28.0%) identified the lung lesions.

The correlations between the timing of CT and the results are summarized in Table 3. The rate of an abnormal scan was significantly higher in the follow-up case group (44.2%) than in the new case group (14.2%) (P < .001) and was comparable in the follow-up case group and in the recurrent case group (44.0%). Of 54 scans demonstrating a malignant neoplasm of the lung, histologic confirmation by endoscopic or CT-guided needle biopsy was obtained in 4 patients with a solitary lesion larger than 1 cm. Most of the scans in 49 patients with multiple pulmonary nodules on chest CT were considered radiologically unequivocal, and only 8 (16.3%) underwent biopsy for tissue confirmation. On subsequent clinical and radiologic follow-up, 2 CT scans were considered false-positive results because lesion regression was found without any systemic treatment.

**CASE MANAGEMENT ALTERATIONS**

Among 54 patients with the diagnosis of malignant neoplasm of the lung by initial chest CT, 45 patients (83.3%) had major alterations in their case management. Instead of curative treatment, 34 patients received chemotherapy alone, and 7 patients underwent chemoradiotherapy for palliation. Only 4 patients received aggressive wedge resection of malignant neoplasms of the lung followed by postoperative chemotherapy. The remaining 9 patients refused any treatment, although palliative chemotherapy was suggested. Excluding 2 cases with false-positive results, only 1 patient who received wedge resection and postoperative chemotherapy achieved ultimate disease control.

Among 25 patients with indeterminate lesions on initial chest CT, 2 underwent CT-guided biopsy, and both had histologically negative results. A follow-up chest CT was performed 3 to 6 months later in all 25 patients, and progression of the pulmonary finding was shown in 11 patients (44.0%), changing the diagnosis to a malignant neoplasm of the lung (Table 4). Initial indeterminate lesions manifesting as small solitary nodules had a significantly higher chance of developing into malignant neoplasm of the lung (66.7%) than indeterminate lesions manifesting as multiple air-space opacities (10.0%) (P = .01).

**PREDICTORS OF A MALIGNANT NEOPLASM OF THE LUNG**

Sixty-three of 192 patients with HNSCC (32.8%) eventually developed a malignant neoplasm of the lung. The median interval between the diagnosis of primary HNSCC and the development of a malignant neoplasm of the lung was 9.9 months (range, 1.7-59.7 months). Eighty-four percent of the malignant neoplasms of the lung developed within 2 years. Univariate analysis results for the development of a malignant neoplasm of the lung relative to clinicopathologic factors are summarized in Table 4. N2 or N3 disease (P = .02) and stage IV disease (P = .03) were significantly correlated with the development of a malignant neoplasm of the lung. Recurrent locoregional disease (P < .001) and distant metastasis to another site (P < .001) were also significant predictors for the development of a malignant neoplasm of the lung. Patients with a smoking history (P = .09) or with primary sites at the hypopharynx and supraglottis (P = .07) had a trend to development of a malignant neoplasm of the lung that was statistically nonsignificant. In multivariate analysis, recurrent locoregional disease, N2 or N3 disease, and distant metastasis to another site remained independent predictors for the development of a malignant neoplasm of the lung (Table 5).

Histopathologic results were available in 85 patients who underwent surgery as the primary treatment of HNSCC. Pathologic factors of the primary tumor, including perineural invasion (P = .64), lymphovascular permeation (P = .40), and positive surgical margin (P = .74), were not predictive for the development of a malignant neoplasm of the lung. Fifty-two patients underwent neck dissection as part of their initial treatment, and pathologic cervical metastasis was found in 40 patients (46 without ECS and 21 with ECS). The incidence of a malignant neoplasm of the lung was significantly higher in patients with ECS (57.1%) than in those without ECS (26.3%) (P = .04). However, ECS remained a borderline predictor for the development of a malignant neoplasm of the lung (P = .07) by multivariate analysis in this subgroup of patients.

For patients with HNSCC, chest diagnosis is crucial and may influence their treatment plan. However, routine

**Table 3. Correlation Between Timing of Imaging and Initial Results of 270 Chest Computed Tomographic (CT) Scans**

<table>
<thead>
<tr>
<th>Timing Group</th>
<th>Normal</th>
<th>Malignant</th>
<th>Indeterminate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>New case</td>
<td>115 (85.8)</td>
<td>10 (7.5)</td>
<td>9 (6.7)</td>
<td>134</td>
</tr>
<tr>
<td>Follow-up case</td>
<td>29 (55.8)</td>
<td>17 (32.7)</td>
<td>6 (11.5)</td>
<td>52</td>
</tr>
<tr>
<td>Recurrent case</td>
<td>47 (56.0)</td>
<td>27 (32.1)</td>
<td>10 (11.9)</td>
<td>84</td>
</tr>
<tr>
<td>Total</td>
<td>191 (70.7)</td>
<td>54 (20.0)</td>
<td>25 (9.3)</td>
<td>270</td>
</tr>
</tbody>
</table>

*Residual or recurrent locoregional disease.

**Table 4. Final Results of 25 Indeterminate Lesions on Follow-up Chest Computed Tomographic Scans**

<table>
<thead>
<tr>
<th>Original Finding</th>
<th>Resolution or Progression</th>
<th>No Change</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small solitary nodule</td>
<td>10 (66.7)</td>
<td>5 (33.3)</td>
<td>.1</td>
</tr>
<tr>
<td>Multiple air-space opacity</td>
<td>1 (10.0)</td>
<td>9 (90.0)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11 (44.0)</td>
<td>14 (56.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Multiple nodules had developed in the follow-up scans.

*bMalignant pleural effusion was proved in this case.

(CASE MANAGEMENT ALTERATIONS)

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For patients with HNSCC, chest diagnosis is crucial and may influence their treatment plan. However, routine
yearly chest radiography has been shown by Shah and Applebaum\textsuperscript{7} to contribute little to the overall survival in patients with HNSCC. In the initial 2 to 3 years of follow-up, intensive chest screening has been suggested at 4- to 6-month intervals rather than annually.\textsuperscript{1} Chest CT is superior to radiography in sensitivity and adds little extra time and radiation dose (3-6 msv) when performed with neck CT.\textsuperscript{10,13} However, chest CT is more expensive, and its indications vary widely as a screening tool for HNSCC. In the present study without strict guidelines, 70.7\% of 270 chest CT scans showed normal findings. It is important to understand when and under which conditions chest CT will be cost-effective.

Chest CT performed at the initial diagnosis of primary tumors theoretically has the greatest effect on treatment planning. However, Keski-Säntti et al\textsuperscript{8} and Tan et al\textsuperscript{9} demonstrated limited usefulness of routine chest CT screening in patients newly diagnosed as having HNSCC. Our study also showed a low rate of an abnormal chest CT scan at the initial diagnosis. In contrast, a significantly higher rate of an abnormal chest CT scan was found in the follow-up period. Among 23 abnormal scans in the follow-up case group, 12 had antecedent normal CT scans at the initial diagnosis of their primary tumor. For more effective case management, chest CT during the follow-up period in high-risk patients should be emphasized.

Confirmation of the diagnosis of a malignant neoplasm of the lung theoretically should be supported by endoscopic or CT-guided biopsy. However, it is not always feasible in clinical practice. Brouwer et al\textsuperscript{11} reported that pulmonary lesions were considered malignant if unequivocal radiologic findings were identified on chest CT or if progression of the lesions was demonstrated on a follow-up scan. In our study, lung biopsy was performed in only 8 of 49 patients (16.3\%) with multiple and peripheral pulmonary nodules, as Mesurolle et al\textsuperscript{14} and Ginsberg et al\textsuperscript{15} demonstrated more than 90\% malignant results in such lesions. However, 2 false-positive CT scans were encountered in the present study. Therefore, follow-up CT scans should be mandatory, although false-positive findings are rare. Lung metastasis and second primary lung cancer were categorized as a malignant neoplasm of the lung in this study. Differentiating between them in clinical practice is sometimes difficult for HNSCC, especially when the histologic diagnosis of pulmonary lesions is squamous cell carcinoma.\textsuperscript{16} Advances in molecular genetic approaches may become efficient tools for the differential diagnosis in the future.\textsuperscript{16}

Indeterminate lesions were common on chest CT in our study, and special attention should be paid to them. Based on the progressive change in follow-up scans, 44.0\% of indeterminate lesions were eventually considered a malignant neoplasm of the lung. We also found that small (<1 cm) solitary nodules, which were usually resectable, carried significantly higher chances (66.7\%) of being a malignant neoplasm. For patients with HNSCC, durable disease control has been reported in 34\% of resectable pulmonary metastases after undergoing surgery.\textsuperscript{17} However, under a close imaging follow-up policy, all patients with progression from small solitary nodules developed multiple pulmonary nodules, and their disease could only be managed with chemotherapy for palliation in the present study.

Table 5. Univariate Analysis for Predictors of a Malignant Neoplasm of the Lung Among 192 Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Malignant Neoplasm of the Lung</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Smoking history</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Yes</td>
<td>107</td>
<td>58</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity, oropharynx, glottis</td>
<td>67</td>
<td>24</td>
</tr>
<tr>
<td>Hypopharynx, supraglottis</td>
<td>62</td>
<td>39</td>
</tr>
<tr>
<td>T classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 or T2</td>
<td>47</td>
<td>27</td>
</tr>
<tr>
<td>T3 or T4</td>
<td>82</td>
<td>36</td>
</tr>
<tr>
<td>N classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0 or N1</td>
<td>72</td>
<td>24</td>
</tr>
<tr>
<td>N2 or N3</td>
<td>57</td>
<td>39</td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-III</td>
<td>53</td>
<td>16</td>
</tr>
<tr>
<td>IV</td>
<td>76</td>
<td>47</td>
</tr>
<tr>
<td>Recurrent disease\textsuperscript{b}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>106</td>
<td>28</td>
</tr>
<tr>
<td>Yes</td>
<td>23</td>
<td>35</td>
</tr>
<tr>
<td>Distant metastasis to another site</td>
<td>110</td>
<td>39</td>
</tr>
<tr>
<td>Yes</td>
<td>19</td>
<td>24</td>
</tr>
</tbody>
</table>

\textsuperscript{a}For grouping early and advanced diseases, we used stages I through II in this table, vs stages III through IV (as in Table 2).

\textsuperscript{b}Residual or recurrent locoregional disease.

Table 6. Multivariate Analysis for Predictors of a Malignant Neoplasm of the Lung Among 192 Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N classification (N2 or N3 vs N0 or N1)</td>
<td>2.73 (1.31-5.68)</td>
<td>.01</td>
</tr>
<tr>
<td>Recurrent disease\textsuperscript{a}</td>
<td>8.43 (3.89-18.26)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Distant metastasis to another site</td>
<td>4.35 (1.93-9.78)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Residual or recurrent locoregional disease.

The evaluation and management of potentially controllable small solitary pulmonary nodules remain great challenges. Computed tomography–guided biopsy has been reported by Quint et al\textsuperscript{18} to be a valuable tool for larger (5-30 mm) pulmonary nodules. However, biopsy of small indeterminate nodules is associated with low accuracy, and pneumothorax may occur.\textsuperscript{19} Positron emission tomography with fludeoxyglucose F 18 (FDG-PET) has been advocated for high sensitivity.\textsuperscript{20,21} However, it is not widely available and has been reported to be no more accurate in detecting a malignant neoplasm of the lung than chest CT.\textsuperscript{20,22} Confirmation of abnormal findings on FDG-PET is necessary because false-positive results occur in 20\% to 67\% of cases.\textsuperscript{20,21} When appropriate, aggressive surgical excision is another choice for definitive diagnosis and management.

Because the chance of disease control is low in patients with a malignant neoplasm of the lung at the initial diagnosis of HNSCC or after locoregional treatment failure, an abnormal chest CT scan can affect the treat-
ment plan and prognosis. For patients with HNSCC who develop unresectable malignant neoplasm of the lung, the treatment policy should mostly be palliative. Only for patients with potentially resectable malignant neoplasm of the lung should aggressive curative treatment at the primary site and the lung be considered for possible long-term disease control.17,23

Several limitations should be noted in this study. Although ECS had been reported as a predictor of distant metastasis,24 we showed that its predictive value in only a small subgroup of patients with pathologic N disease or greater by univariate analysis. Further analysis in a larger study population whose initial treatment includes neck dissection is needed to clarify the relation between ECS and the development of a malignant neoplasm of the lung. Other limitations included selection bias in performing chest CT, the retrospective study design, and the limited follow-up period in some patients. Therefore, our results should be interpreted with caution. In the present study, CT was performed based on physician choice in patients with multiple unfavorable factors and with high likelihood of distant metastasis. A prospective study in consecutive patients with longer follow-up time is needed for more substantial results.

In conclusion, chest CT is recommended for high-risk patients, especially every 6 months for the first 2 years during the follow-up period, although its role is controversial for patients newly diagnosed as having HNSCC. High-risk patients include those with N2 or N3 disease, stage IV disease, or locoregional recurrence. For patients with indeterminate small (< 1 cm) solitary pulmonary nodules, aggressive evaluation and management are imperative because of the high rate of a malignant neoplasm of the lung.

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Author Contributions: Drs Hsu and Tai 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. Study concept and design: Hsu and Tai. Acquisition of data: Chu, Lan, Chang, Tsai, Huang, and Wang. Analysis and interpretation of data: Hsu, Liu, and Tai. Drafting of the manuscript: Hsu. Critical revision of the manuscript for important intellectual content: Chu, Liu, Lan, Chang, Tsai, Huang, Wang, and Tai. Statistical analysis: Hsu and Tai. Administrative, technical, and material support: Liu, Lan, Chang, Tsai, Huang, and Wang. Study supervision: Chu and Tai.

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REFERENCES