Original Investigation

Accuracy of Computed Tomography in the Prediction of Extracapsular Spread of Lymph Node Metastases in Squamous Cell Carcinoma of the Head and Neck

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IMPORTANCE At many institutions, computed tomography with iodinated intravenous contrast medium is the preferred imaging modality for staging of the neck in squamous cell carcinoma of the head and neck. However, few studies have specifically assessed the diagnostic accuracy of computed tomography for determining the presence or absence of extracapsular spread (ECS).

OBJECTIVE To determine the accuracy of modern, contrast-enhanced, multidetector computed tomography in the diagnosis of ECS of cervical lymph node metastases from squamous cell carcinoma of the head and neck.

DESIGN, SETTING, AND PARTICIPANTS Retrospective observational study at an academic tertiary referral center among 100 consecutive patients between May 1, 2007, and February 1, 2012, who underwent a lateral cervical neck dissection for squamous cell carcinoma of the head and neck with neck metastases of at least 1 cm in diameter on pathologic assessment. Exclusion criteria included malignant neoplasms other than squamous cell carcinoma, a delay in surgery longer than 6 weeks from the time of staging computed tomography, and prior treatment of the neck or recurrent disease or a second primary.

MAIN OUTCOMES AND MEASURES Each patient was independently assigned a subjective score for the presence of ECS by 2 Certificate of Added Qualification-certified neuroradiologists according to a 5-point scale. Receiver operating characteristic curves were generated, and sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were calculated for each observer.

RESULTS The areas under the receiver operating characteristic curve for observers 1 and 2 are 0.678 (95% CI, 0.578-0.768) and 0.621 (95% CI, 0.518-0.716), respectively. For observer 1, the positive and negative predictive values for the detection of ECS were 84% (95% CI, 68%-93%) and 49% (95% CI, 36%-62%), respectively. For observer 2, the positive and negative predictive values for the detection of ECS were 71% (95% CI, 57%-82%) and 48% (95% CI, 32%-64%), respectively.

CONCLUSIONS AND RELEVANCE Computed tomography cannot be used to reliably determine the presence of pathologic ECS. Radiologic findings suggestive of ECS should not be relied on for treatment planning in squamous cell carcinoma of the head and neck.

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Extracapsular spread (ECS) of cervical lymph node metastases from squamous cell carcinoma of the head and neck (HNSCC) has a strong negative effect on patient prognosis. Cervical lymph node metastases alone predict reduced survival and increased disease recurrence.\(^1\)\(^-\)\(^3\) Compared with patients having disease confined to the lymph nodes, the presence of ECS in patients having regional neck disease dramatically decreases 5-year survival from 70% to 27%.\(^4\) Significant increases in the rates of locoregional recurrence and distant metastases have been associated with ECS.\(^5\)\(^,\)\(^6\)

It has been suggested that ECS is the single most important prognostic marker for recurrence and survival in patients with HNSCC.\(^7\)\(^,\)\(^8\)

Because it is a marker for biologically aggressive disease, accurate pretreatment detection of ECS would be helpful for prognostication and treatment planning in patient populations that may require multimodality treatment. In the adjuvant setting, postoperative chemoradiotherapy has been shown to improve overall survival compared with radiation therapy alone in patients with positive surgical margins or ECS.\(^9\)

However, concomitant adjuvant chemoradiotherapy comes at the expense of a substantial increase in the incidence of high-grade toxic effects.\(^10\)\(^,\)\(^11\) This is particularly important when deciding which patients are candidates for transoral robotic surgery (TORS), which has become an alternative treatment to definitive chemoradiotherapy for select patients. Because of the increased toxic effects of adding chemotherapy, it is important to accurately determine ECS status before surgery. Patients with ECS (who require adjuvant chemoradiotherapy) may be better treated with definitive chemoradiotherapy rather than surgery.

At many institutions, computed tomography (CT) with iodinated intravenous contrast medium is the preferred imaging modality for staging of the neck in HNSCC. However, few studies have specifically assessed the diagnostic accuracy of CT for determining the presence or absence of ECS. Two studies\(^12\)\(^,\)\(^13\) from the early 1990s are contradictory, revealing sensitivities for the detection of ECS from 60% to almost 100%. More recent studies\(^14\)\(^-\)\(^16\) have demonstrated sensitivities between 65% and 80% but have consistently demonstrated specificities higher than 90%. However, none of these studies used modern, multidetector CT technology, and results were reported without the use of receiver operating characteristic curves. Therefore, the radiologic literature has conflicting, and potentially outdated, data regarding the accuracy of CT for detecting ECS. The objectives of this study were to perform a retrospective observational study to determine the accuracy of modern, contrast-enhanced, multidetector CT in the diagnosis of ECS of cervical lymph node metastases from HNSCC.

### Methods

#### Study Design

As a retrospective review, this study was granted exemption from informed consent by the institutional review board under the University of Pittsburgh Institutional Review Board guidelines for exempt review (institutional review board identification No. PRO11110009). Patients who had undergone a lateral cervical neck dissection (selective, modified, or radical) for squamous cell carcinoma with neck metastases found on histologic assessment were identified from pathology records at the University of Pittsburgh Medical Center (UPMC) between May 1, 2007, and February 1, 2012. Pathology records were searched by using a natural language search function through UPMC’s electronic patient information retrieval database, the Medical Archival Retrieval System. Clinical records for candidate patients were then reviewed using the Medical Archival Retrieval System, as well as 2 commercially available systems (Cerner Powerchart Electronic Medical Records System [Cerner Corporation] and the picCare Ambulatory Electronic Medical Record [Epic Systems Corporation]).

Clinical information obtained via medical record review included demographic data, medical history, radiology reports, operative reports, and pathology reports. Patients with a staging contrast-enhanced neck CT after 1.5-mm-thick axial section reconstructions performed within the UPMC system were included in the study.

Exclusion criteria included a delay in surgery longer than 6 weeks from the time of staging CT, head and neck malignant neoplasm other than squamous cell carcinoma, largest pathologic lymph node less than 1 cm in maximum diameter on histologic assessment, and recurrent disease or a second primary or prior treatment of disease with surgery, radiation therapy, or chemotherapy. All patients underwent surgery by 1 of 5 head and neck surgical oncologists (J.T.J., R.L.F., and U.D.) in the UPMC Department of Otolaryngology.

The sample size was calculated for a descriptive study of a dichotomous variable with a 95% CI of ±10%. Given a pre-study estimate of 70% for the prevalence of ECS among our study population, a minimum sample size of 81 neck dissections was determined. Therefore, we identified a cohort of the most recent 100 consecutive patients meeting our inclusion and exclusion criteria.

Pathologic analysis was performed by 1 of 4 head and neck pathologists in the UPMC Department of Pathology. Extracapsular spread is defined during histologic assessment as tumor infiltrating from the capsule of a metastatic lymph node and can range from slight involvement of perinodal fibroadipose tissue to gross involvement of adjacent anatomical structures. Microscopic ECS is not identified during sectioning and is only seen on microscopic evaluation. Macroscopic and microscopic ECS are not routinely differentiated in our cohort.

All patients underwent imaging on 1 of several commercially available CT systems with multidetector capability ranging from 8 to 64 channels (GE Healthcare). The technique variable according to the system used, but most sessions were performed on 64-channel imaging systems, and section thickness or spacing was always 2.5 mm. Typical imaging variables are the following: field of view of 22 cm, voltage of 120 kV (peak), pitch of 0.969 mm per rotation, gantry rotation time of 0.8 seconds, detector collimation of 6 × 0.625 mm, 2.5-mm axial reconstructed section thickness with soft-tissue and bone algorithms, and tube current of 100 to 550 mA (automatic tube current modulation with a noise index of 0.1). Images were obtained from the orbits through the thoracic inlet 45 seconds...
following the administration of 100 mL of intravenous iopamidol (Isovue-370; Bracco Diagnostics) at a rate of 2.0 mL/s. Coronal and sagittal reconstructions were not included in all patients and were not used for image interpretation.

Radiologic images were reviewed using a commercially available system (iSite Picture Archive and Communications System; Philips Healthcare). Two of us who are board certified with Certificates of Added Qualification in neuroradiology and 5 and 12 years of dedicated head and neck experience, respectively (T.J.R. and B.F.B.), independently reviewed CT images without knowledge of the histopathologic findings. All CT studies were evaluated by both radiologists for quality defects, such as motion artifact, dental amalgam artifact, or poor soft-tissue contrast, because of suboptimal contrast bolus. All images included in the study were deemed diagnostically adequate by both radiologists.

Criteria used to distinguish ECS include capsular contour irregularity, poorly defined nodal margins, and infiltration of adjacent fat planes. Each patient was assigned a subjective score according to the following 5-point scale: 1 (definitely not ECS), 2 (likely not ECS), 3 (equivocal ECS), 4 (likely ECS), and 5 (definitely ECS). No time limit was imposed for reading images. The order of patient images was randomized between observers. The score for a patient was the likelihood of ECS being present in any cervical node; no attempt was made to correlate specific nodes between radiologic and histopathologic data. This reflects more accurately the clinical efficacy of staging CT, where treatment decisions would be based on an overall assessment of the presence or absence of ECS.

The 2 radiologists jointly reviewed the CT images to determine the presence of matted nodes. Matted nodes were defined as 3 adjacent nodes abutting one another with loss of an intervening fat plane, as described by Spector et al.16

Statistical Analysis
Receiver operating characteristic curves were generated to quantify observer performance. Detection accuracy was measured according to the area under the receiver operating characteristic curve (AUC). We defined an AUC of less than 0.70 as poor, 0.70 to 0.79 as fair, 0.80 to 0.89 as good, and 0.90 to 1.00 as excellent in terms of predictive value. Exact binomial 95% CIs for the AUC were calculated to report statistical significance. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were calculated from the optimal threshold estimated from the Youden Index.27 A Cohen weighted k statistic with 95% CIs was calculated to evaluate interobserver agreement. Observer agreement was categorized by k values as poor (<0.20), fair (0.20–0.39), moderate (0.40–0.59), good (0.60–0.79), or excellent (≥0.80).18 All statistical analyses were performed using data analysis software (MedCalc; MedCalc Software).

Patients were stratified by pathologic N stage, and the χ² test was used to compare sensitivities and specificities from both observers for patients with single (N1 and N2a) and multiple (N2b and N2c) metastatic lymph nodes on pathologic examination. For all statistical analyses, P < .05 was considered indicative of a significant difference.

Table 1. Characteristics of 100 Patients

<table>
<thead>
<tr>
<th>Characteristic Value</th>
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<tbody>
<tr>
<td>Sex, No.</td>
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<tr>
<td></td>
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<tr>
<td>Age, y</td>
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<td></td>
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<tr>
<td>Disease site, No.</td>
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<td></td>
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<tr>
<td></td>
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<tr>
<td>HPV status for oropharyngeal primary, No.</td>
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<tr>
<td></td>
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<tr>
<td>N stage, No.</td>
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<td></td>
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<tr>
<td></td>
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<tr>
<td>Histopathologic status of metastatic lymph nodes, No.</td>
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</table>

Abbreviations: ECS, extracapsular spread; HPV, human papillomavirus.

Results

A total of 100 patients with node-positive HNSCC between May 1, 2007, and February 1, 2012, were evaluated (Table 1). Sixty-three patients were initially seen with ECS. There were 79 men and 21 women. The mean (SD) age was 62 (12) years. The oral cavity was the primary tumor site in 62 patients. Most patients were initially seen with N2b or N2c disease. Of 13 patients with oropharyngeal primary malignant neoplasms, 12 had p16-positive disease. However, 2 of these patients had p16-positive and human papillomavirus-negative disease.

Most patients with oral cavity, larynx, skin, and unknown primary malignant neoplasms were initially seen with ECS (39 of 62 patients, 12 of 18 patients, 6 of 6 patients, and 1 of 1 patient, respectively). Five of 13 patients with oropharyngeal primary malignant neoplasms had evidence of ECS. Microscopic ECS was identified in 5 patients. Of these, 3 were rated as demonstrating likely ECS by at least 1 observer. For 1 patient with microscopic ECS and unilateral node-positive disease, both observers rated the patient as demonstrating definitely ECS.

Data from both observers are summarized in Table 2. Observers 1 and 2 correctly rated 9 and 17 patients, respectively, as demonstrating definitely ECS when ECS was seen on pathologic examination. Similarly, observers 1 and 2 correctly rated
22 and 14 patients, respectively, as demonstrating likely ECS when the final pathology report identified ECS. Metastatic lymph nodes were incorrectly rated as likely ECS when in fact ECS was not present in 21% and 39% of patients evaluated by observers 1 and 2, respectively (Figure 1). Observer 2 rated 3 patients as demonstrating definitely ECS when pathologic examination did not reveal ECS. Observers 1 and 2 rated 9 and 8 patients, respectively, as demonstrating definitely not ECS when histopathologic assessment showed evidence of ECS (Figure 2).

The receiver operating characteristic curves are shown in Figure 3. The AUCs for observers 1 and 2 are 0.678 (95% CI, 0.578-0.768) and 0.621 (95% CI, 0.518-0.716), respectively. Both AUCs meet our definition for a poor predictive test. Interobserver agreement was rated as fair, with a weighted k statistic of 0.371 (95% CI, 0.243-0.499).

### Table 2. Radiographic Scoring of Patients

<table>
<thead>
<tr>
<th>Radiology Scorea</th>
<th>Negative for ECS (n = 37)</th>
<th>Positive for ECS (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observer 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (n = 18)</td>
<td>9 (50)</td>
<td>9 (50)</td>
</tr>
<tr>
<td>2 (n = 45)</td>
<td>22 (49)</td>
<td>23 (51)</td>
</tr>
<tr>
<td>3 (n = 0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4 (n = 28)</td>
<td>6 (21)</td>
<td>22 (79)</td>
</tr>
<tr>
<td>5 (n = 9)</td>
<td>0</td>
<td>9 (100)</td>
</tr>
<tr>
<td>Observer 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (n = 14)</td>
<td>6 (43)</td>
<td>8 (57)</td>
</tr>
<tr>
<td>2 (n = 28)</td>
<td>14 (50)</td>
<td>14 (50)</td>
</tr>
<tr>
<td>3 (n = 15)</td>
<td>5 (33)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>4 (n = 23)</td>
<td>9 (39)</td>
<td>14 (61)</td>
</tr>
<tr>
<td>5 (n = 20)</td>
<td>3 (15)</td>
<td>17 (85)</td>
</tr>
</tbody>
</table>

Abbreviation: ECS, extracapsular spread.

* Each patient was assigned a subjective score according to the following 5-point scale: 1 (definitely not ECS), 2 (likely not ECS), 3 (equivocal ECS), 4 (likely ECS), and 5 (definitely ECS).

* Given are the percentages of patients with pathologically positive or negative ECS within a radiology score.

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Contrast-enhanced computed tomographic scan shows a metastatic enlarged right level IIA lymph node (arrow) with central low attenuation, irregular margins, and infiltration of surrounding fat that was incorrectly interpreted as probable extracapsular spread by both observers. No extracapsular spread was present on pathologic examination.

Contrast-enhanced computed tomographic scan shows a nonenlarged enhancing right level IIA lymph node (arrow) with central low attenuation that was incorrectly interpreted as no extracapsular spread by both observers. Extracapsular spread was found on pathologic examination.
Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for the detection of ECS were assessed. These results are summarized in Table 3.

When patients were stratified by N stage, the sensitivity and specificity for the detection of ECS in patients with a single pathologic node (N1 and N2a) were 33% and 85%, respectively, for observer 1 and 58% and 54%, respectively, for observer 2 (Table 4). For patients with multiple pathologic nodes (N2b and N2c), the sensitivity and specificity for the detection of ECS were 52% and 83%, respectively, for observer 1 and 66% and 54%, respectively, for observer 2. No significant difference in sensitivity and specificity was seen in patients with a single pathologic node compared with multiple pathologic nodes.

The prevalence of matted nodes was 30.0%. The sensitivity, specificity, positive predictive value, and negative predictive value of the radiographic determination of matted nodes for the detection of pathologic ECS were 38% (95% CI, 26%-51%), 84% (95% CI, 68%-94%), 80% (95% CI, 61%-92%), and 44% (95% CI, 32%-57%), respectively. These results are shown in Figure 4.

Discussion

The primary objective of this study was to assess the predictive value of modern, contrast-enhanced, multidetector CT in the detection of ECS. Results of this study demonstrate that modern, contrast-enhanced, multidetector CT with 2.5-mm-thick axial reconstructions is a poor predictor of ECS and that treatment decisions based on CT findings of ECS should be made with caution. The receiver operating characteristic curves provide a powerful method for evaluating the performance of diagnostic tests without relying on arbitrary thresholds for the calculation of sensitivities and specificities. With calculated AUCs of 0.678 and 0.621, CT was a poor predictive test of the diagnosis of ECS for both observers.

However, sensitivity, specificity, positive predictive value, and negative predictive value remain useful, particularly for comparison between different studies. Using the Youden Index for calculating an optimal threshold, ratings of equivocal ECS, likely ECS, and definitely ECS were considered a positive test. Our study demonstrated low interobserver agreement, with a weighted k statistic of 0.371, reflecting the subjective nature of imaging criteria for the diagnosis of ECS. Negative predictive values for both observers were poor at 49% and 48%. Positive predictive values ranged from 71% to 84%, with a false-positive rate of almost one-third in images read by observer 2. The required diagnostic accuracy for a test to influence treatment is not well defined. However, given the poor interobserver agreement for the presence of ECS by CT and the substantial morbidity associated with adjuvant chemoradiotherapy, we believe the rate of false-positive results when using CT to predict ECS is unacceptably high to direct patient care.

The poor negative predictive value in our study is not surprising because microscopic ECS cannot be expected to be detected on CT. Macroscopic ECS is evident to the naked eye during gross inspection. Microscopic ECS can only be determined on histologic examination when the tumor extends beyond the lymph node capsule and is limited to the adjacent perinodal fibroadipose tissue. Our institution does not routinely distinguish between macroscopic and microscopic ECS; the recommendation to distinguish the two was only recently reported in the seventh edition of the American Joint Committee on Cancer staging system. Because of the lack of internationally accepted reproducible criteria for the histologic assessment of ECS, pathologists commonly disagree on the presence of microscopic ECS. Retrospective data suggest that the extent of extracapsular extension beyond the lymph node does not affect prognosis, although this remains controversial.

In 3 of 5 patients in our cohort in whom microscopic ECS was specifically mentioned, at least 1 observer rated imaging as demonstrating likely ECS or definitely ECS. This further highlights the low positive predictive value in our study. However, this is also not surprising. Because axial section thickness decreases with newer imaging technology, improved spatial resolution allows more of the margin of each lymph node to be evaluated. Commonly accepted radiographic criteria for ECS, such as an ill-defined margin, are subjective and open to wide variation in interpretation, as evidenced by our low interobserver agreement. Therefore, with more of the lymph node margin available for analysis, the rate of false-positive results increases.

Matted nodes have been identified as a novel marker for poor prognosis in patients with oropharyngeal squamous cell carcinoma independent of established prognostic factors, including T stage, human papillomavirus status, and epidermal growth factor receptor expression, as well as tobacco use. Matted nodes, as defined by Spector et al, are adjacent cervical lymph nodes abutting one another with loss of an intervening fat plane. By definition, all patients with matted nodes have obvious radiographic ECS. In our study, the presence of matted nodes has a positive predictive value of only 80% for the detection of true pathologic ECS. These data further reinforce the unacceptably high false-positive rate in our study.

Few prior studies have specifically addressed the usefulness of CT in detecting ECS. An early 1983 study by Mancuso et al prospectively evaluated 39 patients, with the primary objective of determining the value of CT in clinical staging of cervical nodes. Four-millimeter-thick axial sections were performed at 4-mm increments (through palpable tumor and nodal masses) or 8-mm increments (clinically negative regions of the neck thought likely to harbor metastases). Criteria for extranodal extension included an ill-defined margin with

### Table 3. Analysis of Diagnostic Accuracy per Observer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Observer 1 % (95% CI)</th>
<th>Observer 2 % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>49 (37-62)</td>
<td>65 (52-76)</td>
</tr>
<tr>
<td>Specificity</td>
<td>84 (68-93)</td>
<td>54 (37-70)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>62 (53-72)</td>
<td>61 (51-71)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>84 (68-93)</td>
<td>71 (57-82)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>49 (36-62)</td>
<td>48 (32-64)</td>
</tr>
</tbody>
</table>

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obliteration of surrounding fat planes and edema of surrounding fibroadipose tissue or muscle. Of 39 patients, 25 underwent surgical confirmation of disease. Extranodal spread was confirmed by surgical findings or histologic examination. Computed tomography correctly predicted ECS in 9 of 11 patients.

A 1991 study by Carvalho et al12 examined 28 patients with 4-mm axial CT sections performed at 5-mm intervals. Of these patients, 6 had received prior radiation therapy. Imaging criteria for ECS included irregular borders, invasion of adjacent structures, loss of surrounding fat planes, and thickening of adjacent fascia. Individual nodes were dissected and described by a single pathologist. The authors reported a sensitivity of 62.5% and a specificity of 60% for the detection of ECS by CT.

In the past 20 years, we can identify only 1 study in the English literature that has been performed to specifically assess the accuracy of CT in diagnosing ECS. In 2009, Souter et al14 evaluated 149 neck dissections with CT image thickness between 3 and 5 mm. Iodinated contrast medium was not consistently used for all imaging studies. Imaging criteria for ECS included enhancing nodal margins, alterations in adjacent fat, and loss of margin definition. An attempt was made to correlate specific nodes radiologically and histopathologically. Assessment of ECS was performed by 2 observers, with sensitivities of 66% and 80% and specificities of 91% and 90%.

A small study15 evaluated the detection of ECS by magnetic resonance (MR) imaging compared with CT in 17 patients; CT had a low sensitivity of 65% but a high specificity of 93%. Patients underwent helical CT with a collimation of 3 to 5 mm. Identification of each node for pathologic-radiologic correlation was attempted. Radiologic ECS was determined by the presence of indistinct margins, irregular capsular enhancement, and infiltration into surrounding structures.

Our study design differs from these prior studies by the use of modern helical CT and the incorporation of stringent inclusion and exclusion criteria. All patients had contrast-enhanced staging neck CT with 2.5-mm-thick axial reconstructions that were all performed within a single institution. This controlled for the variable imaging quality present in CT performed at outside institutions. We included only patients with pathologic evidence of a metastatic node that was at least 1 cm in diameter, reflecting metastases that would be readily identified on imaging per nodal size criteria. Staging CT was performed no later than 6 weeks before the time of surgery to control for ECS that might develop after the acquisition of images. Only patients with squamous cell carcinoma were included because other malignant neoplasms, such as papillary thyroid carcinoma, may initially be seen with varied imaging presentation of metastatic lymphadenopathy.25 Finally, unlike the previous studies, we only included patients without prior treatment for their disease because criteria for the detection of ECS, such as obliteration of adjacent fat planes and poorly defined nodal borders, can be mimicked by prior surgery or radiation therapy. Our radiologic imaging criteria for ECS of contour irregularity, ill-defined lymph node margins, and obliteration of adjacent fat planes are similar to those used by the prior studies.

Several criticisms are applicable to this study. The retrospective nature of our analysis has the inherent potential for selection bias. We attempted to control for this by analyzing consecutive patients who met our inclusion criteria. The order of patients was randomized between observers to further minimize bias.

### Table 4. Analysis of Accuracy by N Stage

<table>
<thead>
<tr>
<th>Variable</th>
<th>% (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single Nodea</td>
<td>Multiple Nodesb</td>
</tr>
<tr>
<td>Observer 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>33 (10-65)</td>
<td>52 (37-66)</td>
</tr>
<tr>
<td>Specificity</td>
<td>85 (55-98)</td>
<td>83 (63-95)</td>
</tr>
<tr>
<td>Observer 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>58 (28-85)</td>
<td>66 (51-79)</td>
</tr>
<tr>
<td>Specificity</td>
<td>54 (25-81)</td>
<td>54 (33-74)</td>
</tr>
</tbody>
</table>

* N1 and N2a.
* N2b and N2c.
Lymph nodes are not routinely oriented during neck dissections for pathologic examination at our institution. Therefore, our study differs from prior investigations by evaluating individual patients for ECS rather than individual lymph nodes. Although this decreased the sample size for our analysis, providing an exact imaging match for any given node is difficult, if not impossible. Surgical cutoffs for classification of anatomical levels of lymph nodes during a neck dissection can be somewhat arbitrary and often differ from levels determined using radiographic landmarks. During the period between staging CT and surgery, changes in the size of lymph nodes are possible. Slight variations in the position of the patient's head or tilt of the imaging system can further affect the precise localization of a specific lymph node radiographically. In clinical practice, patient care is determined by the overall presence or absence of ECS, not by which node is affected.

None of the previous studies specifically addressed the issue of microscopic ECS. Our study also was not designed to differentiate microscopic and macroscopic ECS. Therefore, even with thinner axial sections, our data demonstrated sensitivities similar to those of the more recent studies. The markedly different specificities between our data and those of the other studies are likely explained by the inclusion of thin 2.5-mm axial sections in our study. With the subjective nature of the radiographic interpretation of ECS, evaluating more of the lymph node margin leads to more false-positive results.

The subtlety of accepted radiologic criteria for the diagnosis of ECS is likely a major factor contributing to our low interobserver agreement. A method to improve the detection of subtle infiltration of adjacent planes and irregular nodal margins may be an appropriate setting of acquisition variables. Higher image contrast and an improved contrast-noise ratio would likely enhance the capability of CT to detect ECS. Another institution with different CT scanning parameters resulting in a higher contrast-noise ratio may have an improved ability to identify ECS. However, this typically comes at the expense of an increased irradiation dose and exposure to the patient. New imaging technology using model-based iterative reconstruction has the promise of improved image clarity and spatial resolution at lower irradiation levels and may be a potential avenue for future investigation.

The use of MR imaging has been evaluated in few prior studies for the detection of ECS in cervical lymph nodes. With its superior soft-tissue resolution, one might expect MR imaging to have improved performance in delineating infiltration of adjacent fat planes and contour irregularity compared with CT. However, an early 1992 study demonstrated a maximum sensitivity of 61% to 83% with unenhanced T1-weighted and T2-weighted images. The addition of fat-suppressed, gadolinium-enhanced sequences did not improve diagnostic accuracy. However, a significant limitation of this study was the reliance on CT rather than histopathologic evaluation as the gold standard for determining the presence of ECS. A 2004 study that included 17 patients demonstrated a sensitivity and specificity of 78% and 86%, respectively, of MR imaging for diagnosing ECS. However, no significant difference between CT and MR imaging was seen for sensitivity or specificity. These findings may be explained by the inferior spatial resolution of MR imaging compared with CT, leading to higher false-negative rates of detection. In addition, the quality of MR images may potentially be degraded by motion artifact that would not be present with multidetector helical CT.

High-resolution ultrasonography is an imaging modality that offers several theoretical advantages over CT and MR imaging for the detection of ECS. Ultrasonography has the highest spatial resolution of these modalities and can reveal structural details that are not readily apparent on CT or MR imaging. In addition, ultrasonography lacks ionizing irradiation and can provide complementary information with Doppler imaging. Sonographic features, including node matting, perinodal edema, and indeterminate lymph node margins, have a high specificity for the prediction of ECS in axillary lymph nodes of patients with biopsy-proved breast cancer. Only 1 study has been published in the English literature to date on the use of ultrasonography for the detection of cervical ECS in patients with HNSCC. In an analysis of 47 patients, ultrasonography had a sensitivity and specificity of 80% and 74%, respectively, for the detection of macroscopic ECS. No significant difference in diagnostic accuracy was seen between ultrasonography and CT.

Pretreatment detection of ECS in HNSCC can potentially change the management for patients. Transoral robotic surgery has become an alternative primary treatment for patients with oropharyngeal squamous cell carcinoma. The potential advantage of TORS is that it may allow treatment deintensification. Surgery, followed by a shortened course of radiation therapy without chemotherapy, may have fewer late toxic effects than definitive chemoradiotherapy. However, the treatment decision is partly dependent on accurate pretreatment detection of ECS. Patients with ECS identified after TORS and neck dissection will still require adjuvant chemotherapy and near full-level radiation therapy, attenuating the potential advantages of TORS. If patients are known to have ECS on presurgical staging, they may be better treated with definitive chemoradiotherapy alone rather than surgical resection that is followed by chemoradiotherapy. Such a decision may come at the expense of significant unnecessary toxic effects if the patient ultimately does not have ECS, although recent data suggest that ECS may not be a strong negative prognostic factor in the human papillomavirus-related, p16-positive population.

In conclusion, modern CT is a poor diagnostic test for ECS. Interobserver agreement is rated as fair, reflecting the subjective nature of imaging criteria in the detection of ECS. Because of its low negative predictive value, CT cannot be used to reliably determine the presence of pathologic ECS. Likewise, radiologic findings suggestive of ECS should not be relied on for treatment planning because an unacceptably high false-positive rate may lead to overtreatment and avoidable toxic effects. Surgical pathologic examination remains the gold standard for detecting ECS, and CT alone is unable to predict ECS with the requisite sensitivity and specificity on which to base clinical decision making.
Accuracy of CT in the Prediction of LN Metastases

Research

Original Investigation

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