Timing of Restaging PET/CT and Neck Dissection after Chemoradiation for Advanced Head and Neck Squamous Cell Carcinoma

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Abstract

Background: Concomitant chemoradiation therapy (CRT) is widely accepted as a primary treatment of advanced head and neck squamous cell carcinoma (HNSCC). However, controversy exists regarding the treatment of patients with no clinically evident nodal disease after CRT. PET/CT imaging has therefore become increasingly popular to aid in the selection of patients who would benefit from post-CRT neck dissection. However, there are several compelling concerns regarding the timing of PET/CT and planned neck dissection. The aims of this study were to assess how (i) the detection of residual neck disease by PET/CT and (ii) the incidence of viable carcinoma in neck dissection specimens differ with time after CRT for advanced HNSCC.

Methods: Retrospective review of 121 patients who underwent PET/CT and planned neck dissection following primary CRT for N2 or greater HNSCC. The sensitivity and specificity of PET/CT for detection of residual neck disease after CRT were determined. Rates of negative, non-viable, or positive pathologic results in neck dissection specimens were also assessed.

Results: PET/CT results following CRT were analyzed for a total of 116 neck sides. The sensitivity and specificity of PET/CT for residual neck disease were 42.3% and 90.4%, respectively. Specificity tended to increase with time, whereas sensitivity decreased. Sixty patients underwent planned neck dissection earlier than 12 weeks following completion of CRT, and 61 patients underwent neck dissection 12 weeks or later. Viable carcinoma was detected in 31.4% of surgical specimens. Rates of negative, non-viable, or positive pathologic results were similar in neck dissections performed before versus after 12 weeks following CRT (p=0.951).

Conclusions: PET/CT is limited by low predictive value, but specificity tends to increase with time. Rates of viable carcinoma do not differ with time; histologic evidence of tumor lysis does not appear to continue beyond 12 weeks after CRT.

Keywords: Head and neck squamous cell carcinoma; Neck dissection; Viable carcinoma

Abbreviations: CRT: Chemoradiation Therapy; HNSCC: Head and Neck Squamous Cell Carcinoma; HPV: Human Papillomavirus; PET/CT: Positron Emission Tomography/Computed Tomography; PPV: Positive Predictive Value; NPV: Negative Predictive Value

Introduction

Concomitant chemoradiation therapy (CRT) has become a widely accepted strategy for the primary treatment of locoregionally advanced head and neck squamous cell carcinoma (HNSCC). CRT achieves excellent tumor response rates, while allowing for organ preservation and decreased morbidity compared to surgery [1]. For N1 disease, CRT alone provides sufficient regional control, with no need for subsequent neck dissection unless there is evidence of neck disease following CRT. For N2 or greater disease, however, management has traditionally involved planned neck dissection after CRT, regardless of treatment response [2]. The practice of planned neck dissection initially arose because, historically, radiotherapy alone yielded high regional failure rates, and surgical salvage rates were poor [3]. Rates of residual microscopic neck disease of as high as 20 to 40% after CRT have also been cited as additional support for planned neck dissections [2,4,5]. However, the improved efficacy of combination therapy in the treatment of HNSCC has resulted in considerable controversy regarding the overtreatment of patients with no clinically evident nodal disease after CRT [6,7]. The need for routine planned neck dissection has also been questioned in light of the increasing incidence of human papillomavirus (HPV)-positive HNSCC of the oropharynx, which confers a more favorable prognosis and improved response to CRT as compared to HPV-negative disease [8-11].

Combined 18F-FDG positron emission tomography/computed tomography (PET/CT) imaging has increasingly become part of the decision-making algorithm in the selection of patients who would benefit from post-CRT neck dissection. Several studies have demonstrated that PET scans have high specificity but low sensitivity.

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for detecting regional disease [12,13]. However, the value of PET/CT to predict residual disease varies depending on the timing of the imaging. An interval of 12 weeks between completion of CRT and acquisition of restaging PET/CT imaging is typically recommended [14].

However, if planned neck dissection is decided upon, it is generally recommended that surgery be performed within 4 to 12 weeks after the conclusion of CRT [2]. Delaying surgery for several weeks after CRT allows for the resolution of acute post-radiation effects, including radiation dermatitis, that could hamper post-operative recovery and wound healing [15]. In addition, the cytotoxic effects of radiation are known to continue for up to three months after the end of therapy, and it is presumed that early neck dissection may result in artificially high rates of persistent, viable carcinoma [3]. Accounting for these CRT-related effects, the ideal time period for an intervention is 12 weeks after CRT. However, it has been reported that rates of surgical complications increase if neck dissections are performed after 12 weeks following CRT [2].

Given the competing concerns with regards to the timing of PET/CT and planned neck dissection, we sought to evaluate the impact of timing of each on various clinical measures. Specifically, we wanted to clarify the role of PET/CT in predicting residual neck disease and to determine whether the predictive value of PET/CT changes depending on the timing after CRT. We also sought to assess whether the incidence of viable carcinoma differs with early versus late neck dissection, as the phenomenon of continued tumor lysis might help explain why PET/CT scans are felt to be more accurate after twelve weeks. In addition, given the differences in clinical behavior of HPV-positive and HPV-negative disease, we investigated whether HPV status affects the rate of viable carcinoma in neck dissection specimens.

**Methods**

**Study subjects**

The medical records of 121 patients who underwent planned neck dissection following primary CRT for previously untreated, non-metastatic squamous cell carcinoma of the oropharynx, hypopharynx, or larynx of advanced nodal stage (N2 or N3) were retrospectively reviewed. All patients were treated at the Greater Baltimore Medical Center (GBMC), a community cancer center, between 2000 and 2011. All patients had a histologic diagnosis of squamous cell carcinoma and were staged according to American Joint Committee on Cancer (AJCC) guidelines [16]. When possible, tumor samples were tested for HPV-16 DNA via in situ hybridization-catalyzed signal amplification as previously described [5]. Patients with cancers of the salivary glands, sinuses, or unknown primary sites were excluded, as were patients with recurrent tumors or previous chemoradiation or radiation to the head or neck. The study proposal was reviewed and approved by the institutional review board of GBMC.

**Chemoradiation**

All patients were treated with primary CRT with curative intent. Patients received either of two cisplatin-based chemotherapy regimens, based on the timing of diagnosis and treatment. The first consisted of concomitant cisplatin (12 mg/m²/1h) and 5-fluorouracil (600 mg/m²/20 h), dosed daily for five consecutive days during weeks one and six of radiation therapy. The second consisted of concomitant cisplatin (30 mg/m²/1h), dosed once a week for 6 cycles. All patients received a uniform radiation therapy regimen, consisting of hyperfractionated doses of 125 cGy delivered twice daily for 28-33 days for a total dose of 67-72 Gy to the primary tumor site and 60 Gy to involved cervical lymph nodes.

**PET/CT imaging**

PET/CT studies were performed at 4 to 16 weeks after the completion of CRT. Studies were performed at several locations, but imaging protocols were similar for all locations. Patients fasted for 4 to 6 hours prior to the study. No oral or intravenous contrast was used for the CT portion of the study. Images were obtained 60 minutes after intravenous administration of [¹⁸F]-FDG. Imaging was performed from the skull vertex to the proximal thigh. PET, CT, and fused PET/CT images were then reviewed by the assigned nuclear radiologist. PET/CT results were based on radiology reports generated by the nuclear radiologists, when these reports were available in the medical record. Alternatively, if a radiology report was unavailable, PET/CT results were extrapolated from the medical record. PET/CT results were categorized as positive, negative, or indeterminate for each side of the neck. PET/CT studies were considered positive if the radiologist indicated concern for residual malignancy, demonstrated by persistent or increased FDG uptake, of one or more levels on that side of the neck. PET/CT studies were considered negative if the radiologist indicated that there was no evidence for continued malignancy in the neck on that side. In some instances, due to ambiguous wording of the radiology report, it was unclear whether there was residual neck disease. These studies were categorized as indeterminate.

**Neck dissections and surgical pathology**

All patients underwent planned cervical lymph node dissections at 6 to 27 weeks after the completion of CRT. Determinations of (i) selective versus comprehensive and (ii) unilateral versus bilateral neck dissection were made on an individual patient basis. All surgical specimens were processed using standard histopathological techniques and evaluated by board-certified pathologists, who were blinded to the PET/CT findings, in a team-based approach. Pathology reports were categorized as positive, negative, or non-viable for each side of the neck. Specimens were considered positive if one or more cervical lymph nodes originating from one or more levels of that side of the neck were noted to contain “residual” or “viable” carcinoma. Specimens were considered negative if there was no evidence of metastatic disease on that side of the neck. Specimens with metastatic disease, treated metastasis, or necrotic lymph nodes were considered “non-viable” if it was also noted within the pathology report that there was no evidence of viable tumor. For analysis of the predictive value of PET/CT, both negative and non-viable pathology were considered negative. For analysis of the timing of neck dissection, negative and non-viable pathology were considered separate categories.

**Patient follow-up**

After treatment, patients returned for follow-up every 2-3 months in years 1-2, every 3-6 months in years 3-5, and every 6-12 months thereafter, or sooner in the event of a clinical concern requiring closer scrutiny.

**Statistical Analysis**

All variables were summarized using descriptive statistics. Associations between PET/CT findings and pathology results, as well as between pathology results of the early and late neck dissection groups, were evaluated using the chi-square test. Comparisons of patient and tumor characteristics of the early and late neck dissection groups and of HPV-positive and HPV-negative groups were made using t-tests. Computations were performed using Stata 11 (College Station, TX). A two-sided p-value less than 0.05 was considered statistically significant.
Results

One-hundred twenty-one patients were eligible for this study. All patients had N2 or greater disease at time of presentation and underwent planned neck dissection after completion of CRT. The median follow-up of all patients was 33.4 months (range 3.5 to 137.8).

Timing of restaging PET/CT imaging

Of the 121 eligible subjects, 100 patients (82.6%) underwent restaging PET/CT imaging after completion of CRT and prior to neck dissection. Dates of PET/CT studies were unknown for two patients, so these patients were ineligible. The 98 remaining patients were included in the analysis and their characteristics are summarized in table 1. The majority of patients (78.6%) had tumors of the oropharynx. The mean interval between completion of CRT and acquisition of PET/CT imaging was 8.9 weeks (range 4.3 to 16.1 weeks).

Eighty patients underwent unilateral planned neck dissection, and the remaining 18 patients underwent bilateral neck dissections, for a total of 116 neck sides. The distribution of PET/CT results was significantly different from the pathology results from subsequent planned neck dissections (p<0.01, Table 2). PET/CT imaging identified 18 of 116 neck sides (15.5%) as positive and 81 neck sides (69.8%) as negative for residual disease. The remaining 17 neck sides were deemed indeterminate by imaging. Of the neck sides deemed positive on PET/CT, 7 were found to contain no viable disease on pathological analysis, for a false-negative rate of 38.9%. Of the neck sides deemed positive on PET/CT, 15 were histopathologically confirmed to contain viable carcinoma, for a false-positive rate of 18.5%.

Taking into account only the 99 definitive PET/CT results, the sensitivity and specificity of PET/CT imaging for detecting residual carcinoma, for a false-negative rate of 18.5%, resulting in a greater likelihood of PET imaging to detect disease, the sensitivity increases to 53.1%, but the specificity decreases to 78.6%. The PPV decreases to 48.6%, while the NPV remains 81.5%.

In order to investigate whether the utility of PET/CT imaging varies depending on the time the study is obtained, the 116 neck sides were categorized into those obtained before 12 weeks and those obtained at or later than 12 weeks after the completion of CRT. Ninety-eight neck sides were included in the first group and 18 neck sides in the latter group. Indeterminate PET reads were again grouped with the positive reads. Table 3 shows the sensitivity, specificity, PPV, and NPV for both time intervals. The specificity, PPV, and NPV of PET/CT imaging are increased at ≥12 weeks as compared with <12 weeks after completion of CRT. In contrast, the sensitivity of PET/CT imaging to detect residual neck disease is decreased during the time interval ≥12 weeks versus <12 weeks. However, this analysis was limited by the small number of patients in our cohort who underwent PET/CT imaging at or later than 12 weeks.

Timing of planned neck dissection

Patient characteristics of patients undergoing planned neck dissection are listed in table 1. Their tumor and nodal staging at time of presentation are listed in table 4. The mean interval between completion of CRT and neck dissection was 12.3 weeks (range 5.9 to 27.1 weeks). Sixty patients (49.6%) underwent planned neck dissection earlier than 12 weeks following completion of CRT, with a mean interval of 9.2 weeks between completion of CRT and surgery. The remaining 61 patients underwent neck dissection 12 weeks or later following completion of CRT, with a mean interval of 15.3 weeks between completion of CRT and surgery. There are no statistical differences in patient or tumor characteristics between the two groups (p>0.05), shown in table 1.

Residual viable carcinoma was detected in the post-CRT neck dissection specimens of 31.4% (38 of 121 patients) of the entire cohort.

### Table 1: Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with PET/CT data (n=98)</th>
<th>All patients undergoing ND (n=121)</th>
<th>ND &lt;12 weeks (n=60)</th>
<th>ND ≥12 weeks (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (range)</td>
<td>59.0 (39.6-78.7)</td>
<td>58.7 (39.6-78.7)</td>
<td>57.3 (39.6-77.6)</td>
<td>60.1 (44.3-78.7)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>83 (84.7)</td>
<td>101 (83.5)</td>
<td>47 (78.3)</td>
<td>54 (88.5)</td>
</tr>
<tr>
<td>Female</td>
<td>15 (15.3)</td>
<td>20 (16.5)</td>
<td>13 (21.7)</td>
<td>7 (11.5)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>90 (91.8)</td>
<td>108 (89.3)</td>
<td>51 (85.0)</td>
<td>57 (93.4)</td>
</tr>
<tr>
<td>African-American</td>
<td>8 (8.2)</td>
<td>13 (10.7)</td>
<td>9 (15.0)</td>
<td>4 (6.6)</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>30 (30.6)</td>
<td>33 (27.3)</td>
<td>16 (26.7)</td>
<td>17 (27.9)</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>68 (69.4)</td>
<td>88 (72.7)</td>
<td>44 (73.3)</td>
<td>44 (72.1)</td>
</tr>
<tr>
<td>Primary site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>77 (76.8)</td>
<td>96 (79.3)</td>
<td>47 (78.3)</td>
<td>49 (80.3)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>9 (9.2) †</td>
<td>12 (9.9) †</td>
<td>8 (13.3) †</td>
<td>4 (6.8)</td>
</tr>
<tr>
<td>Larynx</td>
<td>14 (14.3) †</td>
<td>15 (12.4) †</td>
<td>6 (10.0)</td>
<td>9 (14.8) †</td>
</tr>
<tr>
<td>HPV status ‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>15 (19.5)</td>
<td>18 (18.8)</td>
<td>11 (23.4)</td>
<td>7 (14.3)</td>
</tr>
<tr>
<td>Positive</td>
<td>35 (45.5)</td>
<td>46 (47.9)</td>
<td>19 (40.4)</td>
<td>27 (55.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>27 (35.1)</td>
<td>32 (33.3)</td>
<td>17 (36.2)</td>
<td>15 (30.6)</td>
</tr>
</tbody>
</table>

Unless otherwise noted, all data are listed as number of patients (percentage).

HPV= human papillomavirus

†One patient presented with synchronous primaries of the oropharynx and larynx

‡HPV status collected only for patients with tumors of the oropharynx

*One patient presented with synchronous primaries of the oropharynx and hypopharynx

<0.01
Pathology results based on HPV status.

<table>
<thead>
<tr>
<th>PET/CT</th>
<th>Positive</th>
<th>Negative*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>17 (37.0)</td>
<td>16 (34.8)</td>
<td>33</td>
</tr>
<tr>
<td>Negative</td>
<td>9 (27.8)</td>
<td>12 (35.3)</td>
<td>21</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>5 (27.8)</td>
<td>1 (5.6)</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>22 (35.4)</td>
<td>29 (48.3)</td>
<td>51</td>
</tr>
</tbody>
</table>

* Includes both negative and non-viable pathology

**Table 2:** The relationship between PET/CT and pathology findings.

<table>
<thead>
<tr>
<th>Time of PET/CT</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 weeks (n=98)*</td>
<td>55.2%</td>
<td>73.9%</td>
<td>47.1%</td>
<td>79.7%</td>
</tr>
<tr>
<td>≥ 12 weeks (n=18)*</td>
<td>33.3%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>88.2%</td>
</tr>
</tbody>
</table>

Abbreviation: PPV=Positive Predictive Value; NPV=Negative Predictive Value

*n refers to number of neck sides

**Table 3:** Predictive value of PET/CT imaging based on timing.

Metastatic nodal disease without evidence of viable carcinoma was detected in an additional 39 patients in the overall cohort (Table 5).

The pathology results for those patients undergoing neck dissection earlier than 12 weeks versus 12 or more weeks after the end of CRT are reported in Table 5. On pathologic evaluation of surgical specimens from patients who underwent neck dissection earlier than 12 weeks, 68.3% had no evidence of nodal disease or evidence of metastatic but non-viable disease, and 31.7% had viable residual carcinoma. For patients who underwent neck dissection at 12 weeks or later, 69.9% of specimens were negative or non-viable, and 31.1% harbored residual viable carcinoma. There was therefore no difference in pathology findings between the early and late neck dissection groups (p=0.951, chi-square).

Clinical outcomes for the early and late neck dissection groups are shown in Table 6. For the overall cohort, nine patients (7.4%) developed local recurrence, seven patients (5.8%) developed regional recurrence, and 25 patients (20.7%) developed distant metastatic disease. In addition, 17 secondary primary malignancies were diagnosed in 14 patients. The most common sites of second primary malignancy were lung (n=3) and colorectal (n=3), followed by HNSCC (n=2), prostate (n=2), cutaneous squamous cell carcinoma (n=2), breast (n=1), medullary thyroid carcinoma (n=1), papillary thyroid carcinoma (n=1), multiple myeloma (n=1), and keratoacanthoma (n=1).

**HPV status and viable carcinoma**

HPV status was available for 64 of the 96 patients (66.7%) in our study population with tumors of the oropharynx. Pathology results of post-CRT neck dissection specimens for HPV-positive and HPV-negative patients are shown in Table 7. Viable carcinoma was detected in the surgical specimens of 28.3% of HPV-positive patients and 27.8% of HPV-negative patients. Therefore, no difference was detected in the frequency of viable carcinoma between HPV-positive and HPV-negative patients undergoing planned neck dissection after CRT (p=0.969, chi-square).

**Discussion**

Planned neck dissection following the conclusion of chemoradiation therapy (CRT) has traditionally been the standard of care for all patients with advanced (N2 or greater) nodal disease. Neck dissections were previously recommended even for patients with no evidence of residual neck disease on physical examination or radiologic imaging [2]. The evidence in support of this practice was the high incidence of residual occult carcinoma found on post-treatment neck dissection specimens, as well as high failure rates of surgical salvage in the event of regional recurrence [3,17].

However, controversies over the management of the post-CRT neck now exist, due in part to advances in imaging and treatment [6,7]. Concerns have been raised over the overtreatment of patients with apparent complete clinical response to CRT. Although it has previously been suggested that planned neck dissection decreased regional recurrence rates and improved overall survival [13], more recent data has called the necessity of planned neck dissections into question. Isolated neck recurrences occur at very low rates following complete response to CRT, and some argue that planned neck dissection does not improve regional failure rates or overall survival [6,7,18].

Given the controversy over the need for planned neck dissections, there is increasing desire to identify those patients who would most benefit from post-CRT neck dissection. Physical examination alone has proven inadequate, particularly in the setting of radiation-induced fibrosis [3]. Instead, combined 18F-FDG PET/CT imaging has become an increasingly popular tool for restaging cervical nodal disease in HNSCC. Many studies have shown, however, that PET/CT imaging still has limitations in the management of advanced neck disease after CRT. Studies of combined modality PET/CT imaging have yielded
varying sensitivities and specificities, in the ranges of 40 to 100% and 25 to 74%, respectively [12,13]. The overall sensitivity of 42.3% observed in this study is lower than most reported studies, which may be due to differences in methodology. Conversely, the specificity of 90.4% in this study is fairly high, which again may be due to differences in study methodology. Taken as a whole, this study supports the conclusion that PET/CT imaging alone is not sufficiently sensitive or specific enough to predict the presence of residual carcinoma in the neck.

As demonstrated in a smaller subset of our study population, one advantage of PET/CT imaging appears to be its high negative predictive value (NPV), of 97% or greater, particularly at 12 weeks or later after the conclusion of CRT [7,14]. Some now argue that neck dissection is not necessary in the case of a negative PET/CT scan obtained at 12 weeks or later after CRT and instead advocate observation with serial imaging as an alternative management strategy [7,14,17]. It has been shown that the predictive value of PET/CT varies with timing after CRT. Just after irradiation, inflammation of the soft tissues of the radiation bed may result in falsely elevated FDG uptake, resulting in a high false-positive rate [19,20]. Conversely, early PET/CT imaging may also falsely underestimate the presence of residual disease, as tumor burden may fall below the detection threshold of PET imaging [14]. Greven et al. found that PET imaging at one month after radiation therapy did not accurately predict residual disease, whereas imaging obtained at four months after radiation was more predictive of disease [21]. Delaying the acquisition of PET/CT imaging may allow acute inflammation to decrease and residual tumor cells to multiply to reach a size that is detectable by PET/CT [13]. In this study, we found that the sensitivity of PET/CT decreased as the time interval between CRT and imaging increased. Specificity, positive predictive value (PPV), and NPV all increased with longer time intervals after CRT, although our analysis was limited by the size of our cohort. Increased specificity and NPV over time are consistent with published reports [20,21], although the NPV of 81.5% in our overall cohort was lower than typically reported (as previously noted, 97% or greater). This may be due to the comparatively early acquisition of imaging in our cohort, with a mean interval of 8.9 weeks between completion of CRT and PET/CT imaging; if the interval were increased, this could conceivably increase both specificity and NPV of the overall cohort. Indeed, the NPV of PET/CT scans obtained at 12 weeks or later were 88.2% compared to 79.7% for PET/CT scans to 88.2% in PET/CT scans obtained earlier than 12 weeks.

Several factors should be considered in determining the optimal timing of planned neck dissections. A “surgical window” of 4 to 12 weeks after the conclusion of CRT has traditionally been recommended [2]. Delaying surgery until at least four weeks after CRT allows for resolution of acute post-radiation injuries, such as radiation dermatitis, mucositis, and pharyngeal and laryngeal edema [15]. Furthermore, the cytotoxic effects of radiation continue for 2 to 3 months after the end of irradiation, so further intervention should ideally be delayed for 12 weeks after CRT to allow for full radiation effect on tumor cells [3]. However, delaying neck dissection for too long after the completion of CRT may also be deleterious. Rates of surgical complications may increase after 12 weeks following CRT, due to chronic radiation changes including radiation fibrosis and vascular damage, although this concept has been challenged by evidence that surgical complication rates and prognosis do not worsen with surgery delayed beyond 12 weeks [15].

Our study demonstrated an incidence of residual viable carcinoma within post-CRT neck dissection specimens of 31.4% for the overall cohort, consistent with previous reports of rates of 20-40% [2,4,5]. However, rates of isolated neck recurrences following complete clinical response to CRT are much lower [17,22]. The presence of viable residual disease on pathological examination, therefore, may not truly be predictive. Multiple studies have nevertheless demonstrated associations between the presence of viable carcinoma and diminished overall recurrence-free, and disease-specific survival outcomes [23-25].

We found that pathology findings, including no or non-viable metastatic disease or viable residual carcinoma, do not differ significantly with the time interval between CRT and neck dissection. This is consistent with Ganly et al. who found no correlation between the timing of neck dissection and rates of viable tumor in a smaller cohort of patients [23]. Our findings suggest that the presumed role of continued radiation effects on tumor cells is not clinically significant.

We also found no difference in the rates of viable residual carcinoma within neck dissection specimens of HPV-positive and HPV-negative patients, which has not previously been reported. HPV-positive patients have a more favorable prognosis, with better overall and recurrence-free survival outcomes, than HPV-negative patients [8,11]. In addition, HPV-positive disease is more responsive to chemoradiation therapy [10]. Despite these differences in clinical behavior, this study demonstrates that these differences are not evident at the histopathological level in post-CRT neck dissection specimens.

Our results may call into question the adequacy of current histopathological analysis of residual tumor cells. Viable cells may be identified by their morphology on hematoxylin-eosin staining or by Ki-67 immunostaining [17]. With hematoxylin-eosin staining, viable cells may be identified as intact phenotypically malignant cells within fibrotic or necrotic treated lymph nodes [25]. Nonviable tumor may be identified by the absence of Ki-67 staining or by the presence of necrotic cellular remnants or cells with signs of irreversible cell injury within granulomatous, fibrotic, or necrotic lymph nodes [17,23,25]. However, the distinction between dying and viable cells may be difficult to make. Furthermore, the detection of viable cells, whether by morphologic features or by Ki-67 staining, does not reliably indicate whether those cells are capable of growth and division [17]. Therefore, there are several limitations to the histopathological assessment of tumor viability on neck dissection specimens.

The current study is limited by its retrospective nature. In addition, there may be a length time bias, as the median length of follow-up for the early and late neck dissection groups differed substantially. There was a general trend towards later neck dissection over the study period, which resulted in shorter overall length of follow-up for this group. If follow-up time had been longer, there may have been additional clinical events, such as local or regional recurrence, to allow for more rigorous statistical analysis. It therefore remains to be seen whether early versus late neck dissection will have significant effects on longer-term clinical outcomes.

In conclusion, the current study has demonstrated that the efficacy of PET/CT imaging is limited by its low predictive value. However, specificity and NPV increase with time from completion of CRT, so delaying PET/CT imaging after CRT is recommended. However, pathology results do not differ in early versus late neck dissection, suggesting that tumor lysis as a result of radiation treatment does not continue beyond 12 weeks.

References


