RESULTS OF A PROSPECTIVE STUDY OF POSITRON EMISSION TOMOGRAPHY–DIRECTED MANAGEMENT OF RESIDUAL NODAL ABNORMALITIES IN NODE-POSITIVE HEAD AND NECK CANCER AFTER DEFINITIVE RADIOThERAPY WITH OR WITHOUT SYSTEMIC THERAPY

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Abstract: Background: The purpose of this study was to present our prospectively evaluated positron emission tomography (PET)-directed policy for managing the neck in node-positive head and neck squamous cell carcinoma (N+HNSCC) after definitive radiotherapy (RT) with or without concurrent systemic therapy.

Methods: One hundred twelve consecutive patients who achieved a complete response at the primary site underwent a 12-week posttherapy nodal response assessment with PET and diagnostic CT. Patients with an equivocal PET underwent a repeat PET 4 to 6 weeks later. Patients with residual CT nodal abnormalities deemed PET-negative were uniformly observed regardless of residual nodal size.

Results: Median follow-up from commencement of RT was 28 months (range, 13–64 months). Residual CT nodal abnormalities were present in 50 patients (45%): 41 PET-negative and 9 PET-positive. All PET-negative residual CT nodal abnormalities were observed without subsequent isolated nodal failure.

Conclusion: PET-directed management of the neck after definitive RT in node-positive HNSCC appropriately spares neck dissections in patients with PET-negative residual CT nodal abnormalities. © 2011 Wiley Periodicals, Inc. Head Neck 00:000–000, 2011

Keywords: head and neck; squamous cell carcinoma; PET; radiotherapy; chemotherapy

The management of residual structural nodal abnormalities after radiotherapy (RT) with or without chemotherapy (chemo+RT) in node-positive mucosal head and neck squamous cell carcinoma (N+ HNSCC) differs among institutions. Previously published articles report up to 20% to 40% of posttherapy residual nodal abnormalities contain pathological residual disease, arguing for a continued policy of planned neck dissections in this group.1,2

Ultrasound-guided fine-needle aspiration cytology of residual nodal abnormalities after chemo+RT has a negative predictive value (NPV) in the order of 80% or less and cannot be relied upon in this setting.3

More recently, functional imaging with [18F] fluoro-deoxyglucose-positron emission tomography (FDG-PET) has become an increasingly valuable tool for staging and response assessment. A growing body of retrospective evidence has demonstrated that an 8- to 12-week re-staging PET after chemo+RT has a high NPV (≥95%) for nodal response assessment4–6; however, some centers still advocate a neck dissection in the presence of residual nodal abnormalities on CT, citing the lack of prospective evidence and concerns over missing the window of opportunity for cure.

We report on a prospective study designed to test a protocol of uniformly omitting a neck dissection in all patients with PET-negative lymph nodes after definitive RT with or without systemic therapy, regardless of the presence or size of residual nodal abnormalities on contrast-enhanced CT. The primary purpose of this analysis was to determine the
proportion of patients that were appropriately spared a neck dissection as defined by the absence of subsequent isolated nodal failure.

**PATIENTS AND METHODS**

**Patient Eligibility.** All patients presenting to our institution with N+ HNSCC suitable for organ preservation with definitive RT, with or without systemic therapy, were screened for enrollment onto this institutional ethics board–approved study. All patients required biopsy proven cervical nodal metastatic squamous cell carcinoma (SCC) and no evidence of distant metastases. Patients with an unknown primary carcinoma presumed to have arisen from a mucosal head and neck site were eligible for participation.

Only patients who ultimately achieved a complete response at the primary site (see definition below) at 12 weeks post-RT and treated according to the PET policy were eligible. Disease in all patients was staged according to the American Joint Commission on Cancer version 6. Tumor p16 status was determined on all available oropharyngeal primary biopsies and nodal disease in unknown primary cases via immunohistochemical (IHC) staining. The p16 positivity was defined as strong and diffuse nuclear and cytoplasmic staining in ≥70% of tumor cells.

**Primary Site Response.** A primary site complete response was determined by the multidisciplinary team at 12 weeks post-RT based on clinical examination, re-staging CT with or without MRI and PET findings. Patients were monitored weekly during treatment and 6 weeks post-RT to ensure disease was not progressing despite receiving therapy. In cases in which there was an equivocal clinical or radiological residual primary abnormality at 12 weeks post-RT, an examination under anesthesia was performed, with or without directed biopsies.

**Radiotherapy and Systemic Treatment.** All patients were treated with 3-dimensional (3D) conformal RT according to the International Commission on Radiation Units 50 and 62 guidelines. Patients were treated with either concomitant boost RT or conventionally fractionated RT with or without systemic therapy. Patients with lower-volume disease (eg, T classification 0–2, N classification N1) were generally considered for single-modality RT.

Elective sites were treated to 50 Gy in 2 Gy/day over 5 weeks. Known sites of disease received either 2 Gy/fraction to a total of 70 Gy over 7 weeks or a concomitant boost schedule to a total of 66 Gy over 5 weeks using a morning dose of 2 Gy/day for 5 weeks and an afternoon boost dose (minimum of 6 hours apart) 1.6 Gy/day in weeks 4 and 5.

Planned concurrent systemic therapy consisted of either high-dose cisplatin (100 mg/m²) given in weeks 1, 4, and 7, or fractionated weekly cisplatin (40 mg/m²). Patients with contraindications to cisplatin, such as renal/hearing impairment or pre-existing neuropathy, received either carboplatin/5-fluorouracil or cetuximab. Selection of systemic therapy was at the discretion of the treating physician.

**Diagnostic CT Imaging Protocol and Definitions.** A diagnostic contrast-enhanced CT of the head, neck, and chest was performed pretherapy and contemporaneously with the 12-week re-staging [¹⁸F] FDG-PET. A staging and re-staging MRI was optional, usually performed to assist in evaluating primary disease extent and/or treatment response. A residual nodal abnormality on structural imaging was defined as a node ≥10 mm and/or any node demonstrating suspicious radiological features such as necrosis or contrast enhancement. The diagnostic CT scans were assessed by an independent qualified radiologist.

**[¹⁸F] Fluorodeoxyglucose Positron Emission Tomography-CT Imaging Protocol and Definitions.** Preparation for imaging was in accordance with the guidelines of the Society of Nuclear Medicine and European Association of Nuclear Medicine.

Studies were acquired on a Philips Gemini GXL PET/CT system operating in 3D mode. Nine bed positions, each of 2-minute duration, were typically acquired from skull vertex to mid-thigh. A low-dose CT for attenuation correction and lesion localization (120 kVp; 30–50 mAs) was acquired of the same region and reconstructed to 3-mm slices. Emission images were reconstructed using the manufacturer’s line-of-response algorithm.

Two qualified nuclear medicine physicians independently reviewed all the datasets on dedicated MedView display systems (MedImage, Ann Arbor, MI). Acquisition parameters of pretreatment and posttreatment studies for each patient were kept as similar as possible to facilitate study comparison.

FDG uptake was considered positive if it was focal, corresponded to a structural abnormality, and was of greater intensity than background liver activity (based on visual assessment). Where focal FDG avidity had dropped to below background liver activity, but was of greater intensity than adjacent normal-tissue activity, this was generally considered equivocal. No residual FDG avidity above background or diffuse uptake in the absence of a corresponding suspicious structural abnormality was considered negative. Standard uptake values were not routinely calculated, given the scarcity of evidence that such quantification improves diagnostic accuracy.

**Positron Emission Tomography-Directed Neck Policy.** The PET-directed neck policy consisted of performing a PET within 3 weeks of commencing RT and around 12 weeks posttherapy. A diagnostic CT
was performed contemporaneously. If the PET demonstrated no nodal FDG avidity patients remained on the observation policy. If the PET demonstrated nodal FDG avidity, a neck dissection was performed. If there was equivocal nodal FDG avidity, then a repeat PET was performed 4 to 6 weeks later, and if still equivocal, it was considered positive and a neck dissection was performed.

Figure 1 summarizes the PET-directed neck policy.

Follow-Up. Patients were subsequently assessed every 3 months for the first year, then every 4 months for the next 2 years, and every 6 months for another 2 years. They also underwent further re-imaging only if clinically indicated. Routine fine-needle aspiration cytology of the residual nodal abnormality in patients undergoing observation or requiring a neck dissection was not performed as it was deemed too unreliable post-RT.

Analysis and Statistical Considerations. This was a prospective single-institution observational study designed to accrue a minimum of 100 patients with at least 12 months of follow-up from the start of RT. The primary objective of this analysis was to assess the proportion of patients with PET-negative residual CT nodal abnormalities who were appropriately spared a neck dissection as defined by the absence of subsequent isolated nodal failure. Isolated nodal failure was defined as nodal recurrence in the absence of any other type of failure, primary and/or distant.

Composite nodal failure was defined as nodal failure that occurred in the presence of another failure site(s).

Survival analysis data was calculated using Stata11 (Statcorp, Dallas, TX) from the date of commencement of RT until failure, death, or the date of last follow-up for isolated nodal failure-free survival (FFS), locoregional (primary site and nodal) FFS, distant metastasis FFS, and overall survival. Life tables were used to describe 2-year survival data. Where there were no failures, binomial 2-sided 95% exact confidence intervals (CIs) were reported. Positive predictive values (PPVs) and NPVs for PET and ce-CT were calculated using 2 x 2 tables for both the entire cohort and the p16-positive subgroup, with corresponding 95% CIs using Fisher exact test. Outcomes based on N classification were also reported.

RESULTS

Patient and Tumor Characteristics. Between January 2005 and April 2009, 121 consecutive patients presenting with N+ HNSCC suitable for organ preservation treatment were screened for enrollment into the study. Four patients (all p16 negative) did not achieve a complete response at the primary site, and 5 patients did not undergo a restaging PET leaving 112 patients (93%) eligible for analysis.

Patient demographics, tumor characteristics, and TNM staging are summarized in Tables 1 and 2, respectively. The median age was 55 years (range, 25–88 years) with the majority being men (81%). The predominant primary site and T and N classification were oropharynx 74%, T2 36%, and N2 75% (N2b 43 of 84).

Fifty-nine of the 76 oropharyngeal tumors evaluable for IHC analysis were positive for p16, comprising 53% of the total study population. An additional patient with an unknown primary had nodal material available for IHC analysis and was found to be p16 negative. Pretreatment median size of the largest node was 30 mm (range, 11–90 mm) and the median time for the first re-staging PET and diagnostic CT was 12 weeks (range, 10–14 weeks). A total of 11 patients had a 12-week equivocal PET, requiring a repeat scan 4 to 6 weeks later (Figure 2).

Treatment Received. One hundred seven patients received conventionally fractionated RT to 70 Gy, and 5 patients received concomitant boost RT. Median RT dose was 70 Gy (range, 66–70 Gy). One hundred two patients received concurrent systemic therapy in the form of cisplatin (n = 86), cetuximab (n = 10), and carboplatin/5FU (n = 6).

FIGURE 1. Positron emission tomography (PET)-directed policy for managing the neck. *A further equivocal PET on repeat scanning was treated as PET positive. †Regardless of structural findings on CT/MRI. Abbreviations: CT, computerised tomography; PET, positron emission tomography; MRI, magnetic emission resonance imaging.

Pre-treatment Assessment
Clinical Examination
Diagnostic CT +/- MRI
PET-CT
(<3 weeks prior to start of RT)

Definitive Radiation Therapy
+/- systemic therapy

6 week post-therapy clinical assessment
Primary tumor progression
Ineligible/Consider Surgery
Primary tumor regressing or stable
Persistent primary disease

12 week re-staging CT(+/-MRI) + PET/CT

Complete response at primary site

PET neck negative
PET neck equivocal† Repeat at 4-6 weeks
PET neck positive
Observe†

Neck dissection
Follow-Up. At the close-out date for analysis, the median follow-up time for all eligible patients from the commencement of RT was 28 months (range, 13–64 months). Fifteen patients (13%) had died, 8 with disease and 7 from other causes.

Nodal Response Assessment and Outcomes. There were a total of 2 isolated nodal failures, both occurring in patients who had undergone a neck dissection for PET-positive, residual CT nodal abnormalities (see below). Figure 2 summarizes isolated nodal failures by CT and PET nodal response criteria.

Fifty of 112 patients (45%) had a posttherapy residual nodal abnormality on CT criteria. Of those, 41 were PET negative with a median residual nodal size of 15 mm (range, 10–40 mm) and 9 patients were PET positive with a median residual nodal size of 14.5 mm (range, 10–25 mm).

All 41 patients with PET-negative residual CT nodal abnormalities were observed with no nodal failures (95% CI, 0% to 9%).

Of the 9 PET-positive patients, 1 had developed concurrent pulmonary metastases with persistent nodal disease (composite nodal failure) and was treated with palliative chemotherapy (p16-positive T3N3 oropharynx), leaving 8 patients who underwent a neck dissection. Neck dissection type included radical (n = 3), modified levels I to IV (n = 2), levels II to IV (n = 2), and levels II to V (n = 1) without any major surgical complications including wound healing. Six of 8 patients had pathological evidence of residual viable tumors with 2 patients subsequently developing an isolated nodal failure within the previous RT and surgical fields. This included a T0N1, p16-negative unknown primary and a T3N2c p16-negative oropharynx. Two patients had no viable tumor in the specimen and remained disease free.

Sixty-two of 112 patients (55%) achieved a complete nodal response on CT and PET and were observed with no subsequent isolated nodal failures (95% CI, 0% to 6%). Two composite nodal failures occurred in this group; 1 smoker with a p16-negative, T2N1 oropharyngeal SCC developed concurrent primary and nodal failure, and 1 smoker with a p16-positive, T3N2c oropharyngeal SCC developed concurrent primary, nodal, and distant failure.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median (range), y 55 (25–88)</td>
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<tr>
<td>Sex</td>
<td>Male 91 (81%)</td>
</tr>
<tr>
<td>Female 21 (19%)</td>
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</tr>
<tr>
<td>Primary site</td>
<td>Oropharynx 83 (74%)</td>
</tr>
<tr>
<td>p16-positive 59</td>
<td></td>
</tr>
<tr>
<td>p16-negative 17</td>
<td></td>
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<tr>
<td>p16 unknown 7</td>
<td></td>
</tr>
<tr>
<td>Unknown primary 5 (4%)</td>
<td></td>
</tr>
<tr>
<td>p16-negative 1</td>
<td></td>
</tr>
<tr>
<td>p16 unknown 4</td>
<td></td>
</tr>
<tr>
<td>Nasopharynx 10 (9%)</td>
<td></td>
</tr>
<tr>
<td>Larynx 7 (6%)</td>
<td></td>
</tr>
<tr>
<td>Hypopharynx 7 (6%)</td>
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<tr>
<td>Differentiation</td>
<td>Well differentiated 2 (2%)</td>
</tr>
<tr>
<td>Moderately differentiated 46 (41%)</td>
<td></td>
</tr>
<tr>
<td>Poorly or undifferentiated 49 (44%)</td>
<td></td>
</tr>
<tr>
<td>Unknown 15 (13%)</td>
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</tr>
<tr>
<td>Smoking status</td>
<td>Current smoker 41 (37%)</td>
</tr>
<tr>
<td>Ex-smoker (ceased &lt;6 mo) 42 (38%)</td>
<td></td>
</tr>
<tr>
<td>Never smoked 28 (25%)</td>
<td></td>
</tr>
<tr>
<td>Unknown 1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>Median (range), mo 28 (13–64)</td>
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</tbody>
</table>

<table>
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<tr>
<th>T classification</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
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<td>3</td>
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<td>5</td>
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<td>32</td>
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<tr>
<td>T4</td>
<td>2</td>
<td>10</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>84</td>
<td>14</td>
<td>112</td>
</tr>
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</table>

Abbreviation: AJCC, American Joint Committee on Cancer.

FIGURE 2. Summary of isolated nodal failures by positron emission tomography (PET) and CT nodal response assessment. *Equivocal PETs were repeated 4–6 weeks later and then classified as either positive or negative. *Developed pulmonary metastases by the 12 week restaging scans. ^Clinical, radiological, and biopsy by 12 weeks. Abbreviations: PET, positron emission tomography; CT, computed tomography; -, negative; +, positive.
Excluding the 2 isolated and 3 composite nodal failures, there were an additional 11 failures. Table 3 summarizes failures based on CT and PET response assessment.

The 2-year isolated nodal FFS for the entire cohort was 98% (95% CI, 91% to 99%), locoregional FFS 93% (95% CI, 85% to 96%), distant metastasis FFS 87% (95% CI, 78% to 92%), and overall survival 88% (95% CI, 78% to 93%).

The NPVs for PET and CT nodal response assessment were 98.1% (95% CI, 93.2% to 99.8%) and 96.8% (95% CI, 88.8% to 99.6%), respectively. False-positive findings occurred in 1.8% of cases for PET and 38% for CT with corresponding PPVs of 77.8% (95% CI, 40% to 97.2%) and 14% (95% CI, 5.8% to 26.7%), respectively.

Outcomes based on N classification and p16 status are described in Figures 3 and 4, respectively. For the p16-positive group, the NPVs and PPVs were 98.2% (95% CI, 90.4% to 100%) and 66.7% (95% CI, 9.4% to 99.2%), respectively, for PET compared to 96.7% (95% CI, 82.8% to 99.9%) and 6.9% (95% CI, 0.8% to 22.8%), respectively, for CT.

An illustration of a case with a PET-negative CT residual nodal abnormality that was observed on the study is shown in Figure 5.

**DISCUSSION**

This study prospectively evaluated the utility of a policy of uniformly omitting neck dissections in patients with N⁺ HNSCC with PET-negative CT residual nodal abnormalities, regardless of size. It is important to highlight that this study was not designed to test the efficacy of chemo+RT in N⁺ HNSCC, nor was the primary purpose to assess the predictive value of the 12-week re-staging PET in isolation, but rather the entire policy. The uniform application of our PET-directed policy resulted in a low rate of neck dissections in our cohort (7%), without compromising the very low isolated nodal failure rates seen in modern series.

Importantly, 41 of the 50 patients with a residual nodal abnormality were spared a neck dissection on the basis of a negative posttherapy PET, with no subsequent nodal failures in this group. This finding confirms the safety of this policy.

Although the NPV of the post-RT diagnostic contrast-enhanced CT in our study was equally high, the neck dissection rate for our cohort would have increased from 7% with the PET-directed policy to

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**Table 3. Summary of disease failure sites based on nodal response assessments.**

<table>
<thead>
<tr>
<th>Nodal response assessment</th>
<th>Site of first failure</th>
<th>CT–/PET– (n=62)</th>
<th>CT+/PET– (n=41)</th>
<th>CT+/PET+ (n=9)</th>
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<tr>
<td>Isolated nodal</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Isolated primary</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Primary and nodal</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Primary, nodal, and distant</td>
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<td>1</td>
<td>1</td>
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</tr>
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<td>Nodal and distant</td>
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</tr>
<tr>
<td>Primary and distant</td>
<td>5</td>
<td>4</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Isolated distant</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: PET, positron emission tomography.

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**FIGURE 3.** Response assessment and nodal outcomes by initial nodal stage. Abbreviations: ND, neck dissection; CT, computerized tomography; PET, positron emission tomography; –, negative; +, positive.
45% if CT criteria alone were used for response assessment, and up to 88% if a traditional planned neck dissection policy had been adopted for N classification 2 to 3 disease. This held for the p16-positive group \((n = 59)\) in which PET spared all 26 patients (44%) with a residual nodal abnormality from an unnecessary neck dissection.

Several studies have demonstrated an increase in complication rates, severity of late toxicity, and inferior quality of life when RT is combined with a neck dissection.\(^{10–13}\) This study highlights the potential of PET to substantially reduce the number of unnecessary neck dissections and, therefore, limit the associated additional morbidity and cost to patients and health care systems respectively.

To date, there has been only 1 previously reported study that prospectively assessed the value of PET-CT for response assessment in locally advanced

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**FIGURE 4.** Response assessment and nodal outcomes by p16 status. Abbreviations: ND, neck dissection; CT, computerized tomography; PET, positron emission tomography; --, negative; +, positive.

**FIGURE 5.** (a) T1N2bM0 right oropharyngeal squamous cell carcinoma (SCC) on pretherapy CT and positron emission tomography (PET); (b) PET-negative CT residual nodal abnormality 12 weeks posttherapy; (c) remains disease free beyond 12 months after neck observation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
This study found no significant additional benefit for PET-CT, as performed 8 weeks post-RT, over diagnostic contrast-enhanced CT alone for nodal response assessment in unselected patients in terms of NPV (96% and 98%, respectively) and PPV (27% and 23%), although a subset analysis did suggest that the PPV of PET-CT could be improved if limited to “high-risk” patients such as those with HPV-negative disease or smokers. A number of differences between the 2 studies, however, should be highlighted.

Our study used a selected population in which the utility of PET-based nodal response assessment in preventing unnecessary neck dissections could be clearly defined. We limited the analysis to those patients achieving a complete response at the primary site, as a planned neck dissection would not have saved the excluded patients from surgical intervention or failure. We then specifically examined the utility of a PET-directed policy in the group of most interest (ie, those harboring residual nodal abnormalities on CT).

The non-uniform, “discretionary” use of neck dissections in previous reports and the use of pathological surrogate endpoints have made it difficult to truly evaluate the clinical worth of neck dissections in the residual nodal group. The presence of residual “viable” foci of disease on pathological assessment after a neck dissection is not conclusive evidence that a patient was destined for clinical failure in the absence of a neck dissection. Strasser et al15 found that only 3 of 11 post-RT neck dissection specimens harboring residual cancer cells had proliferative capacity as determined by positivity for Ki-67. Among other factors, it is likely that uncertain clonogenic capacity of these residual “viable” cells in part explains the lower event rates seen in studies reporting solely clinical endpoints after observation compared to those incorporating pathological endpoints.1,16–18 Furthermore, a number of those patients would be destined to develop a composite failure (eg, synchronous distant metastases), in which case, they would not have derived any great benefit from a planned neck dissection. The clinical endpoint of isolated nodal failure in a uniformly observed cohort of patients forms the most appropriate basis from which to evaluate the need for neck dissections in this cohort.

In this setting, we were able to show that PET provided additional valuable information over contrast-enhanced CT alone in an appropriately selected population, allowing the avoidance of unnecessary neck dissections. PET seemed to perform similarly well when broken down by p16 status; however, the limited numbers precludes any definitive conclusions.

The timing of the restaging PET is also important. Based upon previous reports, we chose a period of 12 weeks post-RT for the initial scan to allow more time for the resolution of acute inflammatory changes and minimize the false-positive rate.4,5,15,20 This still allows the completion of a necessary neck dissection before the onset of late radiation fibrosis or significant tumor progression.

The high prevalence of p16-positive oropharyngeal tumors undoubtedly contributed to the favorable locoregional control and overall survival rates seen in our cohort. The markedly improved prognosis of patients with HPV-associated oropharyngeal SCC serves to highlight the importance of developing risk-adapted and response-based management algorithms to reduce the morbidity and burden of survivorship after treatment.

In conclusion, this prospective study demonstrates that PET-directed management of the neck after definitive chemoradiotherapy serves to highlight the importance of developing risk-adapted and response-based management algorithms to reduce the morbidity and burden of survivorship after treatment.

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REFERENCES