Objectives/Hypothesis: To review our results with positron emission tomography and computed tomography fusion imaging (PET-CT) surveillance of the postchemoradiotherapy neck in patients with advanced head and neck squamous cell carcinoma.

Study Design: Retrospective.

Methods: Four hundred twenty-eight patients with advanced head and neck squamous cell carcinoma were treated with nonsurgical therapy from September 2002 to March 2007 and followed with post-treatment PET-CT surveillance of the neck. Fifty-two patients meeting inclusion criteria were analyzed. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of PET-CT were determined.

Results: Ten patients had a positive post-treatment PET-CT for residual neck disease, and 42 patients had negative scans. The NPV and PPV were 100% and 40%, respectively. The sensitivity, specificity, and accuracy were 100%, 87.5%, and 88%, respectively.

Conclusions: Planned neck dissection can be deferred with a negative post-treatment PET-CT. Assuming a complete response at the primary site and a negative PET-CT scan, there may be a role for serial PET-CT surveillance in patients with residual palpable cervical lymphadenopathy.

Key Words: PET-CT, nodal metastasis, chemoradiotherapy, surveillance, community setting.

INTRODUCTION

In recent years positron emission tomography and computed tomography fusion imaging (PET-CT) has been used for detection and surveillance of the postchemoradiotherapy neck. Its use in pretreatment evaluation and staging of patients with squamous cell carcinoma of the head and neck has been validated by multiple studies.\(^1\)\(^{-}\)\(^3\) In addition, PET-CT has been shown to be more accurate than PET or CT alone in the evaluation of head and neck cancer.\(^4\) However, the use of PET-CT in post-treatment evaluation remains controversial. Multiple studies have concluded that a planned neck dissection may be deferred with negative PET-CT imaging,\(^5\)\(^{-}\)\(^8\) whereas reports from other studies refute this hypothesis.\(^9\)\(^,\)\(^10\)

The objectives of this study were to review our results with PET-CT imaging surveillance of the postchemoradiotherapy neck in patients with advanced squamous cell carcinoma of the head and neck and compare them to current literature.

MATERIALS AND METHODS

Four hundred twenty-eight patients treated at Mary Bird Perkins Cancer Center (MBPCC) between September 2002 and March 2007, with a biopsy-proven squamous cell carcinoma of the oropharynx, larynx, hypopharynx, or unknown primary of the head and neck with proven metastatic lymphadenopathy were identified by searching the MBPCC patient database with appropriate ICD-9 codes. All patients received primary nonsurgical therapy. The inclusion criteria are listed in Table I. Fifty-two patients who met these criteria were included in the analysis. Three hundred seventy-six patients did not fulfill the inclusion criteria per reasons outlined in Table II.

In all cases, PET-CT surveillance scans were performed within 7 months of primary treatment completion. Further surveillance with serial PET-CT scanning was based on individual physician preference. The images were evaluated by a radiologist, and a dictated report was obtained for all PET-CT scans. These PET-CT scans were classified as positive if the interpreting radiologist stated that the findings were worrisome for residual malignant disease in the neck. This included those patients with residual low fluorodeoxyglucose (FDG)-avidity in the neck, though diminished in comparison to the pretreatment scan. Scans were considered negative if the interpreting
The radiologist stated that there was no evidence of residual disease in the neck. In all cases, the radiologist interpreted the scans as positive or negative based not on standard uptake values, but by the presence or absence of FDG-avidity, comparison to pretreatment scans, and clinical correlation. All scans were PET-CT fusion studies, and most were obtained on a single scanner at MBPCC. Patients were instructed to fast for at least four hours prior to the scan, and were required to have a blood glucose level less than 200 mg/dL to proceed with the scan. Patients were injected with 9 to 16 mCi of 18-fluorodeoxyglucose (FDG) one hour prior to the scan, and were given diazepam (10 mg) and glycopyrrolate (0.1 mg) intravenously, as necessary. Imaging was obtained from the skull base through the midthigh. All patients were then seen in follow-up approximately 1 month after their completion of therapy. The average length of time from the completion of treatment to first follow-up visit was 30.7 days (range, 1–111 days). Patients were then followed for a minimum of 9 months, or until the patient required further surgical treatment, and the average follow-up duration for all patients included in the analysis was 78.1 weeks (range, 15–194 weeks). A statistical analysis was performed and the sensitivity, specificity, positive predictive value, negative predictive value (NPV), and accuracy of PET-CT imaging for the study cohort are reported.

RESULTS
Demographic Data
The mean age of the study cohort was 58.9 years (range, 41–82 years) with a male to female ratio of 43:9. The most common primary tumor site was the oropharynx (56%; 29/52) followed by the larynx (33%; 17/52) (see Table III). Fourteen patients (27%) were N1, eight (15%) were N2a, 15 (29%) were N2b, 13 (25%) were N2c, and three (6%) were N3.

Treatment Details
Fifty-one patients (98%) received intensity-modulated radiation therapy, and one patient received three-dimensional conformal radiotherapy. The average dose to the primary tumor and gross disease in the neck was 69.7 Gy (range, 66–72 Gy). All radiation treatments were delivered at MBPCC. Forty-eight patients (92%) received concurrent chemotherapy, and five patients (9%) additionally received neoadjuvant chemotherapy. Four patients (8%) did not receive any chemotherapy treatment.

Imaging Details
Fifty-one patients (98%) underwent pretreatment PET-CT imaging. The average length of time from the PET-CT to start of treatment was 2.5 weeks (range, 0.7–12 weeks). Post-treatment PET-CT was performed on all patients within 7 months of completion of treatment. The median time from completion of treatment to PET-CT was 11.8 weeks (range, 3.7–29.4 weeks). Patients underwent an average of 2.4 PET-CT scans (range, 1–6 scans).

Patients With Positive Post-Treatment PET-CT
Ten patients (19.2%) had a post-treatment PET-CT positive in the neck for possible residual malignant disease. These patients had their post-treatment PET-CT an average of 11.8 weeks after completion of therapy (range, 4.1–25.4 weeks). Three of these patients (30%) underwent PET-CT imaging within 8 weeks of completion of treatment. Among these 10 patients, initial nodal staging was N1 in 10% (1/10), N2A in 10% (1/10), N2B in 40% (4/10), N2C in 30% (3/10), and N3 in 10% (1/10).

Three patients with positive post-treatment PET-CT then underwent neck dissections an average of 20.8 weeks after completion of therapy (range, 13.1–29 weeks). Two patients demonstrated residual malignant disease in the neck dissection specimens, both of which were partial.
responders in the neck. The third patient had a complete response in the neck with no tumor in the neck dissection specimen. The remaining seven patients (70%) with positive PET-CT scans did not undergo neck dissections. Of these, one patient had a fine needle aspiration biopsy, which confirmed neck disease 14.8 weeks following completion of treatment, but did not undergo surgery due to other comorbidities. In another patient, a positive PET-CT confirmed neck disease, which was seen in conjunction with an obvious residual cancer at the primary site as well as widespread metastatic disease. The remaining five patients with positive post-treatment PET-CT scans who did not have neck dissections were followed closely with serial PET-CT imaging either because they refused further surgical therapy or were unable to undergo surgery due to their poor health status. These five patients had a progressive decrease in the FDG-avidity in the neck in serial scans until the PET-CT scans were eventually read as negative. These patients had an average of 3.4 post-treatment PET-CT scans (range, 2–6 scans). Two of these patients had a palpable lymph node on post-treatment physical examination, performed an average of 33 days after completion of therapy. The average length of time from the completion of therapy until the PET-CT was interpreted as negative was 39.2 weeks (range, 24.8–54 weeks). These patients were followed for an average of 62.7 weeks (range, 36–117 weeks), and none developed recurrences in the neck. At the most recent follow-up, two patients were alive with no evidence of malignant disease, two patients developed distant metastasis, and one patient died of aspiration pneumonia.

Patients With Negative Post-Treatment PET-CT
Forty-two patients (81%) had post-treatment PET-CT imaging that was interpreted as negative for residual disease in the neck. These patients had a post-treatment staging PET-CT an average of 12 weeks after completion of treatment (range, 3.7–29.4 weeks), and 31% (13/42) of these PET-CT scans were performed within 8 weeks of completion of treatment. Of these patients, the initial nodal stage was N1 in 31% (13/42), N2a in 17% (7/42), N2b in 26% (11/42), and N3 in 5%.

Five patients with negative PET-CT scans underwent neck dissections. Of these, two patients had surgery an average of 73 days following completion of therapy for residual palpable lymphadenopathy in spite of a negative PET-CT scan due to clinical suspicion for residual disease. The remaining three patients had neck dissections as a component of further salvage surgery of the primary tumor. Pathologic evaluation of all five neck dissections revealed no evidence of residual neck disease.

The remaining 37 patients with negative PET-CT scans were followed either by serial PET-CT imaging or by clinical examination. These patients had an average of 2.4 surveillance PET-CT scans (range, 1–6 scans). Four patients had palpable lymphadenopathy at the time of physical examination following completion of therapy, an average of 24 days following treatment, which subsequently resolved. Three patients had complete resolution by 90 days, and the fourth had documented resolution 1 year following completion of therapy. These patients were followed for an average of 60.4 weeks (range, 27.4–194.1 weeks). Thirty-one patients remained without evidence of local recurrence in either the primary site or the neck or distant metastatic disease. None of the patients with persistently negative PET-CT scans developed isolated neck recurrences in the follow-up period. Four patients had a recurrence at the primary site, and seven patients developed distant metastases.

Statistical Analysis
Of the 10 patients with a positive post-treatment PET-CT scan for possible residual neck disease, four had conclusive evidence of neck disease (Table IV). Therefore, the positive predictive value of a positive post-treatment PET-CT for residual malignant disease in the neck for the entire cohort was 40%. The PPV of PET-CT scans obtained within 8 weeks of completion of treatment was 33% (1/3), and the PPV of PET-CT scans obtained after 8 weeks was 42% (3/7).

None of the 42 patients with a negative post-treatment PET-CT developed recurrent malignant disease in the neck or had evidence of malignant disease on surgical pathology specimens. Therefore, the negative predictive value of a negative post-treatment PET-CT was 100%. The NPV of PET-CT scans obtained both within 8 weeks (13 patients) and after 8 weeks (29 patients) was 100%.

The sensitivity, specificity, and accuracy of post-treatment PET-CT imaging was calculated to be 100%, 87.5%, and 88%, respectively.

| TABLE IV. Patient Characteristics of Positive and Negative Post-Treatment PET-CT. |
|----------------------|----------------------|----------------------|
| Number of patients   | 10                   | 42                   |
| Median follow-up, wk | 49.8                 | 54                   |
| Number of post-treatment PET-CT scans | 2.4                  | 3.4                  |
| Evidence of residual malignant disease | 4                    | 0                    |
| No evidence of residual malignant disease | 6                    | 42                   |
| Neck dissections     | 3                    | 8                    |
| Neck pathology report| 1/3 negative for malignancy | 8/8 negative for malignancy |

PET-CT = positron emission tomography–computed tomography.
DISCUSSION

Traditionally, patients with advanced nodal disease (N2a or greater) who are treated with primary radiation or chemoradiation therapy are advised to undergo a neck dissection approximately 4 to 12 weeks following completion of nonsurgical treatment, regardless of clinical response. This treatment paradigm was based on several studies that found residual neck disease in approximately one third of patients presenting with advanced nodal disease with no consistent correlation to clinical or radiographic evaluation.12–15 Conversely, patients with early nodal disease (N0-1) are known to respond well to radiation therapy, and for this subgroup of patients, neck dissection was recommended only for partial responders or as a component of salvage surgery for resection of residual disease at the primary site.

The development of PET-CT has added to the evaluation of the postchemoradiotherapy neck, though its role remains controversial. Although some authors have argued that a planned neck dissection may be deferred in patients with a negative PET-CT,5–8 retrospective studies have reported varying results.9,10 In the absence of prospective randomized trials, there remains a lack of consensus regarding the ideal integration of PET-CT in the surveillance of head and neck cancer patients treated with primary nonsurgical means.

This study found a negative PET-CT to be 100% predictive of a complete tumor response in the neck, and no patient with a negative PET-CT scan for residual neck disease developed a neck recurrence. A positive PET-CT was less predictive of residual tumor, with a PPV of 40%. Three of our 10 positive PET-CT scans were obtained within 8 weeks of completion of treatment, and this short time interval could be responsible for a high false positive rate owing to residual treatment-related inflammation. Previous studies have shown that the PPV of post-treatment PET-CT scans is affected by timing. Rogers et al. found post-treatment PET-CT scans obtained 4 weeks following completion of treatment to have a NPV of 14% and PPV of 100%,16 whereas Yao et al. reported that scans obtained at 12 weeks had a NPV of 100% and PPV of 43%.17 In our study, the PPV of scans was not significantly affected by timing of PET-CT scans (35% before and 42% after 8 weeks). The NPV was not impacted by the timing of the PET-CT scans.

Of thirty-eight patients with N2a or higher neck disease, 29 patients had a negative post-treatment PET-CT. Five of these patients underwent a neck dissection, all without pathologic evidence of residual malignancy. The remaining 24 patients were followed with serial PET-CT and clinical examinations, and none developed a relapse in the neck. Therefore, a negative PET-CT accurately predicted treatment response, allowing these patients to avoid unnecessary surgery and its inherent risks.

More recently, some have advocated that planned neck dissections are not necessary in those patients with a complete clinical and radiographic response by PET-CT imaging, and that those with residual cervical lymphadenopathy maybe closely observed, provided the PET-CT is negative.18 In this patient population, 11 patients had palpable disease at their first post-treatment visit, an average of 41.4 days following the completion of therapy (Fig. 1), and six of the 11 patients had negative PET-CT imaging. Of these six, four were followed with serial PET-CT scans, and two had neck dissections with negative pathology. None of the four with residual palpable lymphadenopathy who were followed with serial imaging and clinical exam later developed a recurrence in the neck.

This suggests that palpable lymphadenopathy in the presence of a negative PET-CT scan may suggest a biologically sterile tumor, which may resolve with time. Therefore, in patients who have residual palpable lymphadenopathy with a negative PET scan, there may be a role for surveillance with serial PET-CT scans to observe for clinical regression of palpable disease and continued absence of FDG-avidity. However, these

![Fig. 1. Outcomes of patients with palpable lymphadenopathy (LAD) at completion of treatment. DM = distant metastasis.](image-url)
recommendations need to be validated by prospective studies. In addition, the clinician and the radiologist must be vigilant in following these patients closely and surgical salvage should be considered if there is any discrepancy in the clinical and radiological correlation. If close patient follow-up cannot be ensured, we propose that the standard of care be a neck dissection following definitive radiation or chemoradiation treatment in patients with advanced neck disease to prevent the morbidity and mortality associated with uncontrollable neck disease. The latter is also the reason why the low PPV of PET-CT is this situation is acceptable. 

Patients followed clinically with serial PET-CT imaging had an average of 2.6 surveillance scans. PET-CT is an expensive method of tumor surveillance, and this must be taken into consideration. However, if some patients may avoid surgery and its associated potential complications, a portion of this expense will be offset. A comprehensive cost-effective analysis study is needed to clarify this issue.

The limitations of our study are its retrospective nature, small sample size, and heterogeneity of care. The strength of our results could be improved by obtaining longer follow-up and by standardizing the chemotherapy regimens and timing of post-treatment PET-CT scans.

CONCLUSION
PET-CT scanning is an extremely effective tool in predicting the absence of residual carcinoma in the neck. With careful follow-up, close collaboration between the treating physician and the radiologist, and serial imaging, neck dissection may be deferred in patients with persistently negative PET-CT scans. Assuming a complete response at the primary site, there may be a role for serial PET-CT surveillance in patients with residual palpable cervical lymphadenopathy in the setting of a negative PET-CT scan. Future prospective studies are needed to further evaluate this evolving treatment paradigm.

Acknowledgment
We would like to thank all staff at the MBPCC and at Our Lady of the Lake Regional Medical Center for their support of our research. In particular, we would like to acknowledge Dr. Lo, Dr. King, Dr. Johnson, Dr. Bienvenue, Dr. Billings, Carolyn Madere (Medical Records, MBPCC), Beverly Wood (Medical Records, MBPCC), and the Clinical Research Department, MBPCC for their help.

BIBLIOGRAPHY