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ORIGINAL ARTICLE

Post-treatment PET/CT and p16 status for predicting treatment outcomes in locally advanced head and neck cancer after definitive radiation

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Abstract
Purpose To retrospectively review post-treatment (post-tx) FDG-PET/CT scans in patients with advanced head and neck squamous cell carcinoma (HNSCC) and known p16 status, treated with definitive (chemo)radiation (RT).
Methods A total of 108 eligible patients had N2A or greater HNSCC treated with chemoRT from August 1, 2008, to February 28, 2015, with post-tx PET/CT within 6 months after RT. Kaplan–Meier curves, log-rank statistics, and Cox proportional hazards regression were used for statistical analysis.
Results Median follow-up was 2.38 years. Sixty-eight (63.0%) patients had p16+ and 40 (37.0%) had p16− status. Two-year overall survival and recurrence-free survival were 93.4% and 77.8%, respectively. The negative predictive value (NPV) of PET/CT for local recurrence (LR) was 100%. The NPV for regional recurrence (RR) was 96.5% for all patients, 100% for p16+ patients, and 88.5% for p16− patients. The positive predictive value (PPV) of PET/CT for recurrence was 77.3% for all patients, 50.0% for p16+, and 78.6% for p16−. The PPV for LR was 72.7% for all patients, 50.0% for p16+ patients, and 72.7% for p16− patients. The PPV for RR was 50.0% for all patients, 33% for p16+, and 66.6% for p16−. Post-tx PET/CT and p16 status were independent predictors of recurrence-free survival ($p < 0.01$).
Conclusions Post-tx PET/CT predicts treatment outcomes in both p16 + and p16− patients, and does so independently of p16 status. P16− patients with negative PET have a 10% risk of nodal recurrence, and closer follow-up in these patients is warranted.

Keywords Head and neck cancer · Human papillomavirus · Prognostic factors · Neck dissection · PET/CT

Introduction

Locally advanced head and neck squamous cell carcinomas (HNSCC) are treated using one of two approaches: definitive radiation/chemoradiation (RT/chemoRT) therapy or surgical resection followed by post-operative radiation therapy with or without concurrent chemotherapy, depending on the pathology. Neck dissection after definitive chemoRT therapy has remained controversial, with some institutions recommending aggressive prophylactic neck dissection regardless of response, and others taking a watch-and-wait approach based on treatment response.

Traditionally, HNSCC has been associated with heavy tobacco and alcohol use, but the recent emergence of human papillomavirus (HPV)-associated HNSCC has led to a new population of patients with highly curable disease. Using p16 as a surrogate marker for HPV-associated HNSCC, an

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analysis of Radiation Therapy Oncology Group (RTOG) 0129 led to stratification of HNSCC into three groups: highly favorable prognosis, p16+ patients with less than 10 pack-years of smoking; intermediate prognosis; p16+ patients with 10 or more pack-years of smoking; and poorer prognosis, p16− patients [1]. Patients with p16+ status are less likely to suffer locoregional recurrence, and treatment de-escalation is being examined in this group of patients. Due to the exquisite radiosensitivity of p16+ HNSCC, prophylactic neck dissection may have even less benefit in this population.

Post-treatment (post-tx) 18-fluorodeoxyglucose (^{18}FDG) positron emission tomography and computed tomography (PET/CT) has recently been used to assess treatment response and guide neck dissection after chemoRT in HNSCC. If the post-tx PET/CT demonstrates resolution of locoregional disease, patients undergo observation rather than prophylactic neck dissection. Multiple studies [2–9] have examined the utility of post-tx PET/CT in this setting. In a meta-analysis of 51 studies including 2335 patients, the negative predictive value (NPV) of post-tx PET/CT was estimated as 87.5% (85.2–89.5%) for primary site disease and 94.5% (93.1–95.7%) for regional disease [10]. These high NPVs validate the utility of PET/CT as a decision-making tool for neck dissection, but these studies did not incorporate p16 status into their analysis. Since p16+ patients have excellent responses to chemoRT, with low rates of locoregional failure (LRF), the reported NPVs in the literature may overestimate the NPV in the p16− population, and prophylactic neck dissection may still have a particular benefit in this group. We sought to better characterize the role of post-tx PET/CT in neck management while accounting for the differing biology of p16+ and p16− HNSCC, and we report here our outcomes for the predictive values of post-tx PET/CT stratified by p16 status.

Materials and methods

Patient population

Eligible patients were those with HNSCC of N2A or greater and known p16 status who were treated with definitive RT/chemoRT from August 1, 2008, to February 28, 2015, at the Department of Radiation Oncology, University Hospitals, Cleveland Medical Center, with a post-tx PET/CT within 6 months of radiation therapy completion (median: 12.9 weeks, range: 8.1–23.4 weeks). Post-tx PET/CT is routinely obtained at our institution for all HNSCC patients after chemoradiation to assess treatment response, regardless of clinical suspicion of recurrence. Patients with prior head and neck RT or prior oncologic surgery were excluded. This study received institutional review board approval at University Hospitals. Patients were censored for LRF at first failure.

Clinical PET/CT scanning

The examination was performed on a PET/CT system (Philips Healthcare) equipped with a time-of-flight (TOF) scanner. The patients fasted for at least 4 hours, after which they received an injection of ^{18}FDG to a mean activity of 370 MBq (range: 296–518). The CT consisted of 16-slice multi-detector helical CT and was performed before the PET scan. The CT data were used for generation of the CT transmission map, image fusion, and anatomical correlation with the PET findings. Head and neck images were acquired first with the arms down, and then images of the torso with arms up (if tolerated). The scans were acquired during normal breathing. No oral or intravenous contrast was administered. The parameters for the CT were based on institutional guidelines: 120 kVp, pitch of 0.829 and 100 mAs (patient weight < 150 lbs) or 150 mAs (patient weight ≥ 150 lbs), 5-mm slice thickness. The PET scanner has an active transverse field of view (FOV) of 57.6 cm. For PET scanning, the matrix size was 144 x 144, and the voxel size was 4 x 4 x 4 mm^3. The scan time/bed position was as follows: 1.5 min/bed, patient weight 100–150 lbs; 2.0 min/bed, patient weight 151–200 lbs; 2.5 min/bed, patient weight 201–300 lbs; and 3.0 min/bed, patient weight >300 lbs. List-mode TOF algorithm and line-of-response TruFlight (LOR-TF) row-action maximum likelihood algorithm (RAMLA) method, the so called BLOB-OS-TF, were used for image reconstruction.

Radiotherapy

All patients were treated with intensity-modulated radiotherapy (IMRT) using either the TomoTherapy system with the proprietary treatment planning system or the Elekta linear accelerator using the Pinnacle^3 treatment planning system. Patients were treated using three dose levels: 70 Gy to the gross disease (primary tumor and involved nodes), 56–63 Gy to intermediate areas of disease risk, and 52.5–56 Gy to areas for low-risk elective neck treatment. All but one patient received concurrent chemotherapy.

Assessment of p16 status

At our institution, p16 status is assessed routinely using standard immunohistochemistry techniques. For the current study, this was obtained from pathology reports when available. Immunohistochemistry staining is considered positive for p16 if the sample shows strong nuclear and cytoplasmic positivity in greater than 75% of tumor cells, equivocal for p16 if the sample shows strong nuclear and cytoplasmic positivity in 50–75% of tumor cells, and negative if the sample shows a staining pattern not meeting the criteria for positive or equivocal staining. If these data were not available in pathology reports, tumor specimens were retrospectively obtained and stained to assess for p16 status.

FDG-PET/CT interpretation

Positive FDG-PET/CT was interpreted based on a review of imaging reports. Images with no focal areas of increased FDG uptake were interpreted as negative. Images with increased FDG uptake considered to be physiologic or related to treatment effect were also interpreted as negative. Equivocal PET results were interpreted as positive. A post-tx standardized uptake value (SUV) ≥ 2.5 in the residual node was considered positive.

Statistical analysis

The positive predictive value (PPV) and NPV were calculated for any recurrence, distant metastasis (DM), local recurrence, or regional recurrence for all patients, p16+ patients, and p16− patients. Overall survival, recurrence-free survival, and freedom from neck failure curves were calculated using the Kaplan–Meier product-limit method. The follow-up time was calculated from the date of treatment completion to the date of last follow-up or death. Survival differences were calculated using the log-rank statistic. A value of $p \leq 0.05$ was considered significant. All statistical analyses were performed in R version 3.2.3.

Results

Patient characteristics

A total of 108 patients were eligible, with a median follow-up time of 2.38 years (range: 0.26–7.10). Detailed patient and treatment characteristics are listed in Table 1. Sixty-eight (63.0%) patients had p16+ status and 40 (37.0%) patients had p16− status. Of the p16+ patients, 59 (87.8%) had oropharyngeal primary tumors, five laryngeal primary tumors (7.4%), two (3%) hypopharyngeal primary tumors, and two (3%) unknown primary tumors. Of p16− patients, 20 (50.0%) had oropharyngeal primary tumors, five (12.5%) laryngeal primary tumors, nine (22.5%) hypopharyngeal primary tumors, two (5.0%) oral cavity primary tumors, and four (10.0%) unknown primary tumors.

General outcomes

At last follow-up, 99 (91.7%) patients were alive. The 2-year overall survival and recurrence-free survival were 93.4% and 77.8%, respectively (Fig. 1).

There were 23 (21.3%) patients who experienced failures. One patient had local failure alone, one patient had regional failure alone, nine patients had concurrent local and regional failure, one patient had concurrent local and distant failure, three patients experienced concurrent regional and distant failure, and eight patients had distant failure alone.

Eighty-six patients had negative post-tx PET/CTs and only eight (9.3%) experienced failure (three regional, five DM). The NPV for post-tx PET/CT for all failures was 90.7%, for local recurrence was 100%, and for regional recurrence was 96.5%.

Twenty-two patients had positive post-tx PET/CTs, two with DM alone, two with DM and locoregional (LR) findings, and 18 with isolated LR findings. Thirteen of the 18 biopsied LR findings on PET/CT were pathologically positive. The PPV for post-tx PET/CT for all failures was 77.3%, for local recurrence was 72.7% and for regional recurrence was 50.0%.

Performance of post-tx PET/CT in assessing treatment response in p16+ patients

Among 68 p16+ patients, 60 had negative post-tx PET/CT findings. No patients had developed LRF at last follow-up, but three developed DM alone. Two p16+ patients with negative post-tx PET/CT underwent neck dissections within 1 year of their post-tx PET/CT due to suspicion of recurrence: one had persistent cystic adenopathy, while the other had persistent ulceration in the base of tongue concerning for persistent disease. Both were pathologically negative. The NPV for post-tx PET/CT in p16+ patients for any recurrence was 95%, for local recurrence was 100%, and for regional recurrence was 100%.

Eight patients had positive post-tx PET/CT, one had isolated DM, and seven patients had positive LR findings, one at the primary site alone, three in the neck alone, and three at both sites. These seven patients underwent directed biopsy and/or surgery. Pathology was positive in one patient at the primary site, in one patient in the neck, and in one patient at both sites. The PPV for post-tx PET/CT in p16+ patients for any recurrence was 50%, for local recurrence was 50.0%, and for regional recurrence was 33%.

Performance of post-tx PET/CT in assessing treatment response in p16− patients

Among 40 p16− patients, 26 had negative post-tx PET/CT. Two of these underwent a delayed neck dissection because of persistent nodes at 5 and 10.5 months after post-tx PET/CT, respectively. One had positive pathology. This patient is alive without evidence of disease. Two additional patients developed concurrent regional failure and DM at 18.5 and 54 months after negative post-tx PET/CT, respectively. Two patients developed DM without LRF. The NPV for post-tx PET/CT for p16− patients for any failure was 80.7%, for local recurrence was 100%, and for regional failure was 88.5%.

Among 14 p16− patients who had positive post-tx PET/CT, three had DM and 11 had positive LR findings: two at the

Table 1 Baseline patient characteristics

	Number of patients (%)	p16+	p16−
Age (years)			
< 50	11 (10.2%)	8 (11.8%)	3 (7.5%)
50–59	44 (40.7%)	30 (44.1%)	14 (35.0%)
60–69	34 (31.5%)	21 (30.8%)	13 (32.5%)
≥ 70	19 (17.6%)	9 (13.2%)	10 (25%)
Sex			
Male	88 (81.5%)	59 (86.8%)	29 (72.5%)
Female	20 (18.5%)	9 (13.2%)	11 (27.5%)
Primary tumor site			
Oropharynx	79 (73.1%)	59 (86.8%)	20 (50.0%)
Larynx	10 (9.3%)	5 (7.4%)	5 (12.5%)
Hypopharynx	11 (10.2%)	2 (2.9%)	9 (22.5%)
Oral cavity	2 (1.9%)	0 (0.0%)	2 (5.0%)
Unknown primary	6 (5.6%)	2 (2.9%)	4 (10.0%)
P16 status			
Positive	68 (63.0%)	68 (100%)	0 (0.0%)
Negative	40 (37.0%)	0 (0.0%)	40 (100%)
Chemotherapy			
Cisplatin-based regimen	59 (55.6%)	35 (51.5%)	24 (60.0%)
Single-agent cetuximab	16 (14.8%)	10 (14.7%)	6 (15.0%)
Carboplatin-based regimen	8 (7.4%)	4 (5.9%)	4 (10.0%)
Docetaxel-based regimen	19 (17.6%)	16 (23.5%)	3 (7.5%)
Single-agent erlotinib	1 (0.9%)	0 (0.0%)	1 (2.5%)
Unspecified chemotherapy	4 (3.7%)	2 (2.9%)	2 (5.0%)
No chemotherapy	1 (0.9%)	1 (1.5%)	0 (0.0%)
T-stage			
Tx	6 (5.6%)	2 (2.9%)	4 (10.0%)
T1	11 (10.2%)	4 (5.9%)	7 (17.5%)
T2	30 (27.7%)	28 (41.2%)	2 (5.0%)
T3	22 (20.4%)	14 (20.6%)	8 (20.0%)
T4	39 (36.1%)	20 (29.4%)	19 (47.5%)
N-stage			
N2A	5 (4.6%)	4 (5.9%)	1 (2.5%)
N2B	45 (41.7%)	29 (42.6%)	16 (40.0%)
N2C	45 (41.7%)	31 (45.6%)	14 (35.0%)
N3	13 (12.0%)	4 (5.9%)	9 (22.5%)

primary site alone, four at the primary site and in the neck, and five in the neck alone. Nine patients underwent directed biopsy or surgery, while two were observed because SUV uptake was borderline elevated. Both patients under observation developed late recurrence at 5 and 6 months after post-tx PET/CT. Three patients had no evidence of disease after pathologic analysis. Three of 6 patients with persistent disease were successfully salvaged, with one eventually developing a second cancer. The PPV for post-tx PET/CT for p16− patients for any failure was 78.6%, for local recurrence was 72.7%, and for regional recurrence was 66.6%.

Comparison of p16+ and p16− patients by PET status

Overall survival and recurrence-free survival stratified by p16 status are shown in Fig. 2. There was no significant difference in overall survival stratified by p16 status (log-rank $p = 0.162$), but recurrence-free survival was significantly better in p16+ patients (log-rank $p < 0.0001$). Figure 3 shows recurrence-free survival stratified by both post-tx PET/CT result and p16 status. Among p16+ patients, patients had an estimated 3-year recurrence-free survival of 89.7% with negative PET, compared to 50% with positive PET. Among p16− patients, patients had an

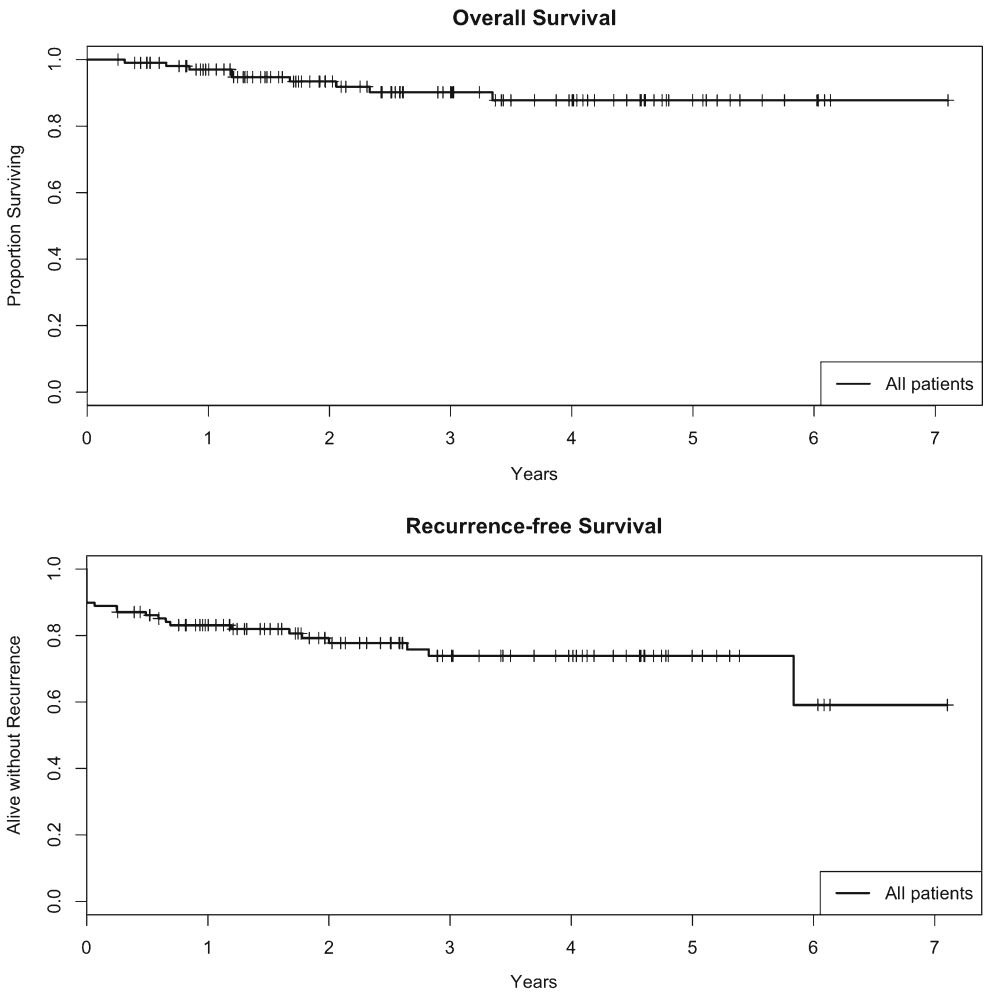


Fig. 1 Kaplan–Meier curve for overall survival and recurrence-free survival among the entire population. The figure shows overall survival and recurrence-free survival curves for the overall population

estimated 3-year recurrence free survival of 72.0% with negative PET, compared to 21.4% with positive PET. To assess whether both post-tx PET/CT results and p16 status were independent predictors of recurrence-free survival, Cox proportional hazards regression was performed including both factors in the model of recurrence-free survival. Both were found to be significant, with $p < 0.01$ for each factor.

For those who had negative post-tx PET/CT, both recurrence-free survival and freedom from neck failure were significantly better in p16+ patients compared to p16− patients (log-rank p for recurrence-free survival = 0.03 and for freedom from neck failure = 0.02; Fig. 4).

Subgroup analysis of oropharyngeal patients

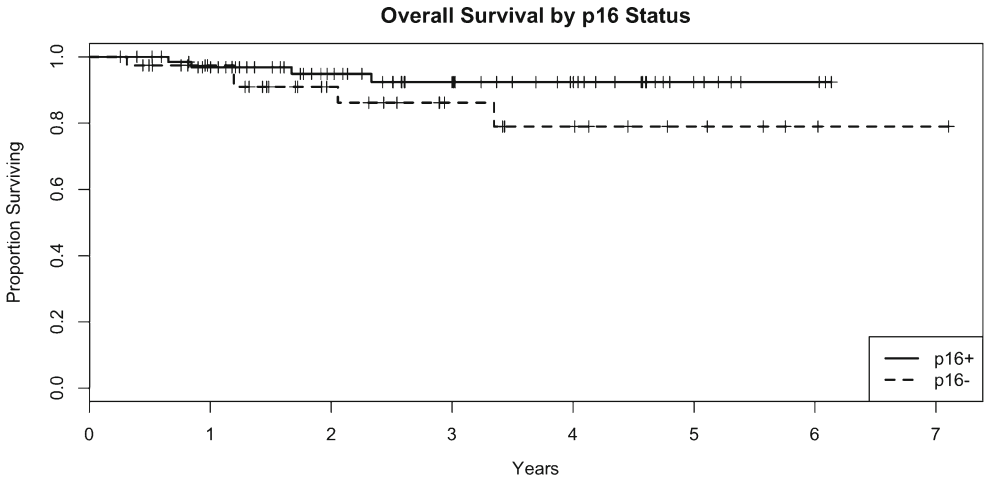
Among the 79 patients with oropharyngeal cancer, there was no significant difference in overall survival stratified by p16 status (log-rank $p = 0.973$), but recurrence-free survival was significantly better in p16+ oropharyngeal cancer patients (log-rank $p = 0.0022$). Figure 5 shows recurrence-free survival stratified by both post-tx PET/CT results and p16 status for oropharyngeal patients. On multivariate analysis, post-tx PET/CT results ($p < 0.001$) independently predicted recurrence-free survival, with a non-significant trend towards p16 status as an independent predictor of recurrence-free survival. ($p = 0.10$).

Subgroup analysis of non-oropharyngeal patients

Among the 29 patients with non-oropharyngeal cancers, there was no significant difference in overall survival stratified by p16 status (log-rank $p = 0.20$), but recurrence-free survival was significantly better in p16+ non-oropharyngeal cancer patients (log-rank $p = 0.044$). Figure 6 shows recurrence-free survival stratified by both post-tx PET/CT results and p16 status for non-oropharyngeal patients. On multivariate analysis, the post-tx PET/CT result ($p = 0.0031$) but not p16 status ($p = 0.99$) independently predicted recurrence-free survival. Of note, no p16+ patient had a negative PET/CT.

Discussion

Multiple studies have examined the value of post-tx PET/CT in assessing treatment response after definitive RT/chemoRT in



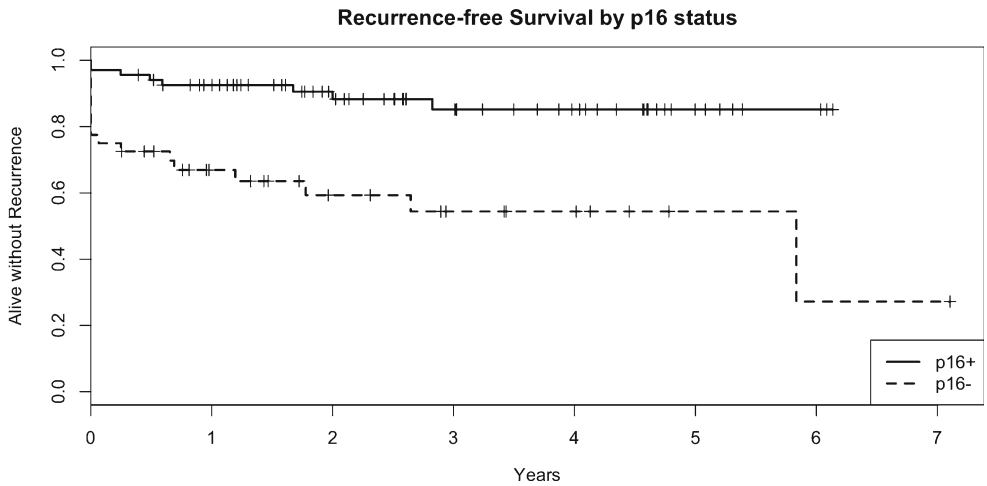


Fig. 2 Kaplan–Meier curve for overall survival and recurrence-free survival stratified by p16 status. There was no significant difference in overall survival among all patients stratified by p16 status, but recurrence-free survival was significantly improved (log-rank $p < 0.05$) in the p16+ population

locally advanced HNSCC, and its utility for decision-making regarding the management of the neck (partly summarized in Table 2). Our results showed that for the group overall, the NPV for post-tx PET/CT for all failures was 90.7% and for LRF was 96.5%, and the PPV for all failures was 77.3% and for LRF was 65.0%. These are consistent with the previous reports that were summarized in the meta-analysis [10]. There was still a 4–6% false-negative rate for locoregional disease, and those with false-negative PET results may have missed the opportunity for immediate effective salvage surgery. Therefore, it is important to reduce the false-negative rate or to identify a group of patients who may contribute to the false-negative PET results.

Most previous studies did not incorporate p16 status, which is a major prognostic factor in HNSCC, especially in

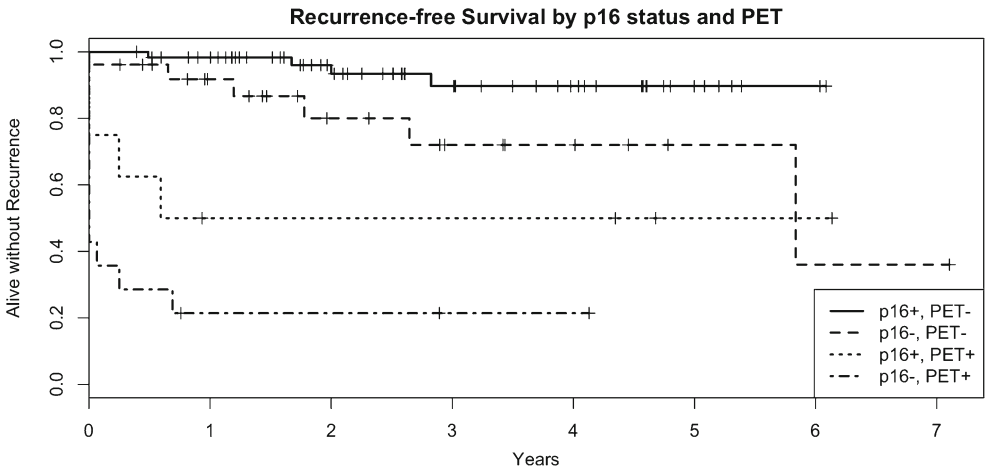


Fig. 3 Recurrence-free survival stratified by both p16 status and post-tx PET/CT. Both p16 status ($p < 0.01$) and post-tx PET/CT ($p < 0.01$) independently predicted recurrence-free survival on Cox proportional hazards regression

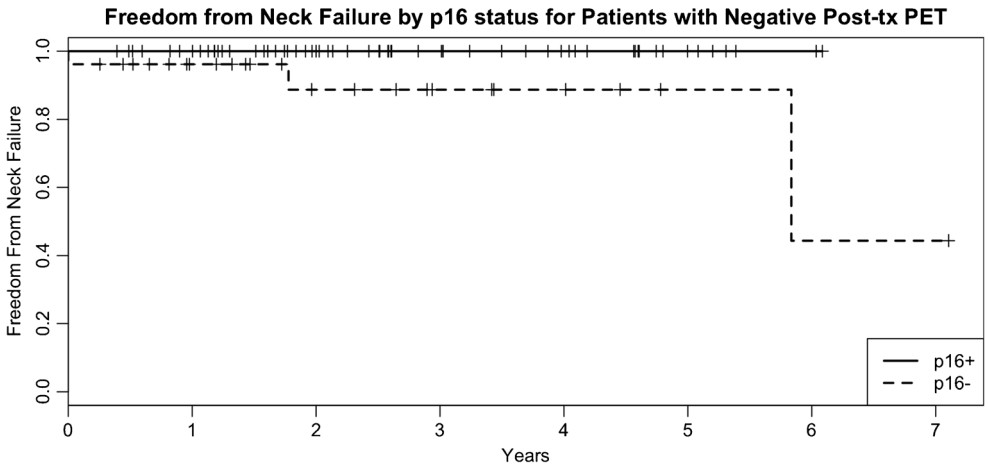


Fig. 4 Freedom From neck failure stratified by p16 status in patients with negative post-tx PET/CT. Freedom from neck failure (log-rank $p = 0.03$) was significantly better in p16+ patients even after post-tx PET/CT

oropharyngeal cancer [1] but also in non-oropharyngeal sub-sites [11]. Here we present a few studies examining post-tx PET/CT stratified by p16 status. We found that among p16+ patients who underwent definitive chemoRT to 70 Gy, most patients (60/68, 88%) had negative post-tx PET/CT results, and the NPV of post-tx PET/CT was 100% for LRF. Therefore, the frequency of follow-up in these patients may have been reduced after a negative post-tx PET/CT. However, the positive predictive value was very poor, with a very high false-positive rate. Fortunately, only a small portion of patients (8/68, 12%) had positive post-tx PET/CT.

In contrast, in p16− patients, even after a negative post-tx PET/CT, there was about a 10% risk of neck failure. This suggests that in p16− patients, close observation with repeated imaging is warranted even after a negative post-tx PET/CT, so that immediate salvage neck dissection can be performed. Unfortunately, many p16− patients with regional failures after a negative post-tx PET/CT also have simultaneous DM, making salvage surgery impossible. In our series, three of 26 p16− patients who had a negative post-tx PET/CT developed a regional recurrence; two of these also had distant disease at the same time. In order to reduce this risk, a second PET/CT 6 months after treatment may be considered in this population.

Though the significance of p16 status in non-oropharyngeal sites has been established [11], the underlying pathogenesis may be different. Among non-oropharyngeal patients, only PET/CT ($p = 0.003$), and not p16 status, was independently predictive of recurrence-free survival on multivariate analysis. However, there were only nine p16+ patients with non-oropharyngeal sub-sites, and none had a positive PET/CT; thus the power of this analysis is limited. Among oropharyngeal patients, on multivariate analysis PET/CT was independently predictive of recurrence-free survival ($p < 0.001$), and p16 status also showed a trend toward independent prediction of the same endpoint ($p = 0.10$). Despite the power limitations of these subgroup analyses, our data suggest the value of both p16 status and PET/CT as independent predictors of recurrence-free survival among oropharyngeal cancer patients, and do not exclude the independent predictive value of p16 status and PET/CT among non-oropharyngeal sub-sites.

A prospective trial from Australia also reported the value of post-tx PET/CT and p16 status in predicting neck cancer recurrence [8]. In their cohort, a single p16+ patient out of 56

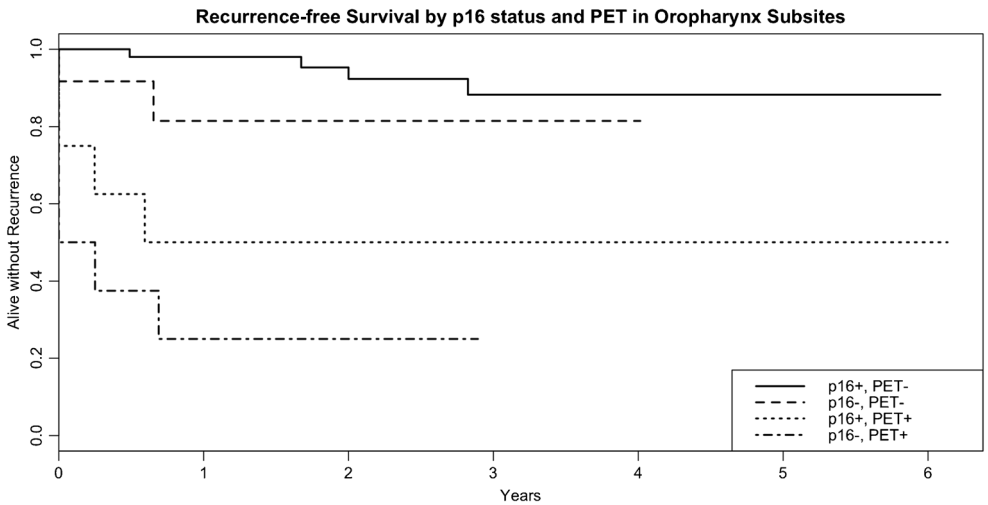


Fig. 5 Recurrence-free survival stratified by both p16 status and post-tx PET/CT in oropharynx sub-sites. Among oropharyngeal cancer patients, PET/CT independently predicted recurrence-free survival ($p < 0.001$), and p16 status also trended toward independent prediction for the same endpoint ($p = 0.10$) on multivariate analysis

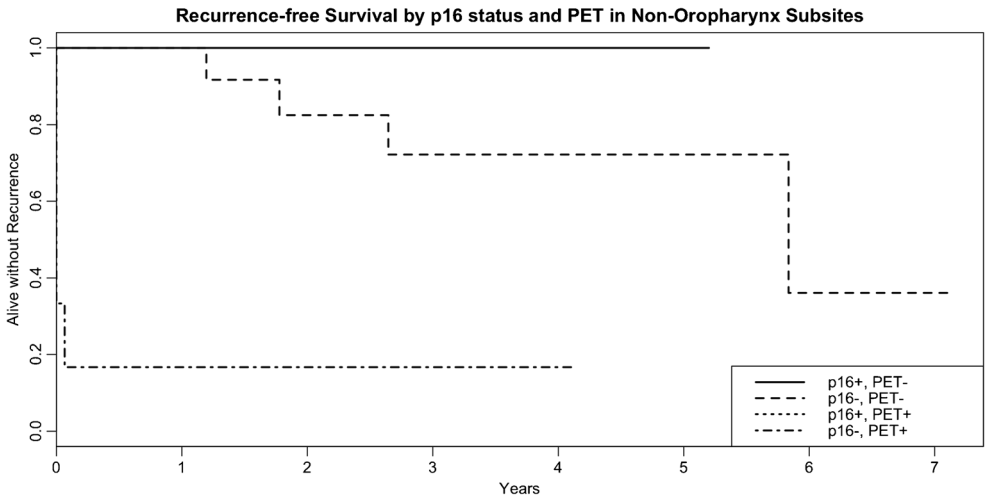


Fig. 6 Recurrence-free survival stratified by both p16 status and post-tx PET/CT in non-oropharynx sub-sites. Among non-oropharyngeal cancer patients, only PET/CT ($p = 0.003$) but not p16 status independently predicted recurrence-free survival on multivariate analysis. Only nine p16+ patients with non-oropharyngeal sub-sites and none had a positive PET/CT; thus the power of this analysis is limited

developed neck cancer recurrence after a negative post-tx PET/CT result (NPV = 98.2%), affirming our results showing a high NPV for post-tx PET/CT in p16+ patients. The NPV of 92.9% for regional control in p16− patients in the Australian study was slightly higher than ours, but there were only 17 p16− patients in that study cohort.

Several studies have examined the prognostic value of post-tx PET/CT in head and neck cancer. Yao et al. [4] demonstrated that any positive finding in post-tx PET correlated with worse 3-year overall survival. Inohara [12] at al. showed that a larger post-tx SUV_{max} correlated with poorer disease control and survival outcomes, while Murphy et al. [13] found a correlation between a post-tx PET metabolic tumor volume of > 18 cc and poorer outcomes, and Xie et al. [14] demonstrated a correlation between a metabolic complete response and better outcomes in nasopharyngeal cancer. Our data in Fig. 3 show that post-tx PET/CT is still a prognostic factor after stratification by p16 ($p < 0.01$). Combining post-tx PET/CT and p16 status nicely separates the four risk groups. It is interesting to note that even though p16 is a strong prognostic factor, p16+ patients with positive post-tx PET had worse recurrence-free survival than p16− patients with negative post-tx PET results (3-year recurrence-free survival 50% vs. 72%, Fig. 3).

A prospective study from the MD Anderson Cancer Center examined the utility of PET/CT for the assessment of radiation response in patients with HNSCC [15], and reported no additional benefit for post-tx PET/CT compared to diagnostic CT alone for the entire cohort. However, in subset analyses of high-risk patients defined as those with p16− disease, non-oropharyngeal primary disease, or a history of tobacco use, post-tx PET/CT was superior to diagnostic CT alone. With a median follow-up of 92 weeks, the NPV for neck control for

Table 2 Predictive values for regional nodal failure by p16 status across multiple experiences

Study	Patient population	Median follow-up	Overall PPV	Overall NPV	P16+ PPV	P16+ NPV	P16− PPV	P16− NPV
Awan Case Medical Center 2016	108 patients with ≥ N2 disease	2.7 years	44.4%	96.5%	42.9%	100%	66.6%	88.5%
Hitchcock University of Florida 2015 [5]	50 patients with ≥ N2 disease	2.0 years	0%	91%	0%	~	0%	~
Goenka MSKCC 2013 [6]	302 patients with N+ oropharynx cancer	2.9 years	12/22	272/276	~	~	~	~
Chan Johns Hopkins 2012 [7]	77 patients with HPV+ ≥ N2 Disease	2.1 years	PET_2 33.3% $PET_{2.5}$ 28.6%	PET_2 98.2% $PET_{2.5}$ 95.0%	PET_2 33.3% $PET_{2.5}$ 28.6%	PET_2 98.2% $PET_{2.5}$ 95.0%	~	~
Porceddu Queensland 2011 [8]	121 patients with N+ disease	2.3 years	77.8%	98.1%	33.3%	98.2%	75.0%	92.9%
Nayak Pittsburgh 2007 [9]	43 patients with ≥ N2 disease	1.5 years	70%	97%	~	~	~	~

PPVs and NPVs for neck failure across multiple studies stratified by p16 status if reported or able to be calculated from reported data. For the Johns Hopkins study, predictive values were stratified by PET threshold value used (PET_2: $SUV_{max} = 2.0$, $PET_{2.5}$: $SUV_{max} = 2.5$)

high-risk patients in their study was 94.7%. While our data on p16− patients are consistent with their report, we believe that in p16+ patients, post-tx PET/CT can also provide additional information for further management. As discussed above, post-tx PET/CT is a prognostic factor for p16+ patients, and can also detect unexpected distant metastases. Furthermore, it may take longer for nodal disease to resolve in p16+ patients [16]. Those with persistent lymph nodes in diagnostic CT but negative PET at 12 weeks after treatment may have neck control even without neck dissection.

Results were recently published for the PET-NECK study, a randomized clinical trial that examined the role of PET-CT-guided neck surveillance 12 weeks after chemoRT in patients with N2/3 HNSCC [17]. Patients were randomized to undergo planned neck dissection without PET imaging versus neck dissection for those with PET-avid disease at 12 weeks after treatment. A total of 564 patients were recruited, and 75% of 446 patients tested were p16+. With a median follow-up of 36 months, the 2-year overall survival rates were similar between these two groups, 81.5% for those with planned neck dissection versus 84.9% for those with PET-CT-guided neck dissection ($p = 0.004$ for non-inferiority). PET-CT-guided surveillance resulted in fewer neck dissections than did planned neck dissection, with savings of $2190 per person over the duration of the trial. This trial provides level 1 evidence for the role of PET-CT in neck dissection after chemoRT in locally advanced HNSCC.

We should note that our data presented here for p16+ patients with 100% NPV for post-tx PET/CT in predicting LRF were obtained from patients treated to 70 Gy, and most with concurrent chemotherapy. Due to the favorable outcomes recently reported for patients with HPV-related oropharyngeal cancer, clinical trials of treatment de-escalation using various strategies are currently under way [1, 18–22]. The NRG Oncology Group's NRG-HN002 is one such de-escalation trial. This is a randomized phase II trial looking at radiation dose de-escalation to either 60 Gy in 5 weeks without chemotherapy or 60 Gy in 6 weeks with concurrent weekly cisplatin (ClinicalTrials.gov, NCT02254278). We recommend caution in extending our experience to a de-escalated radiation dose setting such as this. In NRG-HN002, a secondary study of post-tx PET/CT for predicting treatment outcomes including locoregional control is also incorporated, and results will not be available within the next few years.

Conclusions

Our data validate the utility of post-tx PET/CT in neck management of locally advanced HNSCC and further elucidate the importance of p16 status in interpreting post-tx PET/CT and in making treatment decisions. In p16+ patients, the risk of local failure is low after 70 Gy of radiation and negative post-tx PET/CT, and may justify fewer follow-up scans after treatment. In p16− patients, there is still a 10% risk of regional failures even after negative post-tx PET/CT, and close observation with repeated imaging in this population is warranted.

Compliance with ethical standards

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Conflict of interest Mitchell Machtay is a consultant for Bristol-Myers, AbbVie, and Novocure. All other authors declare that they have no conflict of interest.

Ethical approval This is a retrospective, minimal-risk study. Institutional review board approval was obtained for retrospective review of patient charts. This was performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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