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Post-treatment PET/CT for p16-positive oropharynx cancer treated with definitive proton therapy

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ABSTRACT

Objectives: Given emerging data suggesting that uncertainty in the relative biologic effectiveness at the distal end of the Bragg peak results in increased mucosal injury in patients with oropharynx cancer receiving adjuvant proton therapy, we evaluated the results of post-treatment positron emission tomography–computed tomography (PET/CT) in patients with p16-positive oropharynx cancer (p16+OPC) treated with definitive intensity-modulated proton therapy (IMPT).

Material and Methods: A retrospective cohort study of patients with p16+OPC treated with definitive IMPT between 2016 and 2022 was performed at a single institution. Patients with PET/CT scans within 6 months following completion of IMPT were included in the study. Positive post-treatment scans were defined by a maximum standard uptake values (SUVmax) >4.0 or a <65% reduction in SUVmax in either the primary tumor or lymph node. The Fisher's exact test was used to evaluate factors associated with positive post-treatment PET/CT values.

Results: Sixty-two patients were included for analysis. Median follow-up was 21 months (range: 3–71 months) with a median time to post-treatment PET/CT of 3 months (range: 2–6 months). Median post-treatment SUVmax of the primary disease and nodal disease was 0 (mean: 0.8, range: 0–7.7) and 0 (mean: 0.7, range: 0–9.5), respectively. Median post-treatment percent reduction in SUVmax for the primary site and lymph node was 100% (mean: 94%, range: 31.3–100%) and 100% (mean: 89%, range: 23–100%), respectively. Eleven patients had a positive post-treatment PET/CT with one biopsy-proven recurrence. Negative and positive predictive values (NPV and PPV) were 98% and 9.1%, respectively. There were no factors associated with positive post-treatment PET/CT.

Conclusion: Similar to patients treated with photon-based radiation therapy, post-treatment PET/CT has a high NPV for patients with p16+OPC treated with definitive proton therapy and should be used to guide patient management. Additional patients and more events are needed to confirm the PPV of a post-treatment PET/CT in this favorable patient cohort.

Keywords: Oropharynx, Proton therapy, p16, Human papillomavirus, Positron emission tomography/computed tomography

INTRODUCTION

The excellent prognosis and increasing incidence of human papillomavirus (HPV) associated oropharyngeal cancers (hereafter p16-positive oropharynx cancer [p16+OPC]) have led to significant efforts at reducing the acute and long-term toxicities of treatment. Areas of ongoing

and reported research include the use of transoral robotic surgery,[1] reduction of radiotherapy target volumes,[2] reduction of target volume margins,[3-6] deintensification of radiotherapy dose,[7] omission or deintensification of concurrent systemic therapy,[7,8] and use of advanced radiotherapy techniques such as IMRT/volumetric modulated arc therapy and proton therapy.[9,10] Given the attractive physical properties of proton therapy, increasing accessibility, and pending phase III data, proton therapy has the potential to play a larger role in the management of p16+OPC.

Variability in the relative biologic effectiveness (RBE) at the distal end of the Bragg peak needs to be considered in proton therapy planning.[11] Indeed, preclinical studies have demonstrated that the distal end of the Bragg peak may have increased RBE, and emerging clinical data have implicated increased RBE in unexpected toxicities.[12-14] In the setting of adjuvant proton therapy for p16+OPC, increases in RBE have recently been postulated to be responsible for observed increased standard uptake values (SUV) uptake in the post-operative tumor bed.[15] While this report should be interpreted with caution given its retrospective nature and limited patient numbers, the findings warrant further exploration. As post-treatment positron emission tomography–computed tomography (PET/CT) scans have emerged as part of the standard follow-up, possible inflammation-related post-treatment fluorodeoxyglucose (FDG) avidity in patients treated with proton therapy may result in falsely positive results putting patients at risk for unnecessary morbidity from invasive workup or surgical intervention and added anxiety. Conversely, it is also important to not be overly dismissive of positive PET/CT findings consistent with residual or recurrent disease as residual disease is best treated with early surgical salvage.

The utility and role of post-radiation PET/CT have been well-established, are widely practiced, and are based on series from patients with p16+OPC treated with photon therapy. It is important to evaluate these results in patients treated with proton therapy especially given their increasing use and potential for persistent inflammation and mucosal injury.

MATERIAL AND METHODS

Patient population

We performed an IRB-approved single-institution retrospective analysis of all patients with non-metastatic p16+OPC treated with definitive intensity-modulated proton therapy (IMPT) treated between 2016 and 2022. Patients with a pre-treatment PET/CT and initial post-treatment PET/CT following completion of IMPT available for analysis were included in the study. Pre-treatment and post-treatment maximum SUV (SUVmax) for the primary and nodal disease if present were recorded. On post-treatment PET/CT, a SUVmax decrease <65% from the baseline examination or SUVmax >4.0 was considered to have residual PET activity based on thresholds defined in other studies.[16,17] Patient records were reviewed to assess for locoregional recurrence. Negative and positive predictive values (PPV) of the post-treatment scans were calculated. A scan was only considered to be positively predictive if the patient had both a positive post-treatment PET/CT and recurrent/residual disease in an area with previously identified FDG avidity. A patient with a positive post-treatment PET/CT who developed a tumor in the head and neck outside of the areas of FDG avidity in either pretreatment or post-treatment PET/CT was defined as a false-positive scan.

Treatment and treatment planning

Patients were treated definitively with or without systemic therapy at the treating medical oncologist's discretion. High-, intermediate-, and low-risk clinical target volumes (CTVs) were most commonly prescribed 70 Gy, 59.4 Gy, and 52.8 Gy in 33 fractions using a simultaneous integrated boost technique. High-risk CTV included gross tumor volume with or without the addition of margin for subclinical disease per the decision of the treating radiation oncologist.

For CT simulation, patients were immobilized in a 5-point thermoplastic mask with or without the use of intravenous contrast. Treatment planning was performed using Eclipse (Varian Medical Systems, Crawley, United Kingdom) or RayStation (RaySearch Laboratories, Stockholm, Sweden). Most commonly, a four-field beam arrangement using 0°, 70°, 180°, and 290° beam angles was employed. Occasionally, to avoid dental implants near the target volume, a four-field arrangement of 40°, 140°, 220°, and 320° was used. To avoid unnecessary dose to the shoulder and to minimize parallelism to the base of the skull, a couch kick of approximately 15° was commonly performed. The plan robustness was evaluated with 12 scenarios of combinations of ±3 mm patient set-up uncertainties and ±3.5% range uncertainties. Multifield optimization was used with a maximum contribution of 70% per beam. Spot editing to keep spots between 1.1-100 MU/fraction and Monte Carlo dose calculations were done. Quality assurance CT scans were routinely performed, generally during the 1st week and every other week thereafter. The decision to replan was at the treating physician's discretion.

PET/CT scans

The institutional practice was to obtain post-treatment scans approximately 3 months following completion of IMPT. Per institutional standard protocol, patients were to have fasted for a minimum of 4 h before PET/CT. Approximately 60 min before imaging; patients were injected with fluorine-18 FDG.

The patient was imaged from the top of the skull to the mid thighs using a (Siemens) dedicated full-ring PET/CT scanner, with image reconstruction in the sagittal, transverse, and coronal axes. SUV were computed as the maximum value for abnormal regions. CT data were used for attenuation correction and lesion localization, often with full diagnostic CT of the neck performed as requested by the referring provider. The SUV of the primary site and lymph nodes were independently evaluated and post-treatment scans were compared to their respective baseline values.

Statistical analysis

Fisher's exact test was used to compare patients who had positive post-treatment PET/CT to those who did not. Patient factors of male versus female, white versus non-white, use of CTV margin versus no CTV margin, smoking history versus no smoking history, >10 pack year history versus ≤10 pack year history, tonsil versus base of tongue subsite, T1–T2 versus T3–T4, chemoradiotherapy versus radiotherapy alone, N0 versus > N0, and locoregionally recurrent disease versus no locoregional recurrence disease were analyzed.

RESULTS

Sixty-two patients treated between 2016 and 2022 were included for analysis with a median follow-up of 21 months (range: 3–71 months). Patient characteristics are shown in Table 1. The median time from treatment completion to post-treatment PET/CT was 3.1 months (range: 2–6 months, interquartile range: 2.7–3.5 months). The median SUVmax of the primary disease was 13.3 (mean: 14.4; range: 5.1–29) and the median SUVmax of the most FDG avid nodal disease per patient was 7.4 (mean: 8.0; range: 0–26.2). Following treatment, the median SUVmax of the primary disease and nodal disease was 0 (mean: 0.8, range: 0–7.7) and 0 (mean: 0.7, range: 0–9.5), respectively. The median percent reduction in SUVmax for the primary site was 100% (mean: 94%, range: 31.3–100%) and the median reduction in the highest SUVmax nodal site was 100% (mean: 89%, range: 23–100%). Eleven of the patients had a positive post-treatment PET/CT as defined by residual SUV >4.0 or <65% reduction from pretreatment PET/CT of either primary or nodal disease, while 51 had a negative post-treatment PET/CT.

One patient with a positive post-treatment PET/CT developed recurrent/residual disease. This patient had both an SUVmax >4.0 and <65% reduction from baseline. After a short period of close interval follow-up during which time he had increasing pain and mucosal changes, a biopsy confirmed persistent/residual disease. He ultimately underwent surgical salvage. One patient who initially had a tonsillar primary with a post-treatment SUVmax of 4.2 in a lymph node went onto develop a new primary tumor in the base of the tongue in an area outside of any prior FDG avidity. The FDG avid cervical lymph node resolved on serial imaging. The nine other patients with a positive post-treatment PET/CT were monitored with close clinical follow-up at the discretion of the treating physician, which included repeat PET/CT, serial contrast-enhanced CT examinations, or clinical examination. The average time for a negative follow-up PET/CT scan for patients with an initial positive post-treatment PET/CT was 4 months (range 3.7–4.3 months). No patients in this cohort underwent unnecessary salvage surgical resection or invasive biopsy. Summaries of imaging findings and clinical management of these 11 patients are summarized in Table 2. Overall, the PPV was 9.1%. Of the patients who had a negative PET/CT, only one patient developed a biopsy-proven locoregional recurrence yielding a negative predictive value (NPV) of 98%.

Table 1: Patient, tumor and treatment characteristics.

	n=62	%
Sex		
Male	59	95.2
Female	3	4.8
Race		
White	58	93.5
Nonwhite	4	6.5
Smoking History		
No	26	41.9
Yes	36	58.1
>10 pack year history		
No	42	69.4
Yes	19	30.6
Primary Site		
Tonsil	34	54.8
BOT	28	45.2
T stage		
T1	13	21.0
T2	19	30.6
T3	8	12.9
T4	2	3.26
N Stage (AJCC 7th)		
N0	10	16.1
N1	19	30.6
N2a	6	9.7
N2b	15	24.2
N2c	10	16.1
N3a	0	0
N3b	2	3.2
N Stage (AJCC 8th)		
N0	10	16.1
N1	40	64.5
N2	12	19.4
Concurrent chemotherapy		
No	10	16.1
Yes	52	83.9
Radiation Dose – median (range)	70 Gy	range, 63.52-70 Gy

Table 2: Imaging characteristics and clinical outcomes of patients with positive post-treatment PET/CT.

Subsite	Initial SUV Primary	Initial SUV LN	PTS SUV Primary	PTS SUV LN	Follow Up	Clinical Management
Tonsil	21.72	7.57	1.6	5.43	8 mo.	Serial clinical exam.
Tonsil	11.2	7.4	7.7	9.5	32 mo.	Serial clinical exam and repeat imaging with contrast enhanced CT.
BOT	14.51	0	5.28	0	27 mo.	Serial clinical exam and repeat imaging with PET CT with resolution of avidity.
Tonsil	12.0	5	0	4.2	22 mo.	Development of new primary outside area of PTS PET avidity.
Tonsil	17.2	0	5.8	0	18 mo.	Serial clinical exam and repeat imaging with contrast enhanced CT.
Tonsil	29.0	10.2	5.1	0	16 mo.	Serial clinical exam.
Tonsil	10.3	19.6	5	3.7	19 mo.	Serial clinical exam and repeat imaging with PET CT with resolution of PET avidity.
BOT	14	3.7	0	4.2	3 mo.	Serial clinical exam and repeat imaging with contrast enhanced CT pending.
BOT	14.06	17.68	0	4.2	7 mo.	Serial clinical exam and repeat imaging with contrast enhanced CT.
Tonsil	20.71	9.6	4.1	0	16 mo.	**Persistent residual disease treated with successful surgical salvage.**
BOT	5.1	3.6	0	2.3	41 mo.	Serial clinical exam and repeat imaging with contrast enhanced CT.

SUV: Standard uptake values, PET-CT: Positron emission tomography–computed tomography

Baseline tumor and treatment characteristics were compared between the group with negative post-treatment PET/CT and the group with positive post-treatment PET/CT [Table 3]. For all factors analyzed, there were no statistically significant baseline characteristics that predicted having a positive post-treatment PET/CT. Of those who had a positive post-treatment PET/CT, 91% (10/11) had a CTV margin ($P = 0.152$).

DISCUSSION

It is well-established that post-treatment PET/CT has a high and consistent NPV (92–98%) and a modest and variable PPV (9–56%) in the context of patients with p16+OPC being treated with definitive photon-based (chemo) radiotherapy.[18-21] The uncertainty of the RBE at the distal end of the proton Bragg peak potentially resulting in prolonged inflammation and mucosal injury could affect the NPV and PPV of post-treatment PET/CT in patients with p16+OPC treated with definitive proton therapy. Using the previously defined parameters of a decrease in SUVmax of 65% as a powerful marker of favorable clinical outcome and a post-treatment SUV >4.0 as an indicator of a high probability of residual tumor in patients with head and neck cancer, we report a high NPV and low PPV or 98% and 9.1%, respectively, for patients with p16-positive oropharynx cancer treated with definitive proton therapy.[16,17]

The PPV, in our cohort, was 9.1% as only one of the 11 patients who had a positive post-treatment PET/CT developed locoregionally recurrent disease. The patient who had residual disease on post-treatment PET was surgically salvaged after a short period of close interval follow-up during which he had increasing pain and mucosal changes consistent with disease progression. The decision to undergo invasive workup with biopsy or surgical salvage is a challenging clinical situation, especially as imaging changes from post-treatment inflammatory changes can look very similar to those of residual disease [Figure 1]. Multidisciplinary input and particularly close follow-up are required for those with indeterminate findings. A number of predictive models using clinical examination and non-PET/CT radiographic findings exist. Depending on physician concern and ease of physical examination, the addition of further follow-up imaging such as magnetic resonance imaging can be considered for this patient population.

It has previously been reported that the PPV of PET/CT for patients with HPV+OPC is lower than that for HPV-OPC possibly due to higher rates of local control.[21] If the potential increased RBE of the distal end of the Bragg peak of PT results in an increased inflammatory response, this could further decrease the PPV. Validation of these findings in larger patient cohorts may require a reassessment of the current criteria used to evaluate post-treatment scans. Given the resolution of nearly all patients with falsely positive post-treatment PET/CT scans over time, it is possible that delaying

Table 3: Patient, tumor, and treatment characteristics stratified by post-treatment PET/CT results.

	Positive PET	Negative PET	p-value
Sex			
Male	11	48	1.000
Female	0	3	
Race			
White	11	48	1.000
Non-white	0	4	
CTV Margin			0.152
No	1	17	
Yes	10	34	
Smoking History			0.748
No	4	22	
Yes	7	29	
>10 pack year history			0.726
No	7	35	
Yes	4	15	
Primary Site			0.200
Tonsil	7	21	
BOT	4	30	
T stage			0.735
T1-T2	8	33	
T3-T4	3	18	
N Stage			0.674
N0	1	9	
N1-2	10	42	
Concurrent chemotherapy			0.363
No	3	7	
Yes	8	44	
Loco-regional Failure			0.326
No	10	51	
Yes	1	1	

the initial post-treatment PET/CT scan beyond 3 months may minimize the impact of increased inflammation in IMPT-treated patients.

While we analyzed factors associated with positive post-treatment PET/CT and nothing reached statistical significance, we did note that most positive post-treatment scans included patients whose high-risk volume included a CTV expansion from the gross tumor volume (GTV). With $P = 0.152$, there was a trend toward a CTV margin increasing the risk of a positive post-treatment PET/CT. It is intuitive that those who had more normal tissue irradiated would be at increased risk for post-treatment inflammation resulting in falsely elevated PET avidity. Whether this relationship exists or not would require a comparison of much larger and well-matched patient cohorts as our study is underpowered to examine this possibility. Data sets generated from ongoing randomized clinical trials comparing photon and proton therapy could be used to validate differences in post-treatment PET avidity between treatment modalities. This would be of value to clinicians and patients during routine follow-up for both prognostication and further management.

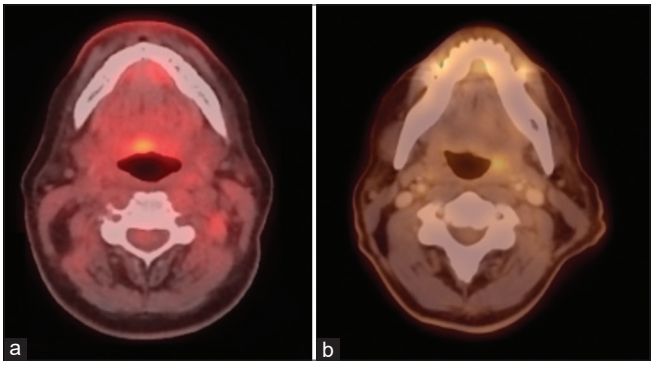

Figure 1: Examples of positron emission tomography (PET) avidity following proton therapy. (a) Patient with residual PET avidity in the base of tongue on post-treatment PET/computed tomography CT who was followed clinically and was without evidence of disease recurrence at last follow-up. (b) Patient with residual PET avidity in the left tonsil on post-treatment scan found to have residual/recurrent tumor that was surgically salvaged.

There are several limitations to this analysis. The sample size of the study was modest with very few locoregional recurrences that may affect NPV and PPV. However, our findings are consistent with previously reported NPV and PPV. The retrospective nature of the data collection did not allow the inclusion of other predictive models such as those using clinical examination findings with non-PET/CT cross-sectional imagining[22,23] or additional PET/CT data such as texture analysis.[24] These limitations underscore the need for validation in larger cohorts. Further, the variability in imaging techniques across centers would be addressed through a collaborative analysis. Finally, we chose two published SUV criteria to define a positive scan but recognize that additional criteria exist that were not feasible for this study as our data set did not include qualitative data used in NI-RADS, Porceddu, Deauville, or Hopkins scoring.[25]

CONCLUSION

Our findings support the previous reports that for patients with p16+OPC treated with proton therapy who have a negative post-treatment PET/CT, the risk of residual or locoregionally recurrent disease is very low. For those who have positive post-treatment PET/CT defined as <65% decrease of pretreatment avidity or SUVmax >4.0, there is a high rate of false positive results with only one of 11 patients having residual disease. This finding may result from high rates of local control and/or increased post-treatment inflammation from RBE differences at the end of the distal end of the Bragg peak. These findings are hypothesis-generating and require validation in larger prospective patient cohorts to incorporate the findings into clinical management.

Declaration of patient consent

Patient's consent not required as patients identity are not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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