



Management of the neck after definitive chemoradiation in patients with HPV-associated oropharyngeal cancer: An institutional experience

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ABSTRACT

Purpose: To investigate the multidisciplinary management of patients with Human Papilloma Virus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) and an incomplete nodal response on restaging PET/CT after definitive chemoradiation (CRT).

Materials and methods: A retrospective chart review was performed of patients diagnosed with node-positive HPV-associated OPSCC from 2012 to 2017, who underwent definitive upfront CRT, and had an incomplete response on post-therapy PET/CT according to NCCN criteria. Post-CRT PET/CT results, management decisions, and clinical outcomes were recorded.

Results: Seventy-four patients with node-positive HPV-associated OPSCC were identified; 20 patients with incomplete neck response on PET/CT according to NCCN criteria were included in the final case series. Median follow-up time was 33 months. Patients were managed as follows: 8 underwent observation and surveillance imaging, 6 underwent ultrasound-guided fine needle aspiration (FNA), and 6 had immediate neck dissection. All the observed patients were disease-free at most recent follow-up. None of the patients who underwent immediate neck dissection had residual neck disease on pathological examination; two patients in this group ultimately developed metastatic disease. Among the 6 who underwent FNA, 1 individual had positive pathology, along with residual primary disease, for which the patient underwent salvage surgery. The 5 remaining individuals had negative FNA results, were subsequently observed, and remained free of disease.

Conclusions: This institutional experience supports the notion of a high threshold for neck dissection in this low-risk population; only 1 of 20 patients with suspicious PET/CT findings had residual disease in the neck. Moreover, these patients should be managed by a multidisciplinary tumor board (MTB) since current algorithms do not universally include HPV status. Finally, the use of restaging PET/CT to guide management of the neck can be improved with changes in terminology and consideration of FDG-avidity at the primary site and on pre-therapy scans.

1. Introduction

1.1. HPV-associated OPSCC

Human papilloma virus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) has become increasingly common in head and neck oncology, with rising incidence year after year. With unique molecular and clinical characteristics, including a better response to treatment and prognosis, HPV-OPSCC is now considered a separate disease entity [1,2]. This new understanding has led to a unique staging system in the 8th edition of the American Joint Committee of Cancer (AJCC) Staging Manual. Moreover, ongoing clinical trials are investigating new therapeutic strategies for patients with HPV-associated OPSCC, such as use of robotic surgery and de-intensified regimens of chemotherapy and radiation [3]. Post-therapy surveillance strategies

continue to evolve as well.

1.2. Restaging PET/CT

Definitive chemoradiation (CRT) is a standard treatment for locally advanced and node-positive HPV-associated OPSCC. With structural and functional data, FDG-PET/CT has become an important modality in assessing treatment response and has several applications in the post-CRT setting according to NCCN guidelines. These include evaluation of an incomplete clinical response, routine surveillance at 12-weeks post-CRT, and assessment of a concerning CT or MRI performed at 8–12 weeks [4]. The use of post-therapy PET/CT has been shown to promote excellent control of disease and be non-inferior to planned neck dissection in regard to survival outcomes [5–9]. However, the positive predictive value (PPV) of PET/CT is low in HPV-associated

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OPSCC [10–13], likely secondary to the lower pre-test probability of residual nodal disease [14], post-CRT inflammation, and prolonged time to complete lymph node involution (< 1 cm) for irradiated HPV-associated lymph nodes [15].

1.3. Objectives of this case series

The low PPV of restaging PET/CT makes it challenging for head and neck oncologists to manage patients with HPV-associated OPSCC and an incomplete nodal response on restaging PET/CT; they must decide between observation and neck dissection. In truth, the optimal approach to these patients is unknown. Therefore, a case series was performed to investigate the multidisciplinary approach to this clinical problem at a multi-site regional health system.

2. Methods

2.1. Study design

The case series was performed with a retrospective review of patients diagnosed with OPSCC at Northwell Health from 2012 to 2017. The study was approved by the Northwell Health Institutional Review Board (IRB) and was compliant with the Health Insurance Portability and Accountability Act (HIPAA). Charts for review were obtained by the tumor registry using the International Classification of Disease (ICD) code 9th and 10th edition for all subsites of oropharyngeal cancer. The electronic medical records of these patients were then used to identify patients with node-positive, HPV-associated OPSCC who underwent definitive CRT. Patients who had incomplete responses on post-therapy PET/CT were separately analyzed.

2.2. Selection Criteria

Patients were considered to have HPV-associated disease if biopsy demonstrated strong and diffuse P16 expression on immunohistochemistry (IHC) or were positive for high-risk HPV subtypes on *in-situ* hybridization (ISH). Patients were identified as having an incomplete response on post-therapy PET/CT according to NCCN criteria, which includes lymphadenopathy size > 1 cm, FDG-avidity, or both. The other inclusion criteria included (a) squamous cell histology (b) non-metastatic, and (c) locally-advanced disease with $N = 1$ or higher. Patients who received upfront surgery, underwent neck dissection before PET/CT, or had no follow-up information were excluded from the study.

2.3. Data collection

The data was recorded with an encrypted excel file and the Research Electronic Data Capture (REDCap) system. The collected variables included demographic information, stage of disease, nodal burden, nodal size, smoking history, P16 IHC status, HPV ISH status, EGFR status, treatment course, clinical response to CRT, interval imaging studies, radiographic response to CRT (including pre- and post-CRT lymph node size and standardized uptake values (SUV), management decisions, pathology reports of biopsies and salvage therapies, results of follow-up imaging studies, and clinical outcomes.

3. Results

3.1. Clinical features and characteristics of the cohort

Seventy-four patients with node-positive HPV-associated OPSCC were identified. Five patients were excluded due to missing clinical data or insufficient follow-up. Twenty patients who met the inclusion criteria for possible residual neck disease were included in the analysis (Table 1). Seventeen were male and 3 were female. Median age at

diagnosis was 54 years (range 40–66 years). There were 2 active smokers, 9 former smokers, and 9 never-smokers. Tumor sites included tonsil (4), base of tongue (BOT) (15), and unknown (1), which was presumed oropharyngeal based on HPV-positive testing on diagnostic neck FNA. Disease stages included AJCC-7th edition III (1) and IVA (19) and AJCC-8th edition I (14), II (5), and III (1). More than half the cohort had unknown tumor grade (12/20); 4 patients had poor differentiation and 4 patients had moderate differentiation. Most patients (17) had > 1 enlarged lymph node at diagnosis (≥ 1 cm); the median size of the largest lymph node was 3.5 cm (range 1.0–5.5). In regard to HPV testing, 19/20 patients had positive p16 IHC (1 negative) and 13/19 patients had positive ISH for high-risk HPV (2 negative, 4 unknown, 1 inconclusive). More than half the cohort had unknown EGFR status (12/20); 6 were positive and 2 were negative. All patients were treated with curative-intent definitive CRT to 7000 cGy.

3.2. Post-therapy PET/CT results

The median time from the end of treatment to initial PET/CT was 12.9 weeks (range 4.1–18.6 weeks). In regard to clinical response post-CRT and before PET/CT, 13 patients had evidence of regression, 6 patients had persistent adenopathy in the neck, and 1 patient was not clinically assessed. Twelve patients had interval scans, most of which were CT scans (10) that demonstrated decreased adenopathy. Two patients had interval FNA, one of which was positive for persistent squamous cell cancer. In regard to post-therapy PET/CT findings, most scans had lymph nodes > 1 cm (17/20) and were FDG-avid (16/20). The exact sizes and SUVs of pre- and post-therapy lymph nodes are reported in Table 2.

3.3. Management decisions and clinical outcomes

All patients were alive at most recent follow up. The median follow-up time was 33 months (range 8.0–67 months). Of the 20 patients in the final case series, 8 were followed with surveillance imaging (contrast-enhanced CT scan), 6 underwent ultrasound-guided FNA, and 6 had immediate neck dissection (Table 3). Of those who were observed with CT imaging, 6 had regression on subsequent CT scans, 1 had no change, and 1 had increased adenopathy that ultimately regressed. All these patients were considered NED (no evidence of disease) at most recent follow-up. None of the patients who underwent immediate neck dissection had confirmed residual neck disease on pathological examination. In this group, two developed metastatic disease; one patient was found to have liver metastases on post-therapy PET/CT while the other was found to have pulmonary metastases on surveillance CT imaging. Among the 6 individuals who underwent FNA, 1 had positive pathology, along with confirmed residual primary disease of the BOT, for which the patient underwent salvage surgery. Of note, this individual had negative p16 IHC and positive ISH for high risk HPV DNA. The disease status of this patient is unclear as follow-up care was transferred to another institution. The 5 remaining patients had negative findings, were subsequently observed, and considered NED at the most follow-up.

4. Discussion

4.1. Higher threshold for neck dissection in HPV-associated OPSCC

Our institutional experience suggests that clinicians adopt a high threshold for immediate neck dissection in patients with HPV-associated OPSCC. In this case series, 6/6 patients who underwent immediate neck dissection had negative pathology. Moreover, all patients who were observed had no evidence of disease at most recent follow-up. This notion of a high threshold for immediate neck dissection in HPV-associated OPSCC is in accordance with numerous publications [5,11]. However, the optimal approach to observing these patients

Table 1
Clinical features and characteristics of the cohort.

Patient ID	Age at diagnosis	Sex	ETOH history	Smoking history/pack years	Tumor site	AJCC-7 T Stage	AJCC-7 N Stage	AJCC-7 M Stage	AJCC-8 T Stage	AJCC-8 N Stage	AJCC-8 M Stage	Tumor grade	Number of Nodes at Diagnosis	Largest Node (cm)	EGFR status	RT Dose (cGy)	RT fractions	Chemotherapy
1	44	Male	Social	Active/20	Tonsil	1	2B	IVA	1	1	I	Unknown	> 1	4.3	Unknown	7420	35	Cisplatin
2	63	Male	Social	Quit/62	BOT	1	2B	IVA	1	1	I	Poor	> 1	4.3	Positive	7000	35	Cisplatin
3	54	Male	Social	Never	BOT	1	2B	IVA	1	1	I	Moderate	> 1	3.5	Unknown	7000	35	Cisplatin
4	64	Male	Never	Never	BOT	3	2C	IVA	3	2	II	Unknown	> 1	2.6	Negative	7600	34	Cisplatin Carboplatin
5	54	Male	Social	Never	Tonsil	2	1	III	2	1	I	Moderate	1	1	Unknown	7000	34	Cisplatin
6	48	Male	Social	Never	BOT	2	2B	IVA	2	1	I	Moderate	> 1	3.8	Unknown	7000	35	Cisplatin
7	63	Female	Social	Quit/8	BOT	2	2B	IVA	2	1	I	Unknown	> 1	2.2	Unknown	6996	33	Cisplatin
8	48	Male	Social	Never	BOT	2	2A	IVA	2	1	I	Poor	> 1	4.7	Unknown	7000	35	Cisplatin
9	56	Male	Social	Active/72	BOT	2	2B	IVA	2	1	I	Unknown	> 1	2.8	Positive	7000	31	Cisplatin
10	48	Female	Social	Quit/10	BOT	3	2B	IVA	3	1	II	Moderate	> 1	3.6	Positive	7000	35	Cisplatin
11	40	Male	Social	Never	BOT	3	2B	IVA	3	1	II	Poor	> 1	5.5	Positive	7000	35	Docetaxel Cisplatin
12	52	Male	Never	Never	BOT	1	2B	IVA	1	1	I	Unknown	> 1	2.3	Positive	7000	35	5-FU Cisplatin
13	45	Male	Social	Quit/2	BOT	2	2B	IVA	2	1	I	Unknown	> 1	3.4	Unknown	7000	35	Cisplatin
14	52	Male	Former Abuse	Quit/15	Unknown	0	2B	IVA	0	1	I	Unknown	> 1	4.5	Negative	7000	33	Cisplatin
15	62	Male	Never	Quit/5	Tonsil	2	2B	IVA	2	1	I	Unknown	> 1	2.2	Unknown	7000	33	Cisplatin
16	42	Male	Abuse	Quit/	BOT	2	2B	IVA	2	1	I	Unknown	1	3.3	Unknown	6784	32	Cisplatin
17	66	Female	Social	Quit/125	BOT	2	2C	IVA	2	2	II	Unknown	> 1	3.5	Unknown	7000	35	Cisplatin
18	54	Male	Social/Abuse	Never	BOT	3	2B	IVA	3	1	II	Unknown	> 1	4	Unknown	7000	35	Cisplatin
19	60	Male	Social	Quit/2	Tonsil	2	2B	IVA	2	1	I	Unknown	1	3.3	Positive	6996	33	Cisplatin
20	57	Male	Never	Never	BOT	4A	2C	IVA	4	2	III	Poor	> 1	2.8	Unknown	7000	35	Carboplatin Paclitaxel

Abbreviations: BOT = base of tongue; unknown = presumed oropharynx based on positive HPV testing on lymph node biopsy but no definitive primary.

Table 2
Clinical and Radiographic Treatment Responses.

Patient #	Time of PET/CT (days)	Clinical response	Interval scan/FNA?	Type of scan	Results of scan	Pre-CRT lymph node size on PET/CT	Post-CRT lymph node size on PET/CT	Pre-CRT FDG-activity (SUV) on PET/CT	Post-CRT FDG-activity (SUV) on PET/CT
1	87	Persistent right neck adenopathy	No	NA	NA	LN1: 4.3 × 4.0 (right level II) LN2: 1.5 × 1 (right level IIb)	LN1: 1.5 × 1.3 (decreased) LN2: 0.9 × 0.7 (decreased)	LN1: 19.9 LN2: 5.2	LN1: resolved LN2: 2.82 (decreased) LN1: 3.1 (decreased)
2	91	Unknown	Yes	CT	Decreased right neck adenopathy	LN1: 4.9 × 2.7 (right level III conglomerate) LN1: 3.5 × 2.7 cm (right level II)	LN1: 2.7 × 1.8 cm (decreased) LN1: 1.1 × 1.0 cm (decreased)	LN1: 9.2 LN1: 14.8	LN1: 3.1 (decreased) LN1: 3.1 (decreased)
3	88	Regression	Yes	CT	Decreased right neck adenopathy	LN1: 3.5 × 2.7 cm (right level II)	LN1: 1.1 × 1.0 cm (decreased)	LN1: 14.8	LN1: 3.1 (decreased)
4	87	Persistent right and left adenopathy	Yes	CT/FNA	Mixed CT response + FNA (right level II and left level III): pathology positive for SCC	LN1: 2.5 × 2.0 (right level II) LN2: 2.2 × 1.9 (left level III) LN1: 1.0 × 0.7 cm (right level IIA)	LN1: 2.0 × 1.5 (decreased) LN2: 1.1 × 0.8 (decreased) LN1: 0.8 × 0.8 (decreased) LN2: 1.1 × 0.8 (left level IIA) LN3: difficult to delineate (left level III)	LN1: 9.6 LN2: 14.7 LN1: 4.7	LN1: 2.1 (decreased) LN2: 1.9 (decreased) LN1: 3.3 (decreased) LN2: 6.2 (new) LN3: 6.6 (new)
5	70	Regression	No	NA	NA	LN1: 1.0 × 0.7 cm (right level IIA) LN2: not reported on prior imaging LN3: not reported on prior imaging	LN1: 1.1 × 0.8 (left level IIA) LN3: difficult to delineate (left level III)	LN1: 4.7	LN1: 3.3 (decreased) LN2: 6.2 (new) LN3: 6.6 (new)
6	91	Persistent left neck adenopathy	Yes	Ultrasound/FNA	FNA (left level II): pathology negative for SCC. Serial ultrasounds showed continued regression.	LN1: 3.8 × 3.0 (left level II) LN2: 1.1 × 0.8 (left level II) LN3: 1.5 × 1.0 (multiple right level II)	LN1: 1.2 × 2.5 (decreased) LN2: 0.9 × 0.4 (decreased) LN3: 1.2 × 0.6 (decreased)	LN1: 11.7 LN2: 4.0 LN3: 2.7	LN1: 4.2 (decreased) LN2: 3.2 (decreased) LN3: 3.4 (increased)
7	87	Persistent left neck adenopathy	Yes	CT	Necrotic left level II with interval decrease in enhancement and interval increase in necrosis, currently measuring 2.4 × 1.7 (previously 2.1 × 1.8). Decreased left neck adenopathy	LN1: 1.3 × 0.7 (left level III/II) LN2: 1.3 × 0.9 (right level IIA)	LN1: 1.1 × 0.5 (decreased) LN2: 1.0 × 0.8 (decreased)	LN1: 3.3 LN2: 3.6	LN1: 6.5 (increased) LN2: 5.7 (increased)
8	108	Regression	Yes	CT	Decreased left neck adenopathy	LN1: 2.0 × 1.4 cm (left level II) LN1: 2.8 × 2.7 (right level II) LN2: 1.5 × 0.8 (left level III)	LN1: 2.0 × 1.4 cm LN1: 1.7 × 0.9 (decreased) LN2: 1.5 × 0.8 (stable)	None LN1: 6.6 LN2: 3.7	None LN1: 3.2 (decreased) LN2: 2.9 (decreased)
9	95	Regression	Yes	MRI	Mixed response	LN1: 1.5 × 0.8 (left level III) LN1: 0.6 cm (right level II) LN1: 1.3 × 0.7 (right level V) Not appreciated	LN1: 0.6 cm (right level II) LN1: 1.1 × 0.6 (decreased) LN1: 0.9 × 0.8 (right level IV) LN2: 0.7 × 0.6 (right level IV) LN3: 0.8 × 0.4 (left level II) LN4: right sub-mandibular gland (level IB)	LN1: none LN1: 2.2 None	LN1: 2.8 (new) LN1: 2.6 (increased) LN1: 5.3 (new) LN2: 8.0 (new) LN3: 2.9 (new) LN4: 3.5 (new)
10	113	Regression	Yes	CT	Decreased left neck adenopathy	LN1: 3.4 × 2.8 (right level II) LN2: 1.9 × 1.4 (right level III) LN3: 2.1 × 1.9 (right level IV) LN4: not reported on prior imaging	LN1: 4.4 × 4.4 (increased) LN2: 1.9 × 1.5 (unchanged) LN3: 1.1 × 0.7 (decreased) LN4: 0.8 × 0.6 (left level II)	LN1: 5.2 LN2: 3.2 LN3: 2.6 LN4: none	LN1: 5.3 (increased) LN2: 4.0 (increased) LN3: 5.2 (increased) LN4: 4.8 (new)
11	130	Regression	Yes	CT	Decreased left neck adenopathy	LN1: 4.5 × 3.8 (right level II) LN1: 2.1 × 1.5 (left level III) LN2: 0.7 × 0.5 (right level III) LN1: (small aggregation of left-sided lymph nodes level II or upper II)	LN1: 1.6 × 1.1 (decreased) LN1: 1.1 × 1.0 (decreased) LN2: 0.7 × 0.5 (unchanged) LN1: 2.8 cm (longitudinal extent unchanged but bulk of nodal mass decreased)	LN1: 23 LN1: 6.5 LN2: none LN1: 3.6 (inferior end of the nodal mass)	LN1: resolved LN1: 4.1 (decreased) LN2: 3.1 (new) LN1: 3 (inferior end decreased) LN2: 2.4 (superior end decreased)
12	104	Regression	Yes	CT	Decreased right neck adenopathy	LN1: 3.4 × 2.8 (right level II) LN2: 1.9 × 1.4 (right level III) LN3: 2.1 × 1.9 (right level IV) LN4: not reported on prior imaging	LN1: 4.4 × 4.4 (increased) LN2: 1.9 × 1.5 (unchanged) LN3: 1.1 × 0.7 (decreased) LN4: 0.8 × 0.6 (left level II)	LN1: 5.2 LN2: 3.2 LN3: 2.6 LN4: none	LN1: 5.3 (increased) LN2: 4.0 (increased) LN3: 5.2 (increased) LN4: 4.8 (new)
13	29	Persistent right neck adenopathy	Yes	CT	Increased right neck adenopathy.	LN1: 3.4 × 2.8 (right level II) LN2: 1.9 × 1.4 (right level III) LN3: 2.1 × 1.9 (right level IV) LN4: not reported on prior imaging	LN1: 4.4 × 4.4 (increased) LN2: 1.9 × 1.5 (unchanged) LN3: 1.1 × 0.7 (decreased) LN4: 0.8 × 0.6 (left level II)	LN1: 5.2 LN2: 3.2 LN3: 2.6 LN4: none	LN1: 5.3 (increased) LN2: 4.0 (increased) LN3: 5.2 (increased) LN4: 4.8 (new)
14	103	Regression	No	NA	NA	LN1: 4.5 × 3.8 (right level II) LN1: 2.1 × 1.5 (left level III) LN2: 0.7 × 0.5 (right level III) LN1: (small aggregation of left-sided lymph nodes level II or upper II)	LN1: 1.6 × 1.1 (decreased) LN1: 1.1 × 1.0 (decreased) LN2: 0.7 × 0.5 (unchanged) LN1: 2.8 cm (longitudinal extent unchanged but bulk of nodal mass decreased)	LN1: 23 LN1: 6.5 LN2: none LN1: 3.6 (inferior end of the nodal mass)	LN1: resolved LN1: 4.1 (decreased) LN2: 3.1 (new) LN1: 3 (inferior end decreased) LN2: 2.4 (superior end decreased)
15	97	Regression	No	NA	NA	LN1: 2.1 × 1.5 (left level III) LN2: 0.7 × 0.5 (right level III) LN1: (small aggregation of left-sided lymph nodes level II or upper II)	LN1: 1.6 × 1.1 (decreased) LN1: 1.1 × 1.0 (decreased) LN2: 0.7 × 0.5 (unchanged) LN1: 2.8 cm (longitudinal extent unchanged but bulk of nodal mass decreased)	LN1: 23 LN1: 6.5 LN2: none LN1: 3.6 (inferior end of the nodal mass)	LN1: resolved LN1: 4.1 (decreased) LN2: 3.1 (new) LN1: 3 (inferior end decreased) LN2: 2.4 (superior end decreased)
16	85	Regression	No	NA	NA	LN1: 4.5 × 3.8 (right level II) LN1: 2.1 × 1.5 (left level III) LN2: 0.7 × 0.5 (right level III) LN1: (small aggregation of left-sided lymph nodes level II or upper II)	LN1: 1.6 × 1.1 (decreased) LN1: 1.1 × 1.0 (decreased) LN2: 0.7 × 0.5 (unchanged) LN1: 2.8 cm (longitudinal extent unchanged but bulk of nodal mass decreased)	LN1: 23 LN1: 6.5 LN2: none LN1: 3.6 (inferior end of the nodal mass)	LN1: resolved LN1: 4.1 (decreased) LN2: 3.1 (new) LN1: 3 (inferior end decreased) LN2: 2.4 (superior end decreased)
17	69	Persistent right neck adenopathy	No	NA	NA	LN1: 3.0 × 2.1 (right level II)	LN1: 1.9 × 1.6 (decreased)	LN1: 15.3	LN1: 2.7 (decreased)
18	82	Regression	Yes	CT	Partial response in left neck adenopathy	LN1: multiple large left-sided lymph nodes up to 4 cm in max diameter	LN1: not reported	LN1: 9.3–13.3	LN1: 2.2–2.6 (decreased)

(continued on next page)

Table 2 (continued)

Patient #	Time of PET/CT (days)	Clinical response	Interval scan/FNA?	Type of scan	Results of scan	Pre-CRT lymph node size on PET/CT	Post-CRT lymph node size on PET/CT	Pre-CRT FDG-activity (SUV) on PET/CT	Post-CRT FDG-activity (SUV) on PET/CT
19	98	Regression	No	NA	NA	LNI: 3.0 × 3.3 (left parapharyngeal space) LNI: 2.8 × 1.8 (left level IV)	LNI: 3.0 × 2.3 (decreased) LNI: up to 1.1 (decreased)	LNI: none	LNI: none
20	87	Regression	No	NA	NA			LNI: none	LNI: none

Abbreviations: CRT = chemoradiation; LN = lymph node; FNA = fine needle aspiration; NA = not applicable; SCC = squamous cell carcinoma.

requires further investigation, including the appropriate imaging modality and its timing. In this study, serial CT imaging was utilized for 8/8 patients that underwent observation after PET/CT. However, a repeat PET/CT allows for assessment of changes in FDG avidity and may be more appropriate.

4.2. Multidisciplinary and multimodal management

All management decisions in this series were discussed by a multidisciplinary tumor board consisting of head and neck surgeons, radiation oncologists, medical oncologists, radiologists, and pathologists. In truth, current follow-up algorithms do not universally include HPV status to guide decision-making. Therefore, individual clinicians may utilize general guidelines for head and neck cancer to select candidates for neck dissection. With multidisciplinary management, different types of clinicians can contribute their experience with this clinical problem and collaborate on an optimal strategy. The results of our institutional experience also promote the use of a multimodality approach since FNA was helpful in sparing several patients an unnecessary neck dissection. However, the accuracy of post-CRT FNA has been questioned given the difficulty in interpreting the viability of irradiated cancer cell and may not be a useful tool in managing these patients [16].

4.3. Equivocal versus positive responses

Post-therapy scans with residual nodal FDG-avidity are challenging to manage. Current algorithms guide decision-making by dividing responses into equivocal and positive. This case series illustrates that categorizing scans in this manner can be confusing in clinical practice. We found that these terms were not consistently used in radiographic reports or clinical documentation. Instead, radiologists reported changes in nodal size and metabolism and indicated that “residual disease could not be ruled out.” We also observed that patients with either increased post-therapy SUVs or SUV values above 5 did not have residual neck disease, demonstrating the practical difficulties in differentiating “equivocal” from “positive” responses. A standardized interpretation criterion with defined PET/CT parameters specific for HPV-associated disease, similar to the Hopkins system [17] for head and neck cancer or the Deauville system [18] for lymphoma, could help resolve the issues associated with qualitative assessment of PET/CT.

4.4. Patterns of FDG-avidity

Several patterns of FDG-avidity were observed from our institutional experience. Firstly, our results suggest that lymph nodes with new post-therapy FDG-uptake should be approached with caution. Three patients developed new FDG-uptake in neck levels previously uninvolved on pre-therapy scans; two of these patients underwent FNA, both with negative pathology, and one patient was observed with CT imaging. All three individuals were disease-free at most recent follow up. Similarly, Wang et al. found that 15% of patients in their study developed new false-positive FDG-avid nodes in previously uninvolved neck levels, none of which ultimately progressed [11]. On the other hand, the only patient with true pathologic residual neck disease also had residual primary site disease, suggesting that patients with uptake in both the primary and the neck may be appropriate for more aggressive surgical therapy. This finding is in accordance with published data from Bird et al.; in their study, 6/6 patients with residual FDG-uptake at both the primary site and neck had pathologically confirmed persistent disease [19].

4.5. Limitations of this study

There are several important limitations of this study. Retrospective review of data may lead to omission of data points that are not identified on a thorough chart review. Moreover, the small sample size and

Table 3
Management Decisions and Clinical Outcomes.

Patient ID	Management decision	Results of follow up imaging or pathology of FNA/neck dissection	Days from treatment end to last follow-up	Vital status at last follow-up	Disease status at last follow-up
1	Observe with CT	No change (persistent right level II adenopathy leading to nondiagnostic FNA and continued observation)	924	Alive	NED (stable right adenopathy)
2	Neck dissection (right neck levels I, III, IV, V)	Negative	398	Alive	Progression (liver metastases noted on 12-week PET/CT with subsequent progression)
3	Observe with CT	Regression	1001	Alive	NED
4	Neck dissection (right levels II, III, IV and left levels II, III, and IV)	Negative	1030	Alive	Progression (lung metastases on surveillance imaging)
5	FNA (right level II and left level III)	Negative (no evidence of SCC, but some monoclonal lymphocytes)	1029	Alive	NED
6	Observe with CT	Regression	1095	Alive	NED
7	FNA (right level II and left level III)	Negative	970	Alive	NED
8	Observe with CT	Regression	1604	Alive	NED
9	Neck dissection (right levels II, III, IV and left levels II and III)	Negative	1743	Alive	NED
10	FNA (right level III)	Negative	1562	Alive	NED
11	Observe with CT	Regression	2027	Alive	NED (stable left adenopathy)
12	FNA (right levels II, IV and left level II)	Negative	1790	Alive	NED
13	Neck dissection (right levels II, III, IV, & V)	Negative	1173	Alive	NED
14	Observe with CT	Larger (leading to nondiagnostic FNA and regression on subsequent imaging studies)	763	Alive	NED
15	Observe with CT	Regression	1000	Alive	NED
16	Neck dissection (left level II and III)	Negative	924	Alive	NED
17	FNA (right level II)	Positive	242	Alive	Pending follow-up imaging ^a
18	FNA (left level II & III)	Negative	761	Alive	NED
19	Neck dissection (left levels II, III & IV)	Negative	1785	Alive	NED
20	Observe with CT	Regression	374	Alive	NED

Abbreviations: CT = cat scan; FNA = fine needle aspiration; BOT = base of tongue; TORS = transoral robotic assisted surgery; SCC = squamous cell carcinoma.

^a This patient underwent right modified neck dissection and BOT biopsy given positive FNA and PET/CT. Pathology was positive for residual primary and neck disease. The patient was observed at her request until she underwent TORS and neck dissection for progression.

qualitative nature of this study limit our ability to generate definitive conclusions. However, locoregional treatment failure after CRT in HPV-associated OPSCC is an uncommon event. Therefore, future studies should use multicenter designs to appropriately power prospective studies of new surveillance protocols. Finally, there was a slight variation in the protocols for treatment among different radiation oncologists in our institution as well as various locations for PET/CT acquisition and interpretation since we are a multi-site regional health system. However, our series represents what occurs in common clinical practice and not in a tightly-controlled academic environment.

5. Conclusion

This institutional experience supports the notion of a high threshold for neck dissection in patients with HPV-associated OPSCC; only 1 of 20 patients with suspicious PET/CT findings had residual disease in the neck. Moreover, these patients should be managed by a multi-disciplinary tumor board as current algorithms do not universally include HPV status. Finally, the use of restaging PET/CT to guide management of the neck can be improved with changes in terminology and consideration of FDG-avidity at the primary site and on pre-therapy scans.

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