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Pitfalls of post-treatment PET after de-intensified chemoradiotherapy for HPV-associated oropharynx cancer: Secondary analysis of a phase 2 trial

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ABSTRACT

Objectives: We evaluated patterns of nodal response and positive predictive value (PPV) of 3 month post-treatment PET in patients with HPV-associated oropharyngeal cancer treated on a multi-institutional de-intensification trial.

Materials and methods: Eligibility criteria included: (1) T0-3, N0-2c, M0, (2) HPV+/p16+ oropharyngeal squamous cell carcinoma, and (3) ≤10 pack-years smoking or ≤30 pack-years and abstinent ≥5 years. Patients received 60 Gy radiation alone (T0-2, N0-1) or with concurrent weekly cisplatin 30 mg/m^2 and surveillance PET three months post-radiation. Nodal responses were categorized as complete (CR), equivocal (ER), or incomplete (IR) using both local and central radiographic review. A "true positive" was ER/IR with clinical/radiographic progression or positive pathology.

Results: 79 node-positive pts (84% N2) were analyzed. Distribution of nodal CR, ER, and IR was 44 (56%), 27 (34%), and 8 (10%), respectively. 29 (37%) had ER/IR in pre-treatment node-positive neck levels, whereas 14 (18%) had ER/IR in pre-treatment node-negative levels. Of patients with ER/IR, 5 were observed clinically, 19 received repeat imaging, and 11 received either biopsy (1) or neck dissection (10). The PPV was 9% for ER/IR and 13% for IR, with 3 patients found to have persistent disease on neck dissection. There was no difference in nodal relapse rate in patients with nodal CR vs. nodal ER/IR.

Conclusion: Post-treatment PET may not accurately predict the presence of persistent disease in patients with favorable-risk oropharynx cancer. These results support close surveillance rather than surgical evaluation in most favorable-risk patients.

Introduction

The management of the neck after definitive chemoradiation (CRT) for oropharynx cancer has evolved from planned neck dissection for all patients towards imaging-based surveillance, reserving neck dissection only for those with concern for residual disease. The safety of this approach was recently confirmed by Mehanna et al. in a large randomized trial showing equivalent survival, better quality of life [1], and higher cost-effectiveness [2] in patients with N2 disease randomized to surveillance PET vs. neck dissection. However, there are no consistent standards regarding who to select for neck dissection based on these post-treatment PET scans.

The negative predictive value (NPV) for post-radiation PET has consistently been shown to be excellent [3–10]. However, in patients with HPV-associated oropharyngeal cancer and/or other low risk features, the positive predictive value (PPV) of post-treatment PET is

Abbreviations: CRT, chemoradiation; NPV, negative predictive value; PPV, positive predictive value; pCR, pathologic complete response; CR, complete response; ER, equivocal response; IR, incomplete response

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generally lower [3,5,11,12]. For example, Vainshtein et al. reported that the PPV of equivocal or incomplete response on post-treatment PET was only 11% [5]. In the Mehanna et al. trial, 24% of patients had equivocal or incomplete responses, and were required to undergo a neck dissection [1]. Over 70% of the patients enrolled on that trial had HPV-associated disease, and performing neck dissections for all such patients with equivocal responses may cause unnecessary morbidity in those found to have pathologic complete response (pCR).

For the last five years, patients in our department with HPV-associated squamous cell carcinoma of the oropharynx have been eligible for several sequential prospective de-intensification trials. In the first, we reported a high rate of pCR in patients receiving de-intensified CRT and protocol-specified post-treatment neck dissection [13]. In our second trial, patients instead receive protocol-specified PET-CT after de-intensified CRT. We herein provide one of the first reports of PET nodal response in patients treated with de-intensified CRT. We analyzed patterns of PET response on a detailed neck level-by-level basis and hypothesized that the PPV of equivocal or incomplete nodal response is low in these favorable-risk patients selected for de-intensified therapy.

Patients and methods

Study design

This is a post hoc, secondary analysis of a prospective multi-institutional IRB-approved single arm Phase 2 trial (ClinicalTrials.gov NCT02281955) enrolling patients at the University of North Carolina and University of Florida. Eligible patients had untreated HPV or p16-positive T0-3, N0-2c, M0 squamous cell carcinoma of the oropharynx or from an unknown primary head and neck site, ≤10 pack year smoking history or ≤30 pack years but abstinent for ≥5 years, ECOG performance status 0–1, and ≥18 years of age. Informed and witnessed consent was obtained from all patients.

Treatment and planned radiologic evaluation

All patients were treated with protocol-specified de-intensified intensity modulated radiation therapy using dose painting to a total of 60 Gy (2 Gy per fraction) to "high risk" areas of gross disease and 54 Gy (1.8 Gy per fraction) to "standard risk" regions considered at risk for subclinical disease. Radiation was delivered over six weeks, five days a week. Patients received concurrent weekly cisplatin 30 mg/m^2 or cetuximab 250 mg/m^2 (without a loading dose). Chemotherapy was omitted in patients with T0-2, N0-1 disease. Three months after radiation, patients received a protocol-specified PET-CT or PET-MRI along with fiberoptic laryngoscopy and clinical examination. Patients with a "positive" PET received a biopsy or surgical evaluation. The decision regarding what constituted a positive PET warranting surgery was made based on the judgment of the treating physician, radiologist, and discussion at a multidisciplinary tumor board. Patients received clinical follow-up every 2–3 months thereafter for the first two years and further imaging studies were optional.

Assessment of post-treatment PET response

The primary analyzed outcome was the rate and PPV of nodal equivocal and/or incomplete response on three month post-treatment PET in patients with node-positive disease. Nodal responses were categorized as complete (CR), equivocal (ER), or incomplete (IR) per the Mehanna et al. trial definitions, which defined IR as "intense FDG uptake at 12 weeks after chemoradiotherapy, with or without enlarged lymph nodes," ER as "mild or no FDG uptake in enlarged nodes or mild FDG uptake in normal-sized nodes," and all others as CR [1]. The location of all equivocal or incompletely responding nodes was recorded (see assessment of pre-treatment nodal status section below). The response assessment was done via two methods:

1. *Local review*: The local review was based on radiology reports associated with each three month post-treatment PET, which were read by a total of 16 different trained radiologists/nuclear medicine physicians. For the local review, the primary investigator (KW) assigned the response based on the Mehanna et al. criteria that best matched the radiology report.
2. *Central review*: For central review, all radiologic studies were acquired and uploaded into MIM Vista (MIM Software Inc, Cleveland, OH). Central review was performed by a single physician with 20 years of experience and board certification in Radiology, PET, and Nuclear Medicine (TZW). The central reviewer was blinded to local review and interpreted each PET scan, assigning responses based on the Mehanna et al. criteria.

Assessment of pre-treatment nodal status

Pre-treatment nodal status was prospectively recorded. Nodal levels were divided into four distinct categories based on the presence of pre-treatment disease, laterality of the node-positive neck(s), and receipt of elective nodal RT:

1. Pre-treatment node-positive levels (in a node-positive neck, receiving elective nodal RT) (Example, Fig. 1A, C).
2. Pre-treatment node-negative levels (in a node-positive neck, receiving elective nodal RT).
3. Pre-treatment node-negative levels (in a node-negative neck, receiving elective nodal RT).
4. Pre-treatment node-negative levels (in a node-negative neck, *not* receiving elective nodal RT) (Example, Fig. 1B).

Assessment of PPV

Patients were included in the PPV analysis if they had at least 6 months of follow-up *after* three month post-treatment PET (≥9 months total follow-up). The PPV was reported independently for patients with IR and for patients with either ER or IR (ER/IR). Patients were counted as "true positives" if they had pathologic confirmation of disease persistence or evidence of clinical or radiographic progression within 6 months of three month post-treatment PET.

Statistical analysis

In addition to the PPV analysis, the Kaplan-Meier method was used to analyze freedom from nodal disease persistence or relapse, with time calculated from the initiation of radiotherapy. Agreement between central and local review was reported using the Cohen kappa. Statistical analyses were performed using SPSS (Armonk, NY).

Results

From September 2014 to November 2016, 101 patients were enrolled. 87 patients completing de-intensified CRT and reaching three-month post-CRT surveillance PET were included in this analysis. Median follow-up was 21 months (range, 10–36 months). Patient characteristics are shown in Table 1. Post-CRT surveillance PET was a PET-CT in 81 patients and PET-MRI in 6 patients. 59 patients (68%) had a pre-treatment PET. Fig. 2 summarizes patient enrollment and the overall results of the nodal response and PPV analyses. Results of both local and central PET review are summarized inTable 2.

Nodal response patterns

79 patients (91%) had node-positive disease and were included in the nodal response analysis. Of these, 84% had N2 disease. Based on local review, distribution of nodal CR, ER, and IR was 44 (56%), 27 (34%), and 8 (10%), respectively, with an overall 44% rate of nodal

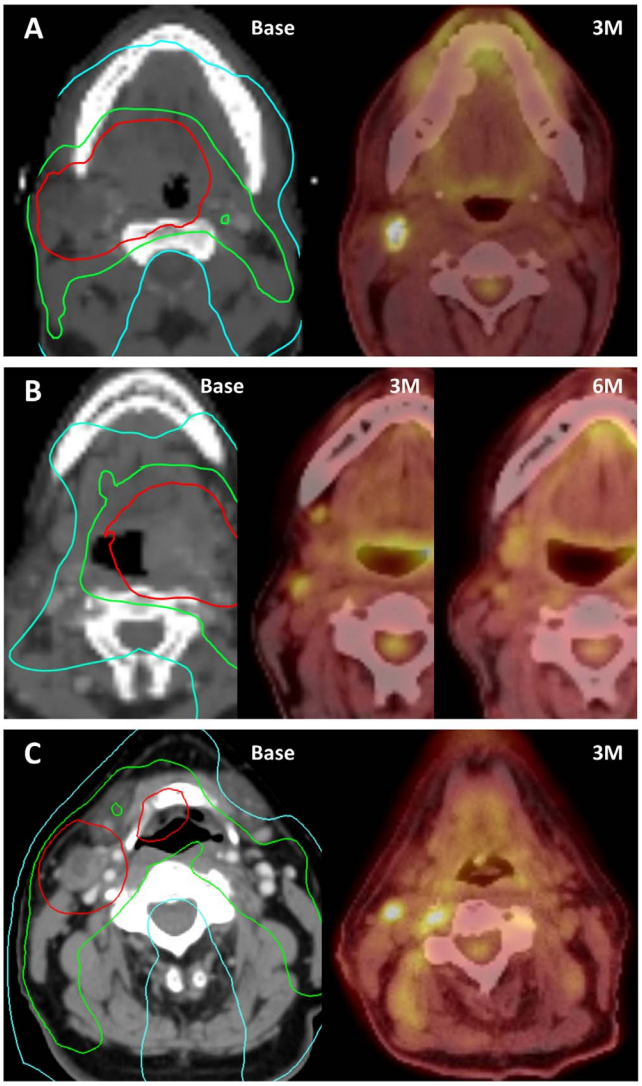

Fig. 1. Example of equivocal/incomplete PET nodal response in three patients: A. False-positive incomplete response in a pre-treatment node-positive level. This patient underwent neck dissection showing complete response, B. False-positive equivocal response in a contralateral node-negative neck not receiving elective RT. Repeat PET showed resolution of suspicious findings, and C: True-positive incomplete response in a pre-treatment node-positive level. Neck dissection showed extensive residual disease. The red, green, and blue lines represent the 60 Gy, 54 Gy, and 30 Gy isodose curves, respectively. Abbreviations: Base, baseline planning scan; 3M, three month post-treatment PET; 6M: six month post-treatment PET.

ER/IR. Central review showed similar results, where the distribution of nodal CR, ER, and IR was 41 (52%), 28 (35%), and 10 (13%), respectively, with an overall 48% rate of nodal ER/IR. Agreement between local and central ascertainment of nodal ER/IR was substantial, with a kappa of 0.72.

Based on local review, 29 patients (37%) had ER/IR in pre-treatment node-positive levels and 14 patients (18%) had new equivocal nodes in pre-treatment node-negative levels. All incomplete responses (IR) occurred in pre-treatment node-positive levels. 3 patients (4%) had new equivocal nodes in pre-treatment node-negative levels in a node-positive neck, 8 patients (10%) had new equivocal nodes in a node-negative neck that received elective nodal RT, and 4 patients (5%) had new equivocal nodes in a node-negative neck that did not receive elective nodal RT. Findings were similar with central PET review, where 44% and 13% of patients had ER/IR in pre-treatment node-positive levels and pre-treatment node-negative levels, respectively.

Table 1
Clinical Characteristics.

Characteristics	*N* = 87	
Median age (range)	62 (37–87)	
Sex		
Male	73	84%
Female	14	16%
Primary tumor site		
Tonsil	44	51%
Base of Tongue	38	44%
Unknown	5	6%
Tobacco use		
Never	44	51%
≤10 pack years	30	34%
> 10 pack years	13	15%
T-Stage		
T0	5	6%
T1	26	30%
T2	47	54%
T3	9	10%
N-stage		
N0	8	9%
N1	13	15%
N2a	3	3%
N2b	46	53%
N2c	17	20%
Elective nodal radiation		
Unilateral	12	14%
Bilateral	75	86%
Chemotherapy		
None	15	17%
Cisplatin	64	74%
Cetuximab	8	9%

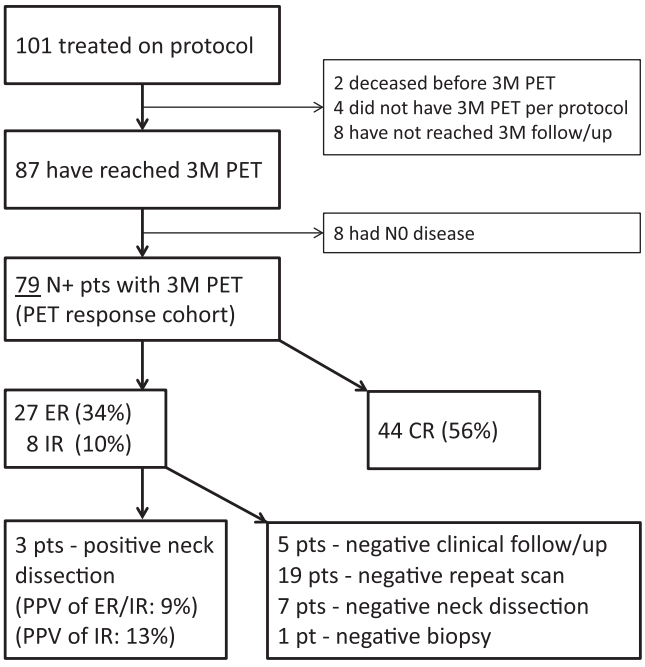

Fig. 2. Summary of enrollment and results for the nodal response and PPV analysis. Abbreviations: 3M, three month post-treatment; ER, equivocal response; IR, incomplete response; CR, complete response.

Follow-up and PPV of nodal ER/IR

All patients with nodal ER or IR on post-treatment PET have had adequate follow-up, including 5 patients followed clinically, 19 patients receiving repeat imaging, and 11 patients receiving biopsy (1 patient)

Table 2a
Patterns and PPV of nodal response (Local review).

Pre-treatment status	ER *or* IR	IR	PPV (ER *or* IR)	PPV (IR)
All patients (N = 79)	35 (44%)	8 (10%)	9% (3/35)	13% (1/8)
Pre-treatment node-positive levels	29 (37%)	8 (10%)	10% (3/29)	13% (1/8)
Pre-treatment node-negative levels	14 (18%)	0 (0%)	0% (0/14)	
Node-pos. neck	3 (4%)	0 (0%)	0% (0/3)	
Node-neg. neck receiving RT	8 (10%	0 (0%)	0% (0/8)	
Node-neg. neck not receiving RT	4 (5%)	0 (0%)	0% (0/4)	

Table 2b
Patterns and PPV of nodal response (Central review).

Pre-treatment status	ER *or* IR	IR	PPV (ER *or* IR)	PPV (IR)
All patients (N = 79)	38 (48%)	10 (13%)	8% (3/38)	20% (2/10)
Pre-treatment node-positive levels	35 (44%)	10 (13%)	9% (3/35)	20% (2/10)
Pre-treatment node-negative levels	10 (13%)	0 (0%)	0% (0/10)	
Node-pos. neck	2 (3%)	0 (0%)	0% (0/2)	
Node-neg. neck receiving RT	6 (8%)	0 (0%)	0% (0/6)	
Node-neg. neck not receiving RT	2 (3%)	0 (0%)	0% (0/2)	

or neck dissection (10 patients). The PPV of a nodal ER/IR was 9% (3/35) based on local review and 8% (3/38) based on central review, with 3 patients found to have persistent disease on neck dissection. Eight patients had pathologic complete response on surgical evaluation and the remaining patients with ER/IR had resolution of concerning findings on repeat scan or negative physical exam on clinical follow-up 6 months after PET. The PPV of a nodal IR was only slightly higher than ER/IR: 13% (1/8) based on local review and 20% (2/10) based on central review. The PPV of a nodal ER/IR in a pre-treatment node-positive level was 10% (3/29), vs. 0% (0/14) in a pre-treatment node-negative level (based on local review).

Freedom from nodal disease persistence/relapse

Freedom from nodal disease persistence or relapse is shown in Fig. 3. There was no difference in freedom from nodal disease persistence/relapse in patients who did vs. did not have a PET nodal CR (log rank P = 0.47). With a 21 month median follow-up, there were three patients with persistent nodal disease (all had PET nodal ER/IR) and two patients with late nodal relapse (both had PET nodal CR).

Primary site analysis

82 patients (94%) had evaluable primary site tumors. The distribution of primary site CR, ER, and IR based on both local and central review was 74 (90%), 8 (10%), and 0 (0%), respectively. Agreement between local and central ascertainment of primary site ER/IR was moderate, with a kappa of 0.58. In the 8 patients with a primary site ER/IR based on local review, the PPV was 13%, with 1 patient having biopsy-confirmed disease persistence, 4 patients with negative clinical follow-up, and 3 patients with a negative repeat scan.

Discussion

We analyzed patterns of PET nodal response in a homogeneous

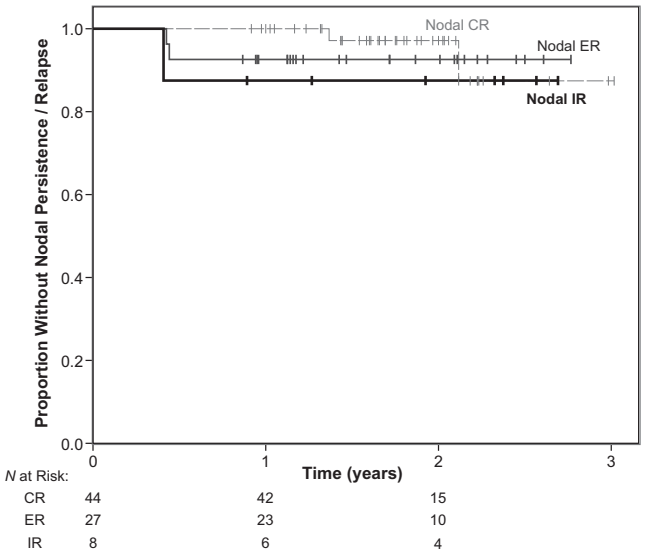

Fig. 3. Freedom from nodal disease persistence/relapse in node-positive patients in patients with nodal complete response (light gray dashed line), nodal equivocal response (dark gray solid line), and nodal incomplete response (black solid line).

population of patients with HPV-associated oropharynx cancer treated with de-intensified chemoradiation on a prospective multi-institutional Phase 2 trial. This is the first study to our knowledge that analyzes the accuracy of post-treatment PET in patients treated with de-intensified CRT, and could aid clinicians in the follow-up of these patients as de-intensification efforts increase. Based on both local and central review of PET scans, equivocal and incomplete nodal responses were very common. These findings on initial post-treatment PET were seen in both pre-treatment node-positive and node-negative neck levels, but usually resolved with subsequent follow-up or had negative pathologic evaluations. These results support continued surveillance (eg, with a repeat scan), rather than surgical evaluation in most favorable-risk patients fitting this scenario.

Over several decades, post-radiation imaging has become preferred over planned neck dissection for most patients. At the same time, outcomes have improved with definitive radiotherapy, likely due to (1) Stage migration due to better imaging [14], (2) Concurrent chemotherapy [15], and (3) Increase in HPV-associated oropharynx cancer [16]. Furthermore, highly sensitive PET scans are increasingly used for both staging and response assessment, but are susceptible to false-positives from physiologic, reactive, and/or inflammatory FDG uptake [17]. Post-radiation PET scans have therefore been shown to reliably exclude patients who do not have disease (good NPV), but not necessarily accurately select the right patients to take to neck dissection (poor PPV). The PPV of a test is directly related to the pre-test probability, and the pre-test probability of residual disease in a radiographically staged, favorable risk HPV-associated oropharynx cancer patient who received chemoradiation is likely to be low [18]. Thus, performing neck dissections on all such patients with equivocal PET responses may lead to overtreatment and unnecessary surgical morbidity.

In this study, we categorized nodal responses on a neck level-by-level basis per the definitions published by Mehanna et al. The rate of ER/IR in pre-treatment node-positive levels was around 40%, but most of these nodes resolved with subsequent follow-up. In the 11 patients who had pathologic evaluation (10 of whom had a neck dissection), only 3 were found to have residual disease. Furthermore, the PPV was poor for both ER/IR (9%) and IR alone (13%). Interestingly, around 15% of patients developed new false-positive PET-avid nodes in previously-uninvolved levels (including in the node-negative contralateral neck). *None* of these "new" nodes progressed, suggesting that new FDG

avidity in this favorable risk population is physiologic/reactive in nature.

Though we therefore advocate close observation rather than neck dissection in most patients with HPV-associated oropharynx cancer, the decision to operate on patients with equivocal responses should always consider individual clinical and patient factors that affect their probability of residual disease, in addition to radiographic appearance. It is important to note that patients in this study were carefully selected to meet inclusion criteria for de-intensified treatment, and did not have risk factors such as T4 or N3 disease or ongoing cigarette smoking. Interestingly, two of three patients in this study with pathologic evidence of persistent disease were in retrospect, higher risk. One patient was on an immunosuppressant, leading to the exclusion of other patients with rheumatologic diseases from enrollment on the de-intensification study [19]. Another patient (Fig. 1C) barely met inclusion criteria with both a 30 pack year cigarette smoking history and ongoing cigar smoking at diagnosis, and also completed only 4 of 6 planned cycles of chemotherapy.

In addition to pre-treatment risk, the PPV of a post-treatment PET is also dependent on the radiographic threshold accepted as a "positive" test. There is substantial variation in what is considered a "positive" PET or what constitutes a "true positive" for PPV calculation (Table 3). Generally, the studies using more stringent definitions of a "positive PET" showed greater PPV [4,6], whereas lower PPV was seen in studies that included equivocal findings as "positives" such as those of Vainshtein et al. and Moeller et al. [3,5] Consistent with our results the PPV in patients with favorable risk characteristics such as HPV-association appear to be lower in other studies as well [3,5]. For example, Moeller et al. found that patients deemed "high risk" (HPV-negative, non-oropharynx primary, or history of tobacco use) had a nodal PPV of 75%, vs. only 14% for "low risk" patients (HPV-positive or oropharynx primary and no tobacco use) [3].

We chose to use the Mehanna et al. definition of equivocal and incomplete PET response because of its simplicity, ease of application in the community, and to capture a patient population that may have been required to undergo a neck dissection in that trial [1]. However, there are other evolving systems for evaluating PET responses to head and neck cancer treatment, such as the Hopkins criteria [20] and the recently proposed NI-RADS criteria [21,22]. These efforts will hopefully facilitate the comparison of studies between different institutions in the future. It is also possible that the PPV of PET scans could be improved by incorporating other imaging (eg, MRI) characteristics or through other advanced techniques [23]. Nonetheless, given the results of this and other studies it may be reasonable to also consider pre-treatment risk (and thereby probability of residual disease) in addition to radiologic characteristics when categorizing response on post-treatment PET scans.

Another question raised is whether post-radiation PET scans could be omitted altogether or replaced with CT alone. On one hand, the high false positive rate in favorable risk patients can lead to unnecessary morbidity and patient anxiety. On the other hand, patients with negative scans perhaps derive psychologic benefit from the "good news". Further, there are still *some* true positives, and it is also possible that early detection of oligometastatic disease could afford an opportunity for salvage treatment. For instance, four patients in this study had distant findings on surveillance PET. Three of these patients were diagnosed with distant metastatic disease, two of whom had oligometastatic disease and received salvage radiation. The drawbacks and benefits of surveillance imaging in these (and other cancer) patients is clearly a topic that warrants further investigation.

Strengths of this study include the homogeneous patient population, treatment on a prospective trial, and systematic analysis of nodal response by neck level with both local and central radiographic review. There are however several limitations. First, the use of nonstandard de-intensified chemoradiation could limit the applicability of this study to patients treated with conventional doses. However, despite the use of less aggressive treatment very few patients developed failures and thus the analysis is valid. Second, radiographic interpretation of PET is subjective and there may be variation in scan quality at different treatment centers. However, variability in PET scan quality and interpretation is another argument for caution when making clinical decisions based on post-treatment imaging in this favorable risk population. Finally, our definition of "true positive" was limited to only failures within six months of surveillance PET, and it is possible that with longer follow-up patients would develop recurrences. However, this definition is used by others, and with a median follow-up of 21 months there was no difference in freedom from nodal disease persistence/relapse based on PET response, with only two patients developing late nodal relapse.

In conclusion, there was a high rate of equivocal findings on post-treatment PET, including new nodes in previously-negative neck levels. In this favorable risk patient population, almost all of these suspicious findings were benign. These data highlight the oft-confusing nature of post-treatment PET and support close observation for most favorable risk patients in order to avoid unnecessary treatment-related morbidity and better select those who may benefit from surgery.

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Table 3
Studies analyzing the nodal predictive value of first post-RT PET in patients with HPV-associated oropharynx cancer.

Study	n	% HPV or p16 +	Rate of "positive" PET	PPV	Definition of "positive "PET"	Definition of "true positive" PET for PPV analysis
Current study[a]	79	100%	44% (ER/IR) 10% (IR)	9% (ER/IR) 13% (IR)	Per Mehanna et al.: Enlarged nodes, mild uptake (ER), and/or intense uptake (IR)	Nodal pathology or nodal failure within 6 months after PET
Vainshtein et al. [5]	98	100%	18%	11%	Near complete response or incomplete response	Any nodal failure
Chan et al. [11]	67	100%	n/a	22%	Nodal SUVmax ≥ 2.0 *and* < 70% reduction in short-axis diameter	Nodal pathology or any isolated nodal failure
Koshkareva et al. [4] (primary and nodal)	61	82%	21%	84%	Moderate or increased uptake	Any failure within 2 years
Sjovall et al. [6][b]	105	73%	20%	56%	"Clearly hypermetabolic" with anatomic correlate	Nodal pathology
Hitchcock et al. [12]	50	64%	10%	0%	Positive or equivocal	Nodal pathology
Moeller et al. [3][b]	75	≥27%	28%	27%	Nodal SUVmax ≥ 2.8	Nodal pathology or locoregional failure within 6 months

Abbreviations: HPV, human papilloma virus; PPV, positive predictive value; ER, equivocal response; IR, incomplete response; SUV, standardized uptake value.

[a] Patients treated in our study were carefully selected and received de-intensified treatment.

[b] 10–30% of patients in these studies had non-oropharynx primary tumors.

Conflict of interest

The authors declare no conflicts of interest.

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