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Reliability of Post-Chemoradiotherapy F-18-FDG PET/CT for Prediction of Locoregional Failure in Human Papillomavirus-Associated Oropharyngeal Cancer

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Abstract

Objectives—Although widely adopted, the accuracy of post-chemoradiotherapy (CRT) ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) for predicting locoregional failure (LRF) in human papillomavirus-related (HPV+) oropharyngeal

cancer (OPC) remains poorly characterized. We assessed the predictive value of 3-month PET/CT response for LRF in this population.

Materials and Methods—101 consecutive patients with stage III-IV HPV+ OPC who underwent definitive CRT with pre-treatment and 3-month post-CRT PET/CT at our institution from 3/2005–3/2011 were included. 3-month PET/CT response was re-classified as complete-response (CR), near-CR, or incomplete-response (<CR) for each the primary site and neck. Accuracy of 3-month PET/CT for predicting local failure (LF) and regional failure (RF) was analyzed.

Results—Among 98 patients with an evaluable primary tumor, LF occurred in 2/67 patients with CR, 0/20 with near-CR, and 1/11 with <CR on 3-month PET/CT. Of 98 node-positive patients, RF occurred in 6/80 with CR, 2/9 with near-CR, and 0/7 with <CR in the neck at 3 months. Sensitivity and positive predictive value (PPV) of 3-month PET/CT response for LF and RF were low (0–33%), despite a high negative predictive value (NPV) (91–98%). SUV_{max} thresholds or % change did not improve the accuracy of 3-month PET/CT. Use of surveillance PET/CT after 3 months in 67 patients accurately detected both LF (96%) and RF (97%).

Conclusions—In the largest study to-date of PET/CT response assessment in HPV+ OPC, 3-month PET/CT response demonstrated high NPV for LRF, though with disappointing sensitivity and PPV. Subsequent PET/CT surveillance showed potential utility for early detection of LRFs.

Keywords

Human papillomavirus; chemoradiotherapy; PET/CT; metabolic response; PET surveillance

Introduction

The increasing use of ^{18} fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) after chemoradiotherapy (CRT) has significantly impacted management of the node-positive neck in patients with head and neck squamous cell carcinoma (HNSCC) in recent years ⁽¹⁾. Historically, due to the low sensitivity of clinical examination for detecting residual disease in patients with initial N2-3 neck disease, planned adjuvant neck dissection after CRT had been considered the standard of care for such patients, with a survival benefit demonstrated even in patients with a clinical complete response (CR) after CRT ⁽²⁾. Similar data supported the standard role of consolidative neck dissection in patients with residual lymphadenopathy after CRT ^(3, 4). More recently, the adoption of PET/CT for evaluation of the neck after CRT has yielded low rates of isolated neck recurrence in the observed necks of patients achieving a metabolic CR, potentially obviating the need for neck dissection in such patients ^(5–10). The high negative predictive value (NPV) of PET/CT in this setting has led to its acceptance as the primary imaging modality to guide surgical management of the neck in node-positive HNSCC after CRT ⁽¹¹⁾.

Although the present evidence to support PET/CT to evaluate CRT response in HNSCC is compelling, it is based on mixed retrospective cohorts. Specific data on the use of PET/CT in human papillomavirus (HPV)-related (+) oropharynx cancer (OPC) is particularly lacking. Moreover, the few published studies in this patient population have reported contradictory findings ^(9, 12). One prospective study which compared CT with PET/CT at 8

weeks after CRT concluded that PET/CT was less accurate than CT for assessing treatment response in a subset analysis of 61 patients with low-risk HNSCC, predominantly composed of patients with HPV+ OPC⁽⁹⁾. These findings contrast with a study of 67 HPV+ OPC patients, which found that PET/CT at 12 weeks after CRT performed superiorly to CT alone⁽¹²⁾. In light of current efforts to reduce the burden of multimodality therapy for this growing favorable prognosis patient population^(13, 14), precise characterization of the reliability of PET/CT in guiding omission of neck dissection and primary site surgery after CRT remains necessary. We therefore sought to characterize the accuracy of PET/CT response at 3 months after CRT for predicting locoregional failure and guiding salvage surgical therapy in patients with HPV+ OPC.

Methods and Materials

Patients

Under an Institutional Review Board-approved protocol, the records of 183 consecutive patients with previously untreated, histologically confirmed, AJCC stage III or IV oropharyngeal SCC without distant metastases who completed definitive radiotherapy with concomitant chemotherapy at our institution between 3/2005–3/2011 were reviewed. HPV detection for all patients was performed on prospectively collected primary tumor tissue using either multiplex polymerase chain reaction (PCR) MassArray following DNA extraction from a core tissue sample as previously described⁽¹⁵⁾, or in-situ hybridization (ISH) for high-risk HPV using the INFORM HPV ISH assay (Ventana Medical Systems Inc., Tucson, AZ) with a cocktail directed against a subset of high-risk HPV genotypes (HPV 16, 18, 33, 35, 39, 45, 51, 52, 56, and 66) on paraffin-embedded tissue. Patients eligible for the present analysis included those with histologically confirmed HPV positive oropharyngeal cancers who underwent PET/CT prior to chemoradiation initiation and within 6 months of completion of chemoradiation. After exclusion patients not meeting eligibility criteria, 101 patients were included in the present analysis.

Treatment

After staging by clinical examination, direct laryngoscopy, and FDG-PET with fused CT, patients underwent CT-simulation in a 5-point thermoplastic mask. All patients were treated with intensity-modulated radiation therapy (IMRT) with concurrent chemotherapy. IMRT prescription doses were 70 Gy to the gross tumor volumes (GTVs) and 56–64 Gy to the at risk clinical target volumes (CTVs). GTV and CTVs were uniformly expanded 3–5 mm to create planning target volumes. IMRT was delivered over 35 daily fractions, with concurrent chemotherapy consisting of weekly carboplatin (AUC 1) and paclitaxel (30 mg/m²) in the majority of patients (98%) and cisplatin-based regimens in the remainder (2%). No patients received induction chemotherapy or underwent pre-radiotherapy neck dissection.

Post-Treatment Surveillance and Surgical Management

All patients were routinely seen in follow-up in the Departments of Radiation Oncology, Otolaryngology, and Hematology/Oncology, with clinical examination performed every 6–12 weeks and post-treatment PET/CT imaging at 3 months. Post-chemoradiotherapy neck management evolved over the study period; in earlier years, patients with advanced nodal

disease at presentation often underwent planned neck dissection, while in later years patients were clinically and radiographically observed, with neck dissection performed only for clinical or PET-based suspicion of residual disease after chemoradiation. Nine (9%) patients in the present cohort underwent consolidative neck dissection as part of their initial course of therapy (i.e. within 6 months within completion of chemoradiation) due to clinical, radiographic, or scintigraphic suspicion for residual disease. Additional PET/CT surveillance, defined as PET/CT scans obtained in the absence of any clinical or radiographic suspicion of recurrence, was performed in 67 (66%) patients.

PET/CT Protocol

FDG-PET/CT was performed prior to treatment initiation and approximately 3 months after completion of chemoradiation for all patients. Patients fasted for >4–6 hours and had glucose levels <250 mg/dL prior to undergoing PET/CT. Sixty minutes following intravenous administration of 300 MBq (8 mCi) of FDG, sequential PET and CT imaging was performed on an integrated PET/CT scanner (Siemens Biograph T6; Siemens Medical Solutions, Hoffman Estates, IL). Helical CT from skull vertex to mid-thigh was performed (CareDose 4D, reference mAs 50, kV 120, 5 mm collimation, pitch 1.0), followed by whole body PET with multiple overlapping bed positions from skull vertex to mid-thigh. Immediately thereafter, with the patient remaining still, 100 ml of non-ionic radioopaque contrast was administered intravenously and dedicated head and neck helical CT from skull base to thoracic inlet was performed (CareDose 4D, reference mAs 150, kV 120, 2 mm collimation, pitch 0.8). Attenuation-corrected FDG-PET tomographic images were reconstructed (TrueD, iterative reconstruction 3 orders, 24 subsets, Gaussian filter 5.0, zoom 1.0) and co-registered to both the whole body and the contrast-enhanced head and neck CT. Per our standard institutional practice, all PET/CT studies were interpreted prospectively by two readers (one head and neck radiologist and one nuclear medicine physician) providing a single read per study, using software with fusion capability (MedImage; MedView Pty, Canton, MI, USA). A region of interest was defined for each primary tumor and for cervical lymph nodes (LNs) displaying FDG uptake above background using the corresponding CT images for anatomic orientation. The maximum standardized uptake values (SUV_{max}) for the primary tumor and for the involved LN with the highest SUV_{max} on the pre-treatment and 3-month PET/CT were retrospectively recorded.

PET/CT and CT Response Assessment

Each prospectively issued 3-month PET/CT interpretation was retrospectively reviewed and re-classified as either complete response (CR) or incomplete response (<CR); equivocal interpretations were classified as near-CR. Primary tumor response and neck response were recorded independently. SUV_{max} thresholds of 6.5 for the primary tumor and 2.8 for LNs, which have been previously suggested as having maximal accuracy for predicting failure after chemoradiation for HNC, were used to distinguish CR from <CR in a separate analysis for comparison with clinical interpretation⁽⁹⁾. The percentage decrease in SUV_{max} (SUV_{max}) between pre-treatment and 3-month PET/CT was also calculated for each the primary tumor and neck for exploratory purposes. For surveillance PET/CT, the prospectively issued clinical interpretation was classified as either positive (suspected recurrence) or negative (no evidence of recurrence).

Post-treatment CT response for LNs was assessed using an adapted version of the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, which defines target lesions as LNs with both short-axis diameter ≥ 1.0 cm and FDG-uptake above background on the corresponding co-registered PET scan; per RECIST 1.1, LNs with short-axis diameter <1.0 cm were excluded⁽¹⁶⁾. CR was defined as regression to short-axis diameter <1.0 cm, and $<CR$ was defined as post-treatment nodal short-axis diameter ≥ 1.0 cm. CT evaluation for primary site response was not performed in this study due to the previously demonstrated poor accuracy of CT in assessing primary tumor extent and treatment response in OPC^(17, 18). The accuracy of 3-month PET/CT and CT response were determined by comparison to the gold standard of histologically confirmed local failure (LF) or regional failure (RF), defined as any evidence of persistent or recurrent squamous cell carcinoma after completion of chemoradiation (including at post-treatment neck dissection).

Statistical Analysis

Independent samples t-test was used to compare means between patient cohorts. The LN with the highest pre-treatment SUV_{max} was used for statistical comparisons of LNs. Sensitivity, false negative rate (1–sensitivity), specificity, false positive (1–specificity) rate, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated individually for the primary tumor and neck for PET/CT response, and for the neck only for CT response. Given the uncertain clinical implications of a PET/CT near-CR at 3-months, clinical PET/CT interpretation test characteristics were calculated separately with (a) near-CR scored as CR and (b) near-CR scored as $<CR$. All statistical analyses were performed using MedCalc with a two-sided p-value <0.05 to denote statistical significance (v12.2.1.0, MedCalc Software, Mariakerke, Belgium).

Results

Baseline characteristics for the 101 patient cohort are shown in Table 1. Three patients who underwent tonsillectomy prior to pre-treatment PET/CT and 3 patients with N0 stage were excluded from the primary site and neck response assessments, respectively. Post-treatment PET/CT was performed at a median of 13.4 weeks after completion of chemoradiation (interquartile range 12.6–14.3 weeks), with 85% of PET/CT scans performed at least 12 weeks post-CRT. Median follow-up for living patients was 44.4 months (range 13.3–77.1 months).

Primary Tumor Response at 3 Months

Three (3%) LFs occurred at a median of 9.3 months (range 8.6–13.3) after completion of chemoradiation. Pre-treatment SUV_{max} at the primary site was similar between patients who did and did not experience LF ($p=0.47$). Post-treatment SUV_{max} at the primary site was similar for patients who experienced LF (mean 5.2 [range 3.7–7.0]) and those in whom the primary site was controlled (mean 4.4 [range 1.3–11.7]) ($p=0.72$). Primary site SUV_{max} was also not different between patients with and without LF (mean SUV_{max} 66.7% vs. 58.2%, respectively; $p=0.48$).

Treatment response at the primary site was classified by PET/CT as CR in 67 (68%) patients, near-CR in 20 (20%) patients, and <CR in 11 (11%) patients. LF occurred in 2/67 cases classified as CR, 0/20 cases classified as near-CR, and 1/11 cases classified as <CR (Table 2). Performance characteristics for accuracy of PET/CT response for the primary site are shown in Table 3, calculated for near-CR classified as a CR and also for near-CR classified as a PR. Irrespective of classification of near-CR, post-treatment PET/CT had low sensitivity and a low PPV for LF, with a false negative rate of 66.7%. The NPV of post-treatment PET/CT for LF was high, however, ranging from 97–98% irrespective for classification of near-CR. Using a post-treatment SUV_{max} threshold 6.5 to classify primary site response produced nearly identical results as the clinical PET/CT interpretation when near-CR was classified as a CR (Tables 2 & 3). No SUV_{max} threshold with performance characteristics superior to that of clinical interpretation could be identified by receiver operating characteristic (ROC) curve analysis. Limiting the analysis to patients who underwent PET/CT at least 12 weeks after chemoradiation did not appreciably change PET/CT performance characteristics for primary site response (data not shown).

Neck Response at 3 Months

Eight (8%) RFs occurred at a median 10.0 months (range 2.6–22.7) after completion of chemoradiation. As observed for the primary site, neither pre-treatment SUV_{max} (mean 11.5 [range 5.5–19.8] vs. mean 10.7 [range 2.5–37.3]; $p=0.91$) nor post-treatment SUV_{max} (mean 2.8 [range 2.1–3.8] vs. mean 2.7 [range 1.5–4.8]; $p=0.23$) differed between patients with RF and those with the neck controlled, respectively. SUV_{max} was also similar between those with and without RF after chemoradiation (mean SUV_{max} 70.9% vs. 65.9%; $p=0.62$).

Neck response was classified by PET/CT as CR in 80 (82%) patients, near-CR in 11 (11%) patients, and <CR in 7 (7%) patients. RF occurred in 6/80 (8%) cases classified as CR, 2/9 (22%) cases classified as near-CR, and 0/7 (0%) cases classified as <CR. Performance characteristics for the accuracy of PET/CT assessment of neck response are shown in Table 3. As observed for the primary site, the sensitivity and PPV of post-treatment PET/CT neck response for RF were low irrespective of how near-CR was classified, with false negative rates of 100% if near-CR was classified as a CR and 75% if near-CR was classified as a <CR. Use of the SUV_{max} cut-point 2.8 was more sensitive for detecting residual neck disease than the clinical interpretation (Tables 2 & 3). It was, however, also substantially less specific (false positive rate 30%), with a low PPV similar to that observed with clinical PET/CT interpretation. No SUV_{max} threshold with superior performance for classifying post-treatment could be identified by ROC curve analysis. Similar results were obtained when the analysis was limited to patients who underwent PET/CT at least 12 weeks after chemoradiation (data not shown).

Neck response by CT was evaluable for 91 patients with involved LNs ≥ 1.0 cm in short-axis diameter. CT neck response was classified as CR in 49 patients and <CR in 42 patients. RF occurred in 3/49 patients with CR and 5/42 patients with <CR. Performance characteristics for the accuracy of CT assessment of neck response are shown in Table 3 (rightmost column). Although post-treatment CT was slightly more sensitive than combined PET/CT for detecting residual neck disease after chemoradiation, sensitivity was still poor, with a

false negative rate of 38%. CT response also resulted in a higher false positive rate (45%) compared to PET/CT (8%–18%, depending on classification of near-CR), resulting in lower overall accuracy of CT (52%) compared to PET/CT interpreted either clinically (78–85%) or by SUV_{max} threshold (69%). Limiting the post-treatment PET accuracy assessment to the 91 patients eligible for the CT analysis yielded nearly identical results (data not shown).

PET/CT Surveillance after 3 Months

Given the low PPV of post-treatment PET/CT at 3-months in HPV+ OPC, we investigated whether PET/CT surveillance after the initial 3-month response scan could effectively discriminate between persistent disease and slow response to therapy in these patients, and thus potentially serve as an alternative to neck dissection or primary site biopsy or resection in patients with <CR or near-CR at 3-months. Sixty-seven patients underwent a total of 127 PET/CT surveillance scans after the initial post-treatment PET/CT. Patients who did and did not undergo PET/CT surveillance did not differ with respect to baseline characteristics or primary tumor or neck response at 3-month PET/CT (data not shown), although patients who did not undergo surveillance were more likely to have <CR by CT criteria (69% vs. 35%, $p=0.006$). Twenty-five patients (37%) had a single surveillance scan, 27 (40%) underwent 2 scans, 9 (13%) underwent 3 scans, and 6 (9%) underwent 4 scans. Median time from completion of chemoradiation to the first surveillance PET/CT was 7.3 months (range 4.3–33.8 months).

Among 67 patients who underwent PET/CT surveillance, 22 had previously achieved near-CR or <CR at the primary site at 3 months; of these, 21 (95%) achieved a CR on subsequent surveillance PET/CT, while the remaining patient eventually achieved CR on PET/CT after direct laryngoscopy and negative biopsies of the primary site, and remained without evidence of primary site failure at 50 months after CRT. Of the 12 patients with a previous near-CR or <CR in the neck at 3-months, 100% subsequently achieved CR on surveillance PET/CT. In total, 2 local recurrences and 6 regional recurrences occurred amongst patients undergoing PET/CT surveillance. The use of surveillance PET/CT detected 1 of 2 LFs (50% sensitivity at the primary site) and 5 of the 6 RFs (83% sensitivity in the neck), and was highly specific (false positive rate 3% at the primary site; 2% in the neck) and accurate (96% for the primary site; 97% for the neck) in assessment of both the primary site and neck (Table 4). Of the 6 patients with locoregional failure detected on surveillance PET/CT, all previously achieved a CR at the eventual site of failure on the 3-month post-treatment PET/CT.

Discussion

The primary findings of this study are that although the use of PET/CT at 3-months to assess treatment response after CRT demonstrated high NPV and overall accuracy, sensitivity for predicting locoregional failure was poor, with false negative rates of 67% for the primary site and 37–100% for the neck. Although CT response for the neck showed higher sensitivity than PET/CT, this was offset by significantly lower specificity and accuracy. Finally, use of PET/CT surveillance after the initial 3-month response scan in two-thirds of patients was highly accurate for both the primary site and neck, demonstrating higher

sensitivity for the primary site (50%) and neck (83%) than observed for 3-month PET/CT (33% and 0–25%, respectively).

Taken in the context of prior studies in mixed cohorts of HNSCC, the findings from this series, which represent the largest study of PET/CT response in HPV+ OPC, are noteworthy. While the high NPV and specificity observed in our study are consistent with prior reports, the sensitivity and PPV of post-treatment PET/CT response at both the primary site and neck were substantially lower than previously reported rates (6, 8–10, 19). This discrepancy with the vast majority of the published literature is likely due to the fact that our study included only patients with HPV+ OPC, which demonstrate greater responsiveness to CRT compared to non-HPV-associated HNSCC, although the possibility of human error in the clinical interpretation of post-treatment PET/CT scans as a contributing factor cannot be excluded (20). The dramatic chemoradiosensitivity of HPV+ OPC is further illustrated by the lack of difference in post-treatment SUV_{max} between patients in our study whose disease was locoregionally controlled and those who experienced locoregional failure, highlighting the limitations of PET/CT for detecting microscopic residual disease in the latter cohort. Similar observations have been reported by Moeller et al., who observed poor sensitivity and PPV for PET/CT response in “low-risk” patients with HNSCC, predominantly consisting of patients with HPV+ OPC (9). Chan et al., in the only other published study which exclusively included patients with HPV+ OPC, demonstrated a similarly low PPV for PET/CT response evaluation (12). Potential strategies to improve the PPV of PET/CT in HPV+ OPC may include reserving PET/CT for patients with residual disease on CT at 3 months, as suggested by others (8, 21), or, in light of the potential utility of surveillance PET/CT suggested by our results, further delaying the time to PET/CT response assessment to 6 months after completion of chemoradiation.

Despite the lack of a statistical difference in post-treatment mean SUV_{max} between incomplete and complete histological responders, the use of a SUV_{max} threshold of 2.8 to distinguish complete and incomplete neck response, as suggested by Moeller et al., increased the sensitivity of post-treatment PET/CT for the neck compared to the clinical interpretation (63% vs. 25%) (9). The improved sensitivity achieved by use of an objective SUV_{max} threshold, however, came at the expense of a higher false positive rate (30% vs. 8–18%) and lower overall accuracy (69% vs. 78–85%) when compared with PET/CT clinical interpretation. Similar tradeoffs resulted from the use of CT criteria to classify neck response. Therefore, despite the limitations of 3-month PET/CT for predicting neck recurrence, its performance in our study was nonetheless superior for guiding surgical neck management after chemoradiotherapy compared with use of SUV_{max} thresholds or CT alone, which would have resulted in unnecessary neck dissections in 28% and 41% of patients assessed by each modality, respectively, compared with 7% of patients assessed by PET/CT (if <CR was used to guide neck dissection).

PET/CT surveillance, which demonstrated a false positive rate of only 2% and a false negative rate of only 17%, appears particularly useful for avoiding unnecessary neck dissection in patients with HPV+ OPC who achieve a near-CR or <CR on 3-month post-treatment PET/CT, given that the vast majority of such patients (89%) either had no evidence of residual tumor on neck dissection or were observed without subsequent neck

recurrence. No institutional policy existed regarding the use of PET/CT surveillance in HNC patients after an initial PET/CT CR at 3 months, and we were further unable to detect any evidence of selection bias between patients who did and did not undergo surveillance PET/CT. The observation that surveillance PET/CT detected 5 of 6 neck failures among patients undergoing surveillance, all of whom had achieved a neck CR on initial post-treatment PET/CT, suggests a potential role for PET/CT surveillance of the neck even amongst patients with an initial CR on 3-month PET/CT.

For both the primary site and neck, the specificity of PET/CT varied depending on whether near-CR was classified as CR or <CR. This distinction was most evident in evaluation of the primary site, where the false positive rate was 32% when near-CR classified as <CR, compared to 10% when near-CR classified as CR. The high false positive rate for near-CR may reflect increased metabolic uptake from persistent low grade mucositis after CRT, which may obscure the accuracy of post-therapy PET/CT evaluation of the primary site. Similarly high false positive rates at the primary site have been observed in prior series, with a pooled false positive rate of 18% reported in one meta-analysis⁽¹⁰⁾. Given the accessibility to the oropharynx to detailed physical examination and the low incidence of LF observed in this and other series of HPV+ OPC treated with CRT, the role of PET/CT for evaluation of primary site response appears to be highly limited, and abnormal metabolic activity at the primary site should be viewed with considerable caution if not otherwise accompanied by clinical suspicion of an incomplete response.

In summary, 3-month PET/CT response after CRT in HPV+ OPC demonstrated high NPV for locoregional recurrence, although sensitivity and PPV were poor. Continued PET/CT surveillance in a subset of patients, however, was highly accurate for detecting neck failures with low rates of false positive and false negative results. Use of PET/CT for response assessment resulted in substantially fewer unnecessary neck dissections than would have been indicated by CT assessment alone.

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Table 1

Baseline Characteristics

<u>Characteristic</u>	<u>Value</u>
Age – Median (range) [years]	55 (34 – 76)
Gender – n (%)	
Male	93 (92%)
Female	8 (8%)
Tumor Site – n (%)	
Base of Tongue	39 (39%)
Tonsil	59 (58%)
Glossotonsillar Sulcus	1 (1%)
Pharyngeal Wall	2 (2%)
T stage – n (%)	
T1	20 (20%)
T2	41 (41%)
T3	17 (15%)
T4	23 (23%)
N stage – n (%)	
N0	3 (3%)
N1	5 (5%)
N2a	7 (7%)
N2b	54 (54%)
N2c	20 (20%)
N3	12 (12%)
AJCC Stage – n (%)	
III	6 (6%)
IV	95 (94%)
Pre-treatment SUV _{max} – median (range; interquartile range)	
Primary Tumor (n=98)	11.7 (3.1 – 27.6; 8.4 – 15.6)
Node (n=98)	9.1 (2.5 – 37.3; 5.6 – 13.5)

Table 2
Accuracy of PET/CT Response at 3 Months after Chemoradiation for Prediction of Clinical Outcome

	PET/CT (n=98) <i>Clinical Interpretation</i>		PET/CT (n=98) <i>SUV_{max} Threshold[^]</i>		CT alone (n=91)	
	Local Control (n [%])	Local Failure (n [%])	Local Control (n [%])	Local Failure (n [%])	Local Control (n [%])	Failures (n [%])
Primary Response by Imaging						
CR	65 (97%)	2 (3%)	86 (98%)	2 (2%)	-	-
Near-CR	20 (100%)	0 (0%)	-	-	-	-
<CR	10 (91%)	1 (9%)	9 (90%)	1 (10%)	-	-
Neck Response by Imaging						
CR	74 (93%)	6 (7%)	63 (95%)	3 (5%)	46 (94%)	3 (6%)
Near-CR	9 (82%)	2 (18%)	-	-	-	-
<CR	7 (100%)	0 (0%)	27 (84%)	5 (16%)	37 (88%)	5 (12%)

* CT analysis excludes 7 patients not assessable for neck response assessment by CT due to lymph node short-axis diameter 1.0 cm (per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria)

[^] SUV_{max} cut-points of 6.5 for the primary site and 2.8 for the neck were applied to differentiate between complete and partial responses, as previously suggested (Moeller et al.)

Table 3
Performance Characteristics of Post-Treatment PET/CT at 3 months for Prediction of Local and Regional Control.

Characteristic	PET/CT			CT alone
	If near-CR classified as CR	If near-CR classified as <CR	Using SUV _{max} Threshold [^]	
PRIMARY TUMOR RESPONSE	N=98			
Sensitivity	33% (1 – 91%)	33% (1 – 91%)	33% (1 – 91%)	-
Specificity	90% (82 – 95%)	68% (58 – 78%)	91% (83 – 96%)	-
Positive Predictive Value	9% (0 – 41%)	3% (0 – 17%)	10% (0 – 45%)	-
Negative Predictive Value	98% (92 – 100%)	97% (90 – 100%)	98% (92 – 100%)	-
Accuracy	88% (70 – 100%)	67% (52 – 86%)	89% (71 – 100%)	-
NECK RESPONSE	N=98			N=91
Sensitivity	0% (0 – 37%)	25% (3 – 65%)	63% (24 – 91%)	62% (25 – 91%)
Specificity	92% (85 – 97%)	82% (73 – 90%)	70% (59 – 79%)	55% (44 – 66%)
Positive Predictive Value	0% (0 – 41%)	11% (1 – 35%)	16% (5 – 33%)	12% (4 – 26%)
Negative Predictive Value	91% (83 – 96%)	93% (84 – 97%)	95% (87 – 99%)	94% (83 – 99%)
Accuracy	85% (67 – 100%)	78% (61 – 97%)	69% (54 – 88%)	52% (39 – 68%)

CR=complete response; <CR=incomplete response; SUV_{max}=maximum standardized uptake value
95% Confidence Intervals in parentheses
* CT analysis excludes 7 patients not assessable for neck response assessment by CT due to lymph node short-axis diameter 1.0 cm
[^] SUV_{max} cut-points of 6.5 for the primary site and 2.8 for the neck were applied to differentiate between complete and partial responses, as previously suggested (9)

Table 4

Performance Characteristics of PET/CT Surveillance for Detection of Local and Regional Recurrences

Characteristic	Value
LOCAL RECURRENCE	
Sensitivity	50% (1 – 99%)
Specificity	97% (89 – 100%)
Positive Predictive Value	33% (1 – 91%)
Negative Predictive Value	98% (92 – 100%)
Accuracy	96% (74 – 100%)
REGIONAL RECURRENCE	
Sensitivity	83% (36 – 100%)
Specificity	98% (91 – 100%)
Positive Predictive Value	83% (36 – 100%)
Negative Predictive Value	98% (91 – 100%)
Accuracy	97% (77 – 100%)

95% confidence interval shown in parentheses