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Post-treatment FDG-PET/CT versus contrast-enhanced CT in patients with Oropharyngeal squamous cell carcinoma: Comparative Effectiveness Study

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Abstract

Objective—To compare the accuracy of same day therapy-assessment positron emission tomography/computed tomography (PET/CT) and conventional contrast-enhanced CT (CECT) in patients with oropharyngeal squamous cell carcinoma (OPSCC).

Methods—110 patients (95 male and 15 women, mean age 59 years) biopsy-proven OPSCC were evaluated with same day PET/CT and CECT pair scans, as part of follow-up therapy assessment. Scans were performed within 6 months after completion of primary treatment, (median time: 3.1 months, range: 0.5–6 m). PET/CT and CECT scans were retrospectively reviewed for residual primary site disease, and right and left cervical lymph node involvement. Histopathology or 6 month clinical/imaging follow up were used as gold standard. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated for the primary site and cervical nodal disease.

Results—Of 110 OPSCC patients, 90.9% were HPV positive, 80.8% were stage 4, and 76.4% received chemo-radiation as the primary treatment. The sensitivity, specificity, PPV, NPV and accuracy of PET/CT and CECT were similar in the evaluation of primary cancer site (PET/CT: 75.0, 91.5, 25.0, 99.0 and 90.9, respectively vs CECT: 75.0, 90.6, 23.1, 99.0 and 90.0, respectively). In evaluating cervical lymph node involvement, PET/CT appeared to have higher accuracy (96.8% vs. 81.7%), specificity (97.7% vs. 81.7%) and PPV (45.8% vs. 16.5%),

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comparable NPV (99.4% for both), and lower sensitivity (65% vs. 75%) as compared to same day CECT.

Conclusion—Same day PET/CT and CECT scans had comparable accuracy in the evaluation of primary tumor sites after completion of therapy in patients with OPSCC. PET/CT showed higher accuracy in the evaluation of cervical lymph node involvement.

Keywords

PET/CT; CECT; post treatment; OPSCC

Introduction

Oropharyngeal squamous cell carcinoma (OPSCC) is the most common subtype of head and neck cancers, with an incidence of 12,000 new cases annually in the United States [1,2]. Although the incidence of other head and neck cancers decreased in the last decade, the number of patients with OPSCC has increased due to oral HPV infections. Palatine tonsil and base of the tongue are the most common sites of HPV related head and neck carcinomas [3]. The other well known risk factors associated with OPSCC are smoking and alcohol consumption [4].

Standard of care therapy for OPSCC include surgery, radiation therapy or chemotherapy, either alone or in combination [5]. National comprehensive cancer network (NCCN) guideline recommends doing a baseline post-treatment imaging in patients with T3-4 or N2-3 OPSCC to assess the primary site and neck within 6 months of treatment [6]. Some of the post-treatment changes include inflammation, fibrosis and deformed anatomy due to surgery, decreasing the accuracy of response assessment, which may lead to delayed or unnecessary treatment [7]. Multiple imaging modalities such as positron emission tomography/computer tomography (PET/CT), contrast enhanced CT (CECT) and magnetic resonance imaging (MRI) are used for therapy assessment in these patients [7,8]. The trend of performing post treatment PET/CT in patients with OPSCC had increased over the last 10 years while that of CT scan had decreased [9].

Previous studies have reported post treatment evaluation by PET/CT to be more accurate than by other conventional imaging modalities[10–12]. However, there is little knowledge comparing the value of same day PET/CT and CECT in therapy assessment of patient with OPSCC. Two previous studies compared the post treatment PET/CT and CT in head and neck cancers in different setting such as different time points or low dose noncontrast CT [13,14]. The objective of the present study is to compare the accuracy of same day PET/CT and CECT in therapy assessment of patients with OPSCC.

Methods

Patient selection and inclusion criteria

This is an Institutional Review Board (IRB) approved study under a waiver of informed consent, following the HIPPA guidelines. Using the PET/CT data base, all patients with biopsy proven OPSCC who had a PET/CT scan in our center from 2000 to 2013 were

identified. Those patients who had same day PET/CT scan and head and neck CECT scan within 6 months from completion of their primary treatment were included in the study. The 6-month time limitation was used following the NCCN guideline recommendation of doing an imaging therapy assessment within 6 month after completion of treatment. A total of 110 patients, who fulfilled the criteria, were included in the study. Demographics and clinical information of these patients were extracted and summarized in Table 1. Patient's electronic medical records (EMR) were reviewed till 6 months from the date of the scans and histopathological results or post imaging clinical information were recorded as the reference standard.

PET/CT protocol

PET/CT scans for assessment of patients with head and neck cancers were performed according to the institutional protocol. All patients were instructed to fast for at least 4 hours before scanning, and their weight, height and glucose level were recorded at the time of the PET study. The blood glucose level was less than 200 mg/dl for all patients, and the ^{18}F -FDG injected dose was 5.55 MBq/kg into one of the peripheral veins. After a 60 minute uptake, patients were scanned with a whole body PET from the clavicle to mid-thigh, with arms above head, followed with a dedicated head and neck PET from the top of the head to the carina, with arms by the side; a low dose, non-contrast CT scan was performed followed each PET scan for attenuation correction and anatomical co-registration purposes. The images are performed using either a Discovery LS (two-dimensional) or Discovery VCT (three-dimensional) (GE Healthcare). The CT for the attenuation correction was performed at 120 kV, 20–200 mA, 8.0 noise index, 512×512 matrix with beam collimation of 10 mm and a pitch of 0.984. The PET images were performed at 4.15 min/bed position, slice thickness 3.75 mm, matrix 128×128, with a field of view of 50 cm for the whole body exam and 25 cm for the head and neck exam.

Contrast enhanced CT protocol

In our center, the requesting physicians order a same day contrast enhanced CT scan in about half of the patients with head and neck cancers in post treatment setting. Right after the whole body and head and neck PET/CT scans were acquired, a contrast-enhanced neck CT was performed using 100 cc contrast agent (Omnipaque-350 or Visipaque-320). The neck CECT scan was acquired using the same scanner that PET/CT and the image parameters were as follow: helical, 120 kV, Smart mA NI 10.0, thickness 0.625, 8.0 noise index, 512×512 matrix with beam collimation of 10 mm and a pitch of 0.984. The PET/CT and the head and neck contrast enhanced CT scans were acquired about 5 minutes apart.

Image analysis and statistical analysis

The post treatment PET/CT and neck CECT scans of all patients were read prospectively by a board certified nuclear medicine physician and a senior radiology resident who also board certified in nuclear medicine, respectively. The readers were completely blinded to any clinical patient information including the baseline and the follow up images, with the exception of knowing that these were post therapy assessment scans in patients with OPSCC. Almost all patients had a baseline PET/CT before therapy but the readers were blinded to any prior imaging, other than the post therapy PET/CT and contrast enhanced CT

performed on the same day. The PET/CT images were read as positive or negative for residual disease at the primary tumor site (oropharynx), right and left side of the neck and distant metastasis, using the Hopkins Criteria[15,16]. The CT scans also were read as positive or negative for residual disease at primary site (oropharynx), right and left neck. Focal hyperenhancement with or without soft tissue mass or necrosis at primary site considered as positive and for the neck lymph nodes, any of the following considered as positive: size > 1.5 cm in level I or II, size > 1 cm in other levels, abnormal enhancement or presence of necrosis and abnormal morphology. Histopathological results and/or post imaging clinical information were recorded for standard reference. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of PET/CT and neck CECT scans for residual malignancy were assessed at the primary site, and at the ipsilateral and contralateral neck sides. Using the SPSS 15.0 (SPSS Inc., Chicago, Illinois, USA) software, Chi-Square test was performed to compare the results.

Results

Patient characteristics

A total of 110 patients (95 male and 15 female, mean age 59 ± 9 years) were included in the study. Sixty percent (66/110) of the patients had the primary tumor at the base of tongue (BOT) and in the remainder 40% of the patients (44/110) at the tonsil. Most of the patients (100/110, 90.9%) had an HPV related OPSCC, and stage 4 disease was the most common (80.8%, 89/110) stage at the initial presentation. The most common treatment modality was chemo radiotherapy (CRT) (84/110, 76.4%). Table 1 summarized characteristics of patients included in the study. A total of 110 PET/CT and 110 neck CECT scans were performed within 6 months from completion of treatment and included for analysis. The therapy assessment scans were performed with a median time of 3.1 months (range 2–25.9 weeks, mean 13.1 weeks) after completion of treatment.

Accuracy of Follow up PET/CT

Sensitivity, specificity, PPV, NPV and accuracy for both PET/CT and neck CECT scans were measured in three different sites: primary cancer site, ipsilateral neck and contralateral neck. The overall value of PET/CT and CECT scans was also calculated. A total of 11 residual disease sites were confirmed by histopathology (n=8) and 6-month clinical follow up (n=3): 4 lesions in the primary site, 5 lesions in the ipsilateral neck and 2 lesions in the contralateral neck.

a. Primary site—In detecting residual disease at the primary site, PET/CT scan showed 97 true negative (TN), 1 false negative (FN), 3 true positive (TP) and 9 false positive (FP) results. While CECT scans demonstrated 96 TN scans, 1 FN scan, 3 TP scans and 10 FP scans for detecting residual disease at the primary site of cancer. Therefore, the sensitivity, specificity, PPV, NPV and accuracy of PET/CT for detecting residual disease in the oropharynx were 75%, 91.5%, 25%, 99% and 90.9%, respectively. Similar values were observed using the neck CECT scan in detecting residual disease at the primary site (75%, 90.6%, 23.1%, 99%, and 90%, respectively) (Table 2).

b. Ipsilateral neck—At the ipsilateral neck, TN, FN, TP and FP were 102, 2, 3 and 3, respectively for PET/CT and 70, 1, 4 and 35, respectively for neck CECT. The sensitivity, specificity, PPV, NPV and accuracy of PET/CT for detecting residual nodal disease at ipsilateral neck were 60%, 97.1%, 50%, 98.1% and 95.5%, respectively. Whereas, neck CECT scan showed higher sensitivity for detecting residual disease at the ipsilateral neck, but lower specificity, PPV, NPV, and accuracy than that of PET/CT (80%, 66.7%, 10.3%, 98.6% and 67.3%, respectively) (Table 2). Statistical analysis showed significantly higher PPV ($p=0.05$) and higher specificity ($p<0.001$) for PET/CT scan.

c. Contralateral neck—At the contralateral neck, TN, FN, TP and FP were 106, 0, 2 and 2, respectively for PET/CT and 102, 0, 2 and 6 respectively for neck CECT. The sensitivity, specificity, PPV, NPV and accuracy of PET/CT for detecting residual disease at the contralateral neck side were 100%, 98.1%, 50%, 100% and 98.2%, respectively. There was significant difference in PET sensitivity for contra lateral nodal disease compared to ipsilateral nodal disease, likely related to lesser number of nodes identified in the contra lateral neck. PET/CT and neck CECT were pretty similar (except for PPV that was higher in PET/CT). The sensitivity, specificity, PPV, NPV and accuracy of neck CECT scan for detecting residual disease at the contralateral neck were 100%, 94.4%, 25%, 100% and 94.5%, respectively (Table 2).

d. Overall accuracy—Besides the primary site and regional lymph node involvement, PET/CT scan was also helpful in evaluating any distant site of metastasis, since it is a whole body scan from skull base to mid-thigh. The sensitivity, specificity, PPV, NPV and accuracy of PET/CT for detecting residual disease at all sites were 77.8%, 88.1%, 36.8%, 97.8% and 87.3%, respectively for FDG PET/CT and 87.5%, 59.8%, 14.6%, 98.4% and 61.8%, respectively, for neck CECT. While neck CECT was more sensitive, using the method of interpretation used in this study, PET/CT scan was more specific and more accurate in detecting residual disease in patients with OPSCC, using the Hopkins Criteria for therapy assessment. Statistical analysis showed significantly higher overall specificity and accuracy for PET/CT scan ($p<0.001$, $p<0.001$).

Discussion

After treatment of OPSCC with surgical resection, chemotherapy or radiation therapy, changes in the normal tissue and anatomy (edema, hyperemia, and fibrosis) may affect the accuracy of imaging modalities in detecting residual disease[1]. Therapy assessment is an important step in the management of patients with OPSCC; since accurate confirmation of complete response can lead to discontinuing treatment. On the other hand, early detection of residual disease leads to starting new treatment[17]. The results of this study showed that post treatment PET/CT and neck CECT have similar accuracy for detecting residual disease at the primary tumor sites. Neck CECT was more sensitive for the neck node residual disease detection while PET/CT has higher specificity and accuracy for detecting residual diseases in neck nodes, using the interpretation methods we used in this study. The size, contrast enhancement, change in morphology and necrosis were considered in reading the post treatment CECT scans while FDG avidity in comparison to blood pool and liver was considered for reading the post treatment PET/CT scans, following Hopkins Criteria.

In our study, the sensitivity, specificity, PPV, NPV and accuracy in detecting residual disease were 77.8%, 88.1%, 36.8%, 97.8% and 87.3%, respectively for PET/CT imaging and 87.5%, 59.8%, 14.6%, 98.4%, and 61.8%, respectively for neck CECT. Chen et al. in a small study compared post treatment PET/CT and CECT in patients with OPSCC and unknown primary head and neck SCC (total 30 patients). They reported a higher accuracy of CECT for evaluation of primary site (85.7% vs 82.1%) and higher accuracy of PET/CT in evaluation of the neck (59.3% vs 74.1%) [18]. In another study, Suenaga et al. included all the patients with head and neck cancers who had a PET/CT, CECT or PET/CECT after completion of treatment (2–78 months) for evaluation of suspected recurrence or active tumor. They reported that both PET/CT and PET/CECT had higher accuracy for detecting recurrence than CECT; moreover, PET/CECT was reported to be the best modality in their study [19]. In a meta-analysis, Isles and colleagues evaluated post treatment and follow up PET/CT scans in patients with head and neck cancers, reporting pooled sensitivity, specificity, PPV, and NPV of 94%, 82%, 75% and 95%, respectively. The results of PET/CT were not compared to that of CT, however, the results of CT, mostly without contrast, and MRI were provided and the values were significantly lower. Authors also claimed that the sensitivity of PET/CT was higher for those scans performed later from the treatment completion [20]. Our results were very similar to those studies that only included the post treatment scan within 6 months of therapy completion [21,22].

Our results showed that while neck CECT was more sensitive, PET/CT was more specific and more accurate, with higher NPV for therapy assessment in patients with OPSCC. Multiple previous studies evaluated the value of PET/CT or CECT in the therapy assessment setting and reported acceptable accuracies [11,23]. For instance, Rangaswamy et al. evaluated 103 patients with different types of head and neck cancers including salivary gland cancers, skin cancers and about 50% of their patient population were diagnosed with OPSCC. They compared the recurrence detection rate of post treatment diagnostic HRCT, PET/CT (low dose CT) and PET/CT performed 18 months after treatment. Their results showed higher sensitivity respectively for PET/HRCT, PET/CT and HRCT in recurrence detection of their heterogeneous patient population [14]. In addition, a few studies comparing the accuracy of these two modalities without accounting for the same day PET/CT and CECT scans have been reported [24–27]. In a prospective trial, Moeller and his colleagues claimed that PET/CT was not superior to CECT scan in therapy assessment of patients with OPSCC. However, investigators enrolled OPSCC patients who were treated with radiation therapy, including PET/CT and CECT scans after 8 weeks of therapy completion [28]. This inclusion criterion (8 weeks), increases the number of false positive results due to post radiation inflammation and inflammatory FDG uptake. The timing of performing post-therapy imaging modalities is an important factor for therapy assessment. Inflammatory FDG uptake could be decreased by time as the inflammation progressively decreases with time; therefore doing PET/CT after a reasonable time post radiation treatment (>12 weeks) will decrease the chance of false positive PET/CT results [29–31]. Enomta et al., evaluated 18 patients with OPSCC in another small prospective study, reported that PET/CT had higher accuracy than CECT in regional recurrence detection (94% vs 78%) while the accuracies of both modalities are the same in local recurrence detection (83%)[13].

Involvement of neck lymph nodes is common in HPV related OPSCC patients, and these lymph nodes usually present with diverse morphologies such as solid, cystic and necrotic features. Multiple characteristics of the CT scans are used to follow the neck lymph nodes after radiation therapy in patients with OPSCC, such as changes in volume, size, density (Hounsfield unit), heterogeneity and other anatomical and morphological features. Although some of these features were helpful in differentiating between the responders versus non responders, none of them showed the perfect method for therapy assessment in patients with OPSCC [32–34]. The value of magnetic resonance imaging (MRI) was also evaluated in response evaluation of the neck in oropharyngeal cancer. In a retrospective cohort study, Lilja-Fischer et al, assessed the value of MRI in neck response assessment of 100 patients with advanced OPSCC. They reported a very low sensitivity and specificity for MRI in this setting (69% and 41% respectively). They concluded that early anatomical imaging may be inappropriate for evaluating neck response in patients with HPV related OPSCC [35]. In another study, ultrasound (US) MRI and PET/CT were evaluated in detection of neck residual disease in patients with OPSCC and concluded that PET/CT combined with neck US could be a reliable and cost effective strategy in this setting [36]. In term of CT scan, neck CECT scans could not differentiate between the residual disease and therapy related changes such as necrotic and scar tissue [1,37]. Finally, dental repair materials, i.e. metal artifacts, may obscure the oropharyngeal area and decrease the value of CECT scan in the therapy assessment setting [14,15]. Considering all of these limitations, CECT still has a great value in management of patients with OPSCC.

On the other hand, PET/CT can differentiate the viable tumor from the necrotic and scar tissue as the later does not uptake FDG. The false positive results of PET/CT due to inflammatory FDG uptake can be decreased by doing the scan after a reasonable time post radiation therapy (>12 weeks) [31]. A common cause of treatment failure in OPSCC is undiagnosed distant metastasis and distant metastasis occurs in about 15–20% of the patients. PET/CT imaging is a whole body imaging study and add value of evaluating for any distant metastasis (lung, liver, bone, etc.) at the same time [1]. However, all pitfalls of CECT will not be resolved by PET/CT due to some limitations as well. PET/CT may not detect small residual disease (<10 mm) due to the low spatial resolution [31,37,38]. Therefore a contrast enhanced PET/CT scan may be the best option in some patients. It was shown that contrast-enhanced PET/CT decreases the need for a separate neck ceCT scan and the scans will be performed in a single study session [1]. Overall individualizing patient's risks and tumor characteristics would be crucial to decide on whether to perform PET/CT or CECT or both in the therapy assessment of patients with OPSCC.

There are limitations to our study. We retrospectively included patients who had same day post treatment PET/CT and CECT scans. There is a possibility of selection bias. The clinician ordered both PET/CT and CECT imaging likely because there was a higher concern for residual malignancy. Furthermore, we used the 6-month clinical follow up as a reference standard when there was no histopathological confirmation. Moreover, biopsy sampling error in the suspicious lesions is a possibility, resulting in false negative results. Our readers were blinded to the staging scans; while some of the imaging therapy response criteria depend on the comparison of post treatment scan with the pretreatment ones. This may decrease the reported accuracy of the readings.

In conclusion, same day PET/CT and neck CECT scans had comparable accuracy in the evaluation of primary tumor sites as part of the therapy assessment of patients with OPSCC; while PET/CT showed higher accuracy in the evaluation of neck lymph node involvement.

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Figure 1.

A 54-year-old gentleman with stage IV base of tongue squamous cell carcinoma, status post curative intent chemoradiotherapy (2 cycles of Taxotere, cis-platinum, and 5-FU followed by concurrent chemoradiation with carboplatin and 70 Gy of external-beam radiation therapy). Treating physician requested a PET/CT (A, B) and CECT (C) for evaluation of treatment response. Both PET and CECT scan were positive for residual tumor in the primary site which were confirmed to be true positive using biopsy confirmation.

Figure 2.

A 73-year-old gentleman with history of T2 N2b squamous cell carcinoma of the left tonsil who underwent definitive chemoradiation (weekly carboplatin). Treating physician requested a PET/CT (A, B) and CECT (C) for evaluation of treatment response. PET/CT scan showed FDG avidity in the primary site suggestive of residual disease and CECT scan was negative for residual tumor in the primary site. The biopsy of the FDG avid lesion was confirmed to be negative (PET/CT false positive and CECT true negative).

Figure 3.

A 54-year-old gentleman with T4 N2c left tonsil squamous cell carcinoma, status post curative intent chemoradiotherapy (3 cycles of cisplatin, cetuximab, and paclitaxel followed by concurrent chemoradiation with carboplatin and 72 Gy of external-beam radiation therapy). Treating physician requested a PET/CT (A, B) and CECT (C) for evaluation of treatment response. Both PET and CECT scan were positive for residual tumor in the neck which were confirmed to be true positive using biopsy confirmation.

Figure 4.

A 73-year-old gentleman with history of T2 N2b squamous cell carcinoma of the left tonsil who underwent definitive chemoradiation (weekly carboplatin). Treating physician requested a PET/CT (A, B) and CECT (C) for evaluation of treatment response. PET/CT scan was negative while CECT scan was suggestive of residual tumor in the neck. Clinical follow up of the patients confirmed the suspicious lesion in the CECT was false positive.

Figure 5.

A 40-year-old gentleman with history of T4 N3 squamous cell carcinoma of the right tonsil who underwent definitive chemoradiation. Treating physician requested a PET/CT (A, B) and CECT (C) for evaluation of treatment response. PET/CT scan was negative while CECT scan was suggestive of residual tumor in the neck. Biopsy of the suspicious lymph node confirmed to be positive (PET/CT false negative, CECT true positive).

Table 1

Characteristics of patients included into the study

Demographics		N=110	%
Age	59 y	53	48.2
	>59 y	57	51.8
Gender	Male	95	86.4
	female	15	13.6
Race	Caucasians	95	86.4
	African American	10	9.1
	Other	5	4.5
Primary site	BOT	66	60.0
	Tonsil	44	40.0
HPV	Positive	100	90.9
	Negative	7	6.4
	Unknown	3	2.7
T	T1	30	27.3
	T2	41	37.3
	T3	12	10.9
	T4a	24	21.8
	T4b	3	2.7
N	N0	12	10.9
	N1	18	16.4
	N2a	11	10.0
	N2b	47	42.7
	N2c	19	17.3
	N3	3	2.7
M	M0	107	97.3
	M1	3	2.7
Stage	1	0	0.0
	2	7	6.4
	3	14	12.7
	4a	82	74.5
	4b	5	4.5
	4c	2	1.8
Treatment	Surgery	2	1.8
	Chemotherapy	1	0.9
	Radiation therapy	2	1.8
	Surgery+radiation	3	2.7
	Chemoradiotherapy	84	76.4
	Surgery+CRT	18	16.4

Table 2
Accuracy of PET/CT and neck CECT scans for therapy assessment in patients with OPSCC

Modality	Region	TN	FN	TP	FP	Sensitivity	Specificity	PPV	NPV	Accuracy
PET/CT	Primary site	97	1	3	9	75.0	91.5	25.0	99.0	90.9
	IL neck	102	2	3	3	60	97.1	50	98.1	95.5
	CL neck	106	0	2	2	100	98.1	50	100	98.2
	Distant mets.	106	0	2	2	100	98.1	50.0	100.0	98.2
	Overall	89	2	7	12	77.8	88.1	36.8	97.8	87.3
Neck CECT	Primary site	96	1	3	10	75.0	90.6	23.1	99.0	90.0
	IL neck	70	1	4	35	80	66.7	10.3	98.6	67.3
	CL neck	102	0	2	6	100	94.4	25	100	94.5
	Overall	61	1	7	41	87.5	59.8	14.6	98.4	61.8

TN: true negative, FN: false negative, TP: true positive, FP: false positive, IL: ipsilateral, CL: contralateral, mets: metastasis