Original Article

A quantitative comparison of gross tumour volumes delineated on [18F]-FDG PET-CT scan and CECT scan in head and neck cancers

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ABSTRACT

Purpose: To compare quantitatively Gross tumor volume (GTV), both primary and nodal areas of head and neck cancers, delineated on [18F]-2fluoro, 2deoxy d-glucose-positron emission tomography/computed tomography ([18F]-FDG-PET-CT) scan to those delineated on Contrast-enhanced CT scan (CECT scan). **Methods:** A total of 26 consecutive patients with squamous cell cancers of head and neck were included in this study. The primary sites were oropharynx ($n = 7$), hypopharynx ($n = 6$), paranasal sinus ($n = 6$), nasopharynx ($n = 4$), oral cavity ($n = 2$), and one with unknown primary and secondary neck node. All patients underwent routine staging work-up. FDG-PET and CECT scans were performed with dedicated PET-CT scanner in single session as a part of the radiotherapy treatment planning for Intensity modulated radiotherapy/Image-guided radiotherapy. **Results:** All patients had abnormal increased uptake in PET-CT scans. PET-CT resulted in changes of CT-based staging in 8 of 26 patients (up-staged in 7 and down-staged in 1). The mean primary and nodal GTV volumes on PET-CT and CT were significantly different (primary: PET-GTV: 48.43 ± 53.21 cc vs. CT 54.78 ± 64.47 cc, $P < 0.001$; nodes: PET-GTV: 12.72 ± 15.46 cc vs. 11.04 ± 14.87 cc, $P < 0.001$). The mismatch between two target volumes was statistically significant ($P = 0.03$ for GTV primary, $P = 0.04$ for GTV node). **Conclusion:** Accuracy of delineation of GTV can be improved along with functional imaging using [18F]-FDG. These metabolically active volumes are significantly smaller than CT-based volumes and could be missed during conventional CT-based target delineations of GTVs.

Keywords: [18F]-fluoro-d-glucose, gross tumor volume, radiotherapy

INTRODUCTION

A large number of patients (70-80%) with head and neck cancers are diagnosed having locally advanced primary disease along with high lymph nodal metastases.[1,2] In recent years, intensity modulated radiotherapy (IMRT) has shown benefits in lowering the toxicities as well as improvements in loco regional control in these patients.[3-5] A crucial step in radiotherapy treatment planning process is to determine the tumor location and its extent. Modern imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, single-photon emission computer tomography, and positron emission tomography (PET) assist the radiation oncologists in localization of the target volume. CT scan is the principle source of imaging data used for defining Gross tumor volume (GTV) for planning conformal therapy for most sites. However, this imaging modality presents several potential pitfalls. It has higher inter-observer variations in demonstrating the true extent of tumor.[6] Recurrence pattern following IMRT shows that most of the recurrences occur only in high-dose region.[7,8] A small error in target delineation can increase the possibility of recurrences in IMRT. So apart from anatomical delineation, functional imaging may improve outcome with IMRT. With the advent of PET scan, it is possible to demonstrate abnormal glucose metabolism in tumor cells using [18F]-2fluoro, 2deoxy d-glucose([18F]-FDG). Recently, [18F]-FDG-PET-CT scan has been applied to tumor volume delineation for many cancer sites in addition to diagnostic purpose.

In this study, we compared quantitatively GTV delineated

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on [18F]-FDG-PET-CT scan to those delineated on contrast-enhanced CT scan (CECT scan) in primary and nodal areas of head and neck cancers.

METHODS

Twenty-six patients with head and neck cancers underwent [18F]-FDG-PET and CECT scans in a dedicated PET-CT scanner in single session from August 2008 to March 2010. The demographic characteristics of all patients are shown in Table 1. This study was approved by the Institutional Review board and the patients were enrolled for the study after an informed consent had been obtained.

Study protocol

PET/CT was performed using the Siemens Biograph 40 True Point PET/CT scanner (Luetium Oxyorthosilicate based 40 slice scanner). It integrates functional sensitivity of PET with the rich anatomical detail of multislice CT. All patients fasted at least 12 h prior to PET/CT. Following administration of 375 MBq of 18F-FDG, the patients were asked to wait in a quiet room for 1 h. We performed diagnostic PET/CT and radiotherapy planning PET/CT in subsequent sessions on the same day. The field of view for diagnostic PET/CT was from the skull to the upper thigh. After the completion of attenuation correction CT scan (120 Kv, 80 mA), PET acquisition was performed. The acquisition time was 120-180 s/bed position. These PET/CT scans were used only for diagnostic and reporting purposes.

After completion of diagnostic PET/CT, the table top was changed to flat one for IMRT planning PET/CT. The patients were immobilized with face mask and were properly aligned in radiotherapy treatment position with the help of lasers. The PET acquisition was performed with the field of view from frontal sinus to D4 vertebral level and acquisition time was 120-180 s/bed position. Immediately following the acquisition of the PET scan, IV contrast of 40 ml was injected. CECT scan was performed using the same slice position with a slice thickness of 5 mm. These CECT scans were used for IMRT contouring and planning. All data were sent through Digital Imaging and Communications in Medicine to a workstation treatment planning system.

Table 1: Characteristics of 26 patients underwent [18F]-2fluoro, 2deoxy d-glucose-positron emission tomography/computed tomography

No. of patients	26
Age (year)	Mean ± SD; 60 ± 13
Gender (%)	
Male	21 (80.8)
Female	5 (19.2)
Sub site (%)	
Oropharynx	7 (26.9)
Paranasal sinuses	6 (23.1)
Hypopharynx	6 (23.1)
Nasopharynx	4 (15.4)
Oral cavity	2 (7.7)
Unknown primary	1 (3.8)

Then CECT scans were fused with PET images acquired in the treatment planning position using inbuilt software in the Siemens' Coherence-Oncologist Treatment Planning System [Figure 1]. While evaluating CECT images, PET images were blinded. Target volumes and organs at risk were contoured and transferred to Oncentra Treatment Planning System for volume analysis.

Delineation of GTV

The primary tumor and abnormal lymph nodes in the neck were delineated by an experienced radiation oncologist. GTV-CT scan (GTV CT) was delineated on the IMRT planning CECT scans according to standard protocols using all available clinical information from physical palpation, available imaging including CT and MRI and direct laryngoscope findings [Figure 2]. Lymph nodes with > 10 mm in shortest dimension, perinodal extension and necrosis in center were included in GTV CT. GTV CTs were contoured by a radiation oncologist after consulting with an experienced radiologist. While contouring GTV CT, FDG-PET images were completely blinded.

GTV-[18F]-FDG-PET/CT (GTV PET) was delineated on fused images using the visual interpretation method along with the opinion of a nuclear medicine physician. Abnormal FDG uptake areas in IMRT planning PET/CT scans above normal background uptake were included in GTV PET. GTVs of primary disease and nodal areas were contoured separately. The absolute GTV CT and image fusion GTV PET volumes were measured. The volumes of intersecting areas were delineated for the purpose of comparison.

Statistical analysis

The GTVs obtained from the PET/CT scans were compared with the CT-based GTV using Student's *t*-test with the help of SPSS 16.0 software. The comparative analysis of two volumes is displayed as a schematic diagram [Figure 3]. The mismatch between two volumes was analyzed by the following method:

Mismatch A to B = (A-intersection volume)/B × 100.

The coverage between two volumes was analyzed by the following method:

Coverage A to B = intersection volume/B × 100.

RESULTS

The distribution of all staging patterns for T, N, and M categories is shown in Table 2. PET scan changed the CT scan-based staging in 8 cases (30.76%). Seven cases (26.92%) were up-staged by PET/CT scan, and only one (0.38%) was down-staged by PET/CT scan. In one patient (patient no. 12) with the unknown primary with secondaries in neck, PET/CT identified primary in soft palate. PET/CT identified one second primary tumor in left pyriform sinus in the case of right pyriform sinus (patient no. 3).

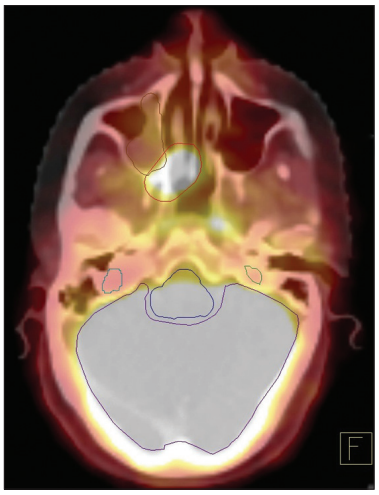

Figure 1: Positron emission tomography/computed tomography of 64 years female with nasal cavity cancer showing clear demarcation of tumor with thickened mucosa

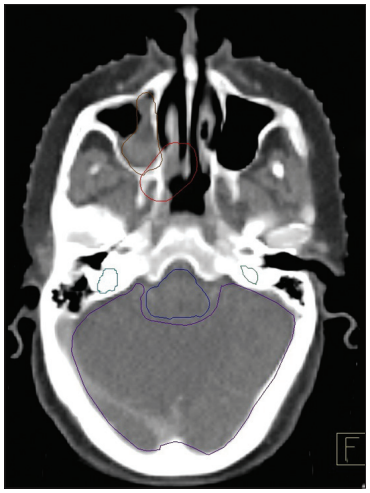

Figure 2: Computed tomography slice of 64 years female with nasal cavity cancer. But CT does not show clear demarcation of tumor with thickened mucosa

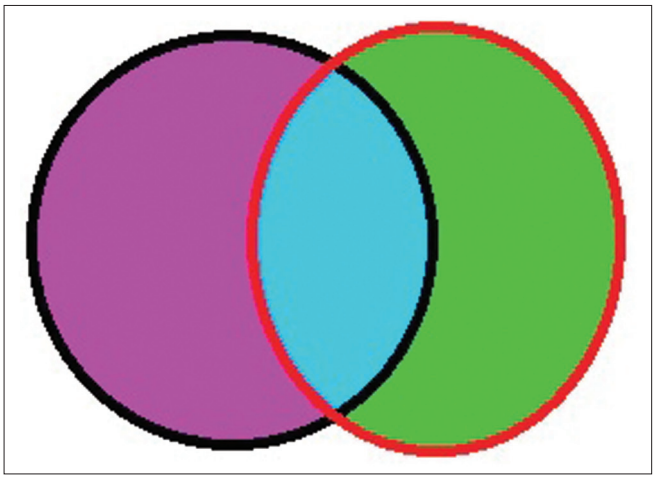

Figure 3: Comparative analysis of two volumes. Gross tumor volume (GTV) Positron emission tomography (PET) (black), GTV CT (red), PET out of CT (purple), CT out of PET (green) and Intersection volume (turquoise) were analyzed

Primary GTV changes

The impact of PET/CT on GTVs is shown in Table 3. The median value of GTV CT was 32.00 cc (range: 0.00-309.10 cc) and the mean was 54.78 cc ± 64.47 cc. The median value of GTV PET was 35.00 cc (range: 3.20-269.50 cc) and the mean was 48.43 cc ± 53.21 cc. GTV CT was significantly larger than GTV PET ($P < 0.001$). The GTV CT was larger than the GTV PET in nine cases (37.5%) and was smaller in 15 cases (62.5%).

The median value of percentage of primary GTV PET covered by CT was 70.07% (range: 32.42-95.52%) and the mean was 65.18% ±18.84%. The median value of percentage of primary GTV CT covered by GTV PET was 68.39% (range: 34.58-88.94%) and the mean was 69.12% ±14.64%.

The median value percentage of mismatch of primary GTV PET to CT was 25.01% (range: 5.00-141.41%) and the mean was 33.63% ±28.96%. The median value of percentage of mismatch of primary GTV CT to PET was 31.97% (range: 2.60-142.67%) and the mean percentage was 46.05% ± 36.92%. Mismatch PET to CT was significantly smaller than CT to PET (P=0.03).

PET scan changed the GTV CT with a median value of -12.52% (range: -131.11-53.74%) and with a mean value of 15.18 ±41.49%. In most of the cases, PET scan identified GTVs outside the volume delineated by CT scan. The median value of primary GTV PET outside CT scan volume was 12.10 cc (range: 1.50-29.80 cc) and the mean value was 12.17 cc ± 7.81 cc.

Nodal GTV changes

The median value of GTV PET was 7.00 cc (range: 0.40-71.70 cc) and the mean was 12.72 cc ± 15.46 cc. The median value of GTV CT was 6.50 cc (range: 0.20-67.00 cc) and the mean was 11.04 cc ± 14.87 cc. GTV CT was significantly larger than GTV PET ($P < 0.001$). The GTV CT was larger than the GTV PET in nine cases (37.5%) and was smaller in 15 cases (62.5%).

The median value percentage of nodal GTV PET covered by CT was 83.73% (range: 31.18-100.00%) and the mean was 81.46 ± 19.48%. The median value of percentage of nodal GTV CT covered by GTV PET was 61.30% (range: 25.81-100.00%) and the mean was 61.02 ± 18.00%.

The median value of percentage of mismatch of nodal GTV PET to CT was 61.88% (range: 0.00-168.42%) and the mean was 63.90 ± 47.53%. The median value percentage of mismatch of nodal GTV CT to PET was 10.86% (range: 0.00-81.82%) and the mean percentage was 18.66 ± 24.65%. Mismatch PET to CT was significantly smaller than CT to PET ($P = 0.04$). The median value of primary GTV PET outside CT scan volume was 3.20 cc (range: 0.00-18.20 cc) and the mean value was 4.44 ± 4.52 cc.

DISCUSSION

In our study, all patients underwent IMRT planning CECT scans along with PET/CT. The use of non-ionic contrast material did

Table 2: Impact of Positron emission tomography/computed tomography on staging and comparison of Gross tumor volume

Patient no.	Sex	Age	Sub site	CT stage	PET stage	GTV PET vol cc.	GTV CT vol cc.	PET out of CT vol cc.	Percentage of change
1	Male	55	Hypopharynx	T3N0M0	T4aN0M0	22.5	52	2.6	−131.11
2	Male	83	Hypopharynx	T3N0M0	T3N0M0	34	25.6	10.7	24.71
3	Male	79	Hypopharynx	T3N2bM0	T3N2bM0	14.4	11.4	4.4	20.83
4	Male	73	Oropharynx	T3N0M0	T3N1M0	17.4	14.7	6.9	15.52
5	Male	53	Oralcavity	T4bN1M0	T4bN0M0	35.6	51	11.3	−43.26
6	Male	54	Paranasal sinus	T4aN0M0	T4aN0M0	29	32	4	−10.34
7	Male	56	Oropharynx	T3N2cM0	T3N2cM0	16.4	25.6	5.9	−56.10
8	Male	53	Oropharynx	T4aN2cM0	T4aN2cM0	42.3	51.2	25.7	−21.04
9	Female	64	Hypopharynx	T4aN0M0	T4aN0M0	22.1	30.4	8.2	−37.56
10	Male	81	Hypopharynx	T2N1M0	T2N1M1	34.6	20.1	15.4	41.91
11	Male	62	Nasopharynx	T4aN2aM0	T4aN2aM0	37.2	52.8	5.2	−41.94
12	Male	57	Oropharynx	T0N2bM0	T3N2bM0	10.5	0	0	0.00
13	Female	43	Paranasal sinus	T4bN1M0	T4bN1M0	269.5	309.1	29.8	−14.69
14	Male	54	Paranasal sinus	T4bN2bM0	T4bN2bM1	99.6	162.8	18.2	−63.45
15	Male	63	Paranasal sinus	T4bN2cM0	T4bN2cM0	84.8	103.6	13.6	−22.17
16	Male	58	Oropharynx	T4aN2bM0	T4bN2cM0	49.3	48.3	9	2.03
17	Male	42	Oropharynx	T2N2bM0	T2N2bM0	6.5	11.4	1.8	−75.38
18	Female	73	Nasopharynx	T4N1M0	T4N1M0	79.6	61.7	26.6	22.49
19	Male	64	Oralcavity	T4aN1M0	T4aN1M0	21.4	9.9	14	53.74
20	Male	58	Paranasalsinus	T4aN2bM0	T4aN2bMo	91.6	97.6	17.4	−6.55
21	Male	85	Hypopharynx	T4aN2aM0	T4aN2aM0	35.3	29.5	12.9	16.43
22	Male	65	Oropharynx	T3N2aM0	T3N2aM0	35	26.9	14.8	23.14
23	Male	48	Unknown primary	T0N2aM0	T0N2aM0	0	0	0	0.00
24	Male	56	Hypopharynx	T4aN0M0	T4aN0M0	67.3	80.9	15.6	−20.21
25	Female	70	Nasopharynx	T1N2M0	T3N2M0	3.2	4.2	1.5	−31.25
26	Female	35	Nasopharynx	T4N2M0	T4N2M0	51.7	56.9	16.5	−10.06

PET: Positron emission tomography, CT: Computed tomography, GTV: Gross tumor volume

Table 3: Impact of Positron emission tomography/Computed tomography in primary and nodal Gross tumor volume

Parameters	GTV primary (mean±SD)	GTV nodal (mean±SD)
PET-GTV	48.43±53.21 cc	12.72±15.46 cc
CT-GTV	54.78±64.47 cc	11.04±14.87 cc
	P<0.001	*P*<0.001
Mismatch of PET to CT volume %	33.63±28.96	63.90±47.53
Mismatch of CT to PET volume %	46.05±39.92	18.66±24.65
	(*P*=0.03)	(*P*=0.04)
% of CT covered by PET	69.12±14.64	61.02±18.00
% of PET covered by CT	65.18±18.84	81.46±19.48
PET volume outside CT scan	12.17±7.81 cc	4.44±4.52 cc

PET: Positron emission tomography, CT: Computed tomography, GTV: Gross tumor volume

not interfere in interpretation of data. Similarly, Antoch, *et al.*, fused CECT scan studies with PET scans for better anatomical delineation for various types of solid cancers.[9]

Incorporation of PET/CT in the management of head and neck cancers has resulted in significant changes in clinical staging.[10-14] Wang, *et al.*, evaluated the impact of FDG-PET fused with planning CT scans on tumor localization.[11] PET/CT changed CT-based staging in 16 of the 28 (57%) patients. In 12 cases, the CT-based T-stage was upgraded by the PET/CT. In six cases, the CT-based nodal information was up-staged by the PET/CT.

Deantonio, *et al.*, analyzed the use of [18F]-PET/CT images for staging and target volume delineation of patients with head and neck carcinoma.[12] PET/CT imaging changed the TNM categories in 5 of the 22 (22%) cases when compared with CT alone. T-stage changed in 3 of 22 (14%) and N-stage in 2 of 22 cases (10%). Similarly, in this study, PET/CT resulted significant discrepancy with CT-based staging in 7 of the 26 patients (up-staged in 6 and down-staged in 1).

Various methods were proposed for accurate contouring of the GTV in PET/CT fusion-guided radiotherapy. Visual interpretation method,[15-17] a fixed 50% threshold of the background subtracted tumor maximum uptake (THR),[10,17,18] an appropriate THR level for an individual patient,[19] software-based automated segmentation,[13,20,21] were most commonly used for PET/CT-based contouring in clinical studies. The most appropriate method for PET/CT-based GTV delineation is still under study.

Various studies compared the GTVs contoured in PET/CT scans with CT scans and demonstrated the role of PET/CT fusion for radiotherapy planning.[11,15,16,18,22-26] Scarfone, *et al.*, prospectively studied the impact of hybrid PET-CT simulation in tumor and normal tissue delineation for RT planning in patients with head and neck cancer.[15] They contoured abnormal PET uptake areas using the visual interpretation method. We also adopted "visual interpretation method" to define GTVs in primary and nodal areas for our study.

Heron, *et al.*, prospectively studied the impact of hybrid PET-CT simulation in tumor and normal tissue delineation for RT planning in patients with head and neck cancers.[16] For primary

disease, PET-based target volumes (mean = 42.7 cm^3) were significantly ($P = 0.002$) smaller compared with CT-based target volumes (mean = 65 cm^3) for all patients.

Daisne, *et al.,* compared CT, MRI, and [18F]-FDG-PET for delineation of GTV in pharyngolaryngeal squamous cell carcinoma.[22] For oropharyngeal tumors and for laryngeal or hypopharyngeal tumors, average GTVs delineated at CT were 32.0 and 21.4 cm^3, respectively, whereas average GTVs at PET were smaller, 20.3 [$P = 0.10$] and 16.4 cm^3 [$P = 0.01$], respectively. In various studies, PET-based GTVs were smaller than CT-based GTVs.[11,15,18,24] In this study, GTV PET was significantly smaller than GTV CT ($P < 0.001$) and consistent with above studies. In contrast, Nishioka, *et al.* showed that GTV volumes were not changed by image fusion between 18F-FDG-PET and MRI/CT in majority of cases[23] and Ashish, *et al.*, found GTV-PET was significantly higher than GTV-CT.[25] Variations in image acquisition procedures, registration methods, and target volume delineation methods are potential factors for this variation.

Mismatch analysis is a potential tool to study the disagreement between CT and PET/CT in contouring of GTV. Many studies analyzed this issue and found that there is a significant mismatch existing between GTV PET and GTV CT.[19,20,27] In a study by Daisne, *et al.,* the average mismatch CT to FDG-PET was 73% and FDG-PET to CT was 14% for oropharyngeal tumors.[20] For laryngeal tumors, average mismatch CT to FDG-PET was 48% and FDG-PET to CT was 17%. EI-Bassiouni, *et al.,* found the mean value for mismatch of GTV PET/GTV CT as 28.9% ± s32.9% and the mismatch of GTV CT/GTV PET as 70.9% ± 50.9%.[19] In this study, the mismatch GTV PET/GTV CT was significantly smaller than mismatch GTV CT/GTV PET ($P = 0.03$).

In this study, the coverage of GTV PET to GTV CT and GTV CT to GTV PET was analyzed to evaluate the difference between two GTV volumes. This was comparable with results of studies done by EI-Bassiouni, *et al.*,[19] and Schinagl *et al.,*[17] In a study by EI-Bassiouni, *et al.,* the median percentage of the GTV PET covered by GTV CT was of 99.5% (range: 41.6-100%) and a mean of 92.4% ± 16.4%, whereas the median percentage of GTVCT covered by PTVPET was 95.1% (range: 44.3-100%) and a mean was 88.2-16.2% ($P = 0.2$).[19]

The major clinical implication of our study is delineation of the metabolically active volumes outside the CT scan. These volumes of diseases could have been missed during radiotherapy treatment planning and could result in in-field recurrences and marginal recurrences. The median value of primary GTV PET outside CT scan volume was 12.10 cc (range: 1.50-29.80 cc) and the mean value was 12.17 ± 7.81 cc. Very few studies analyzed the impact of PET/CT in nodal GTV.[16,24] We analyzed separately for nodal GTVs and obtained findings consistent with primary GTVs. PET/CT has the advantage to identify metabolically active volumes that are used in Simultaneous integrated boost SIB-IMRT and these volumes are also utilized for dose escalation of GTV.

Daisne, *et al.,*[20] Black, *et al.,*[21] Bernard Davis, *et al.*,[13] performed studies in phantoms filled with radioactive material and proposed threshold-based contouring for PET/CT scans in head and neck cancers. However, we adopted the visual interpretation method for target volume delineation mainly because of limitations in our planning systems. This is the limitation of our study. Another limiting factor is that the sample size is small. Twenty-six patients were included in this study. In spite of these limitations, the results of this study are comparable with published studies.

Though this study demonstrated that PET/CT could improve target volume delineation for radiation treatment planning, we feel that more studies are needed to substantiate the importance of PET/CT.

CONCLUSION

PET/CT significantly alters the staging of tumor (T staging) and lymph node metastases (N staging) in head and neck cancers. PET/CT also has the potential to identify GTV outside CT-based GTV that increases the accuracy of radiation planning. We believe that in the era of IMRT/Image-guided radiotherapy (IGRT), PET/CT will increasingly be used for the radiotherapy planning.

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