Physics, Original Article

Optimum Contouring Method for Metabolic Tumor Volume Using PET/CT in Patients with Oral Cavity Squamous Cell Carcinoma

Abdelhafez YG *, Moustafa HM **, Khalil HF **, Saad IE **, Liao CT*,Yen TC ******

* *Radiotherapy and Nuclear Medicine Department, South Egypt Cancer Institute, Assiut University, Egypt.* ** *Department of Clinical Oncology and Nuclear Medicine, KasrAini Hospital, Cairo University, Egypt.* *** *Department of Otorhinolaryngology, Head and Neck Surgery, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan.* **** *Nuclear Medicine Department and Molecular Imaging Center, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan.*

ABSTRACT: The metabolic tumor volume (MTV) is the volume of metabolically-active tumor on PET/CT. Although its potential clinical value has been investigated in many cancers, its routine use has been hampered by the delineation method used to calculate the tumor volume. This may be especially difficult for fuzzyPET images. Previous studies have used a lot of approaches for delineation of tumor volume; however, still there is no clear consensus on which method to be used, especially in the oral cavity region where the contouring may be difficult due to variable grades of physiological FDG uptake. Theaim of this study is to determine best contouring method for the metabolic tumor volume from PET/CT using different absolute and relative SUV values with correlation to the pathology. ***Materials and methods:***We prospectively studied 126 patients with oral cavity squamous cell carcinoma (OCSCC) who underwent PET/CT before definitive treatment by radical surgery. The metabolic tumor volume (MTV) was calculated for the primary tumor according to absolute SUV figures (2.5, 3.0, 3.5 & 4.0) and fixed percentage of SUVmax (30%, 40%, 50%, 60% & 70%). Correlation between the axial diameters generated from these methods and the axial diameter from the fixed pathology specimens was used to determine the best of these methods. ***Results****:* Overall among the 9 contouring methods, absolute SUV 3.0 gave the best correlation *(R = 0.723; P < 0.001)*. Among the methods based on fixed percentage of SUVmax, a threshold of30% gave the best correlation *(R = 0.701; P <0.001)*

Conclusion*:* Contouring the metabolic tumor volume based on absolute SUV 3.0 can be used to represent the best correlation with pathologic data in patients with OCSCC.

Keywords, Contouring, Tumor volume, Oral cavity Squamous cell carcinoma, Positron emission tomography computed tomography, Fluorodeoxyglucose.

Corresponding Author:Abdelhafez YG E-mail: yga1979@gmail.com

INTRODUCTION:

Oral cancer is the eighth most common cancer worldwide, with epidemiologic variations between different geographic regions[1]. The World Health Organization (WHO) expects a worldwide rising incidence in the next decades[2]. Surgery is the main stay for resectable oral squamous cell carcinoma (OSCC). Post-operative radiotherapy (RT) or chemoradiotherapy (CRT) is indicated in the presence of specific adverse features[3]. Positron emission tomography – computed tomography (PET/CT) is increasingly used for staging, re-staging and response evaluation of response to therapy in patients with head and neck cancer. As the name implies, PET/CT combines the information produced by two sophisticated imaging modalities: the functional information from PET with the anatomical information from CT into a single procedure [4].

Standardized uptake value (SUV), a simplified index of glucose uptake of the tumor measured from ^{18}F-fluorodeoxyglucose (FDG) PET/CT, is the most commonly used semi-quantitative parameter[5]. However, the SUV is affected by multiple factors that include time interval between FDG administration and scanning, serum glucose level, extravasations of radiotracer which alters whole-body distribution, patient obesity size and placement of the region of interest (ROI) used to make the SUV calculation[6]. A wide variety of SUV ROI selection metrics has been used: manually defined ROIs; irregular iso-contour ROIs based on a fixed percentage of the SUVmax in the tumor *(e.g., 41%, 50%, 70%, 75%, or 90% of the maximum)*; irregular iso-contour ROIs based on a fixed SUV threshold *(e.g., SUV 2.5, SUV 3)*; irregular iso-contour ROIs based on a background-level threshold *(e.g., relevant background* + 2–3 standard deviations [SDs]) [7].

Another major problem is the partial volume effect (PVE) in small-sized lesions, which simply indicates that some portions of a tomographic image containing part of one anatomic structure and part of another, mixed together, so that there might be spill-in *"from a nearby active uptake"* or spill-out *"from the source or target lesion itself and hence part of its activity is seen outside, leading to misidentification of tumor border"*.This effect typically occurs whenever the tumor size is less than 3 times the system resolution *"full width at half maximum (FWHM) of the reconstructed image resolution"*[8]. SUV can be notated as the maximum value within a lesion (SUVmax), the average value within an ROI drawn around a lesion (SUVavg), or the highest value within a fixed-sized ROI (SUVpeak)[7]. The SUVmax is more robust because it is more reproducible, being less affected by the size and placement in the ROI[9]. However, SUVmax is highly dependent on the statistical quality of the images and the size of the maximal pixel[10].

Segmentation of PET images based on the degree of avidity of tissue to FDG has been studied using different approaches[11, 12]. There are sparse data about gross tumor volume (GTV) contouring using different PET/CT thresholds correlated with pathologic examination. Different institutions use varying methods to define the PET volume; these include the halo phenomenon[13,14], the absolute

standardized uptake value (SUV)[15], a regressive SUV function threshold[16], a percentage of the maximum SUV intensity levels [15], and a simply visual evaluation of PET images [17]. These methods have demonstrated huge alterations in the target volume between CT-based therapy planning and PET/CT-based therapy planning. Because of a lack of uniformity in defining the PET tumor contours in the published literature, interpretation of the available data is difficult and leaves clinicians uncertain as to how they should incorporate PET into the therapy planning process. Because of possible incomplete tumor coverage, the 40%-of-maximum-SUV concept did not appear generally suitable for target volume delineation, and the contrast-oriented methods for contour definition showed more satisfactory results [18]. Other studies examined the impact of varying the CT window and level parameters and the PET intensity thresholds on the radiologic tumor volumes as compared with the measured diameter on pathologic examination[19].

So the aim of this study is to determine the best contouring method for the metabolic tumor volume from PET/CT using different absolute and relative SUV values in correlation to the pathology.

MATERIALS AND METHODS:

Patients:

The institutional review board for Human Research of the Chang Gung Memorial Hospital *(Taoyuan, Taiwan)* approved the study. All patients provided written informed consent. The common eligibility criteria were a histological diagnosis of OSCC; previously untreated tumor scheduled for radical surgery; no other suspected distant metastatic lesions detected by imaging *(including magnetic resonance imaging/computed tomography and FDG-PET)*; and a willingness to undergo computed tomography-guided biopsy or surgical exploration, if necessary. The exclusion criteria included the presence of fasting blood glucose higher than 200 mg/dL, a previous diagnosis of another malignancy, and/or the refusal or inability to receive definitive treatment for the disease.

All of the study participants underwent an extensive preoperative evaluation, including FDG-PET, within 2 weeks before surgery. This included medical history and complete physical examination, flexible fiberopticpharyngoscopy, complete blood count and routine blood biochemistry panel, computed tomography or magnetic resonance imaging scans of the head and neck, chest radiography, bone scan, and liver ultrasonography. Patient staging was performed according to the 1997 American Joint Committee on Cancer (AJCC), 5th edition, staging criteria.

PET/CT imaging

Patients were asked to fast for at least 6 hours before the start of the PET study. Serum glucose level was determined at the time of intravenous injection of 370 MBq*(10 mCi)* of ^{18}F-FDG. PET/CT images were acquired using a combined PET/CT scanner *(Discovery ST 16, GE Healthcare).* The Discovery STE PET*(Advance NXi)*/CT *(Lightspeed 16 - slice)* scanner *(GE Health Care)* scanner is a 24-ring Bismuth Germinate (BGO) system with 15.7 cm axial field of view (FOV) and 70 cm transaxial FOV. There

are 560 BGO crystals in each ring. Individual BGO crystals are 4.7 mm X 6.3 mm X 30 mm *(tangential X axial X radial)*. The DSTE is equipped with a conventional collimator that contains 23 tungsten septa, one between each of the 24 detector rings, plus end-shielding. The septa are 5.4 cm deep and 0.8 mm thick. In addition to this conventional (2D) collimator, two specialized partial collimators were constructed for the DSTE. The two partial collimators had the same geometry as the conventional 2D collimator, but with only 11 septa (2.5D), and seven septa (2.7D).

The data were transferred via the Digital Imaging and Communications in Medicine (DICOM) protocol to a processing workstation *(Siemens Syngo MI.PET/CT 2010A)*. The primary tumor volume was measured using a semiautomatic contouring software *(Siemens TrueD, Siemens Medical Solutions)*. The tumor boundaries were identified and drawn largely enough to include all the tumor volume and carefully enough to exclude areas of physiological uptake ***(Figure 1)***. An isocontour connecting the outlines of the volume of interest (VOI) was set using different approaches, adopting a fixed threshold fraction of the peak FDG uptake in the tumor. The threshold level was selected using different cutoff values for the SUV *(i.e. 2.5, 3.0, 3.5 and 4.0)*. In addition, different fixed percentages of the maximum SUV were used *(i.e. 30%, 40%, 50%, 60% and 70% of the SUVmax)*. To minimize the partial volume effect (PVE) of the primary tumor volume, patients with T1 disease were excluded.

Statistical analysis

Descriptive statistics were summarized using frequencies, percentages, means ± standard deviations, or medians and ranges, as appropriate.Because of its skewed distribution, SUVmax was compared in patients with different clinico-pathological characteristics using the Mann-Whitney *U* test (for two-group comparison) or the Kruskal–Wallis test (for three or more subgroups). Diameters generated from different contouring methods were compared to the diameter generated from the fixed pathology specimens using Pearson correlation analysis. In all analyses, P values < 0.05 (two-tailed) were considered statistically significant.

RESULTS:

General characteristics: A total of 134 consecutive patients with previously untreated OSCC were scheduled for radical surgery between June 2006 and January 2008 at the Chang Gung Memorial Hospital, Taiwan. The follow-up continued until February 2010. Of the eligible subjects, 8 patients were excluded due to the presence T1 disease. Therefore, the final study group consisted of 126 patients. Most of the patients were in advanced stage III and IV ***(Table 1)***. The pathologic specimens revealed maximum axial tumor diameter ranging from 1.0 – 8.0 cm (median 3.0) with a mean of 3.0 ± 1.4 cm.

Table 1: Pathologic staging of the study population

Character	N	*%*
Pathological TNM stage (AJCC 2002)		
pStage II	34	*(27)*
pStage III	25	*(19.8)*
pStage IV	67	*(53.2)*
Pathologic T status		
pT2	65	*(51.6)*
pT3	17	*(13.5)*
pT4	44	*(34.9)*
Pathologic N status		
pN0	59	*(46.8)*
pN1	21	*(16.7)*
pN2b	39	*(31)*
pN2c	7	*(5.6)*

Delineation method: (Table 2) Of the nine different PET volumes tested *(i.e., $MTV_{SUV\ 2.5}$, $MTV_{SUV\ 3.0}$, $MTV_{SUV\ 3.5}$, $MTV_{SUV\ 4.0}$, $MTV_{30\%}$, $MTV_{40\%}$, $MTV_{50\%}$, $MTV_{60\%}$, $MTV_{70\%}$)*, an $MTV_{SUV\ 3.0}$ was associated with the optimal correlation between the maximum axial diameters obtained using our delineation method and the maximum axial diameters calculated in the pathological specimens *(Figure 2; $R = 0.723$; $P < 0.001$).*

Table2: Pearson correlation analysis between the maximum axial pathological diameter and the maximum axial diameters obtained from 9 contouring methods. Also shown are values of the generated metabolic tumor volumes.

Contouring Method	Diameter		MTV		*R*
	Mean	± SD	Mean	± SD	
Absolute threshold (SUV 2.5)	3.3	1.5	22.8	30.5	0.697
Absolute threshold (SUV 3.0)	3.1	1.5	19.4	26.9	0.723 *
Absolute threshold (SUV 3.5)	2.9	1.5	16.4	23.9	0.718
Absolute threshold (SUV 4.0)	2.8	1.5	14.5	21.7	0.701
Threshold (30%)	2.8	1.2	14.0	14.0	0.701
Threshold (40%)	2.5	1.2	9.9	15.2	0.684
Threshold (50%)	2.3	1.1	6.9	10.7	0.670
Threshold (60%)	1.9	1.1	4.4	6.4	0.693
Threshold (70%)	1.7	1.1	2.6	3.5	0.674

All methods show statistical significance.

* *Best correlation*

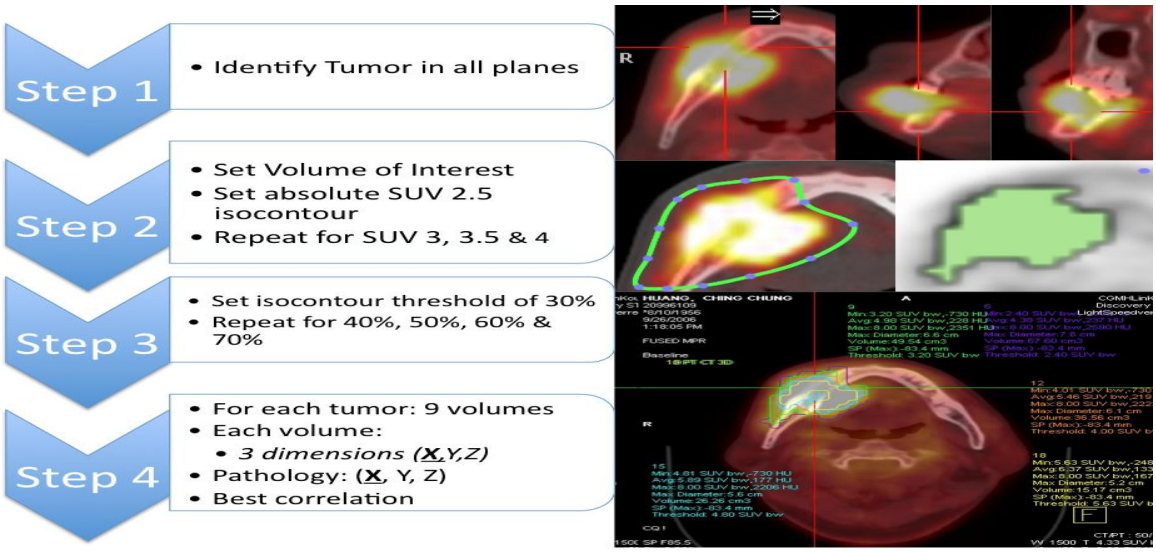

Figure 1: *Schematic illustration of the delineation process of the metabolic tumor volume in 126 patients with oral cavity squamous cell carcinoma.*

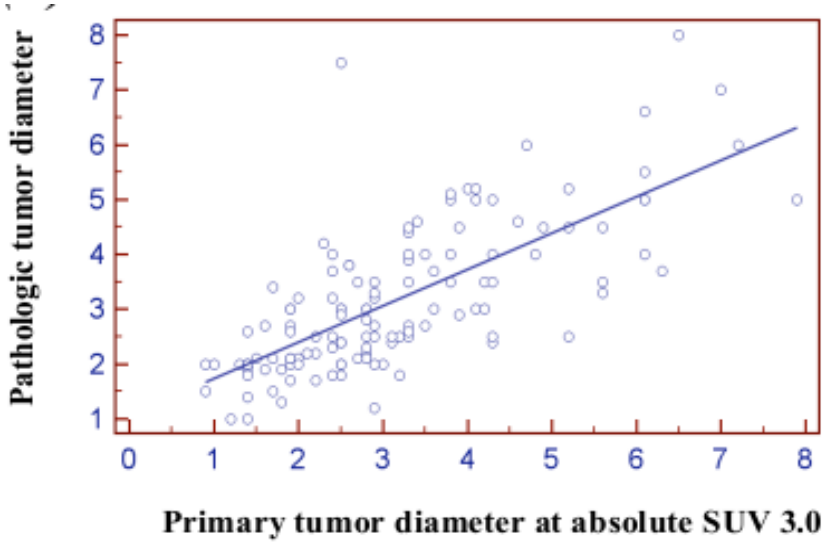

Figure 2: Scatter plots for the relation between maximum pathologic axial diameter of the fixed primary tumor and the diameter derived from tumor delineation using absolute SUV value of 3.0 ($R = 0.713$; $P < 0.001$).

Metabolic tumor volume: Primary tumor SUVmax ranged from 3.7 to 31.8 (median: 13.7). The primary tumor volume at absolute SUV 3.0 ranged from 0.44 to 202.4 ml. The small PET volumes were due to tumors with low FDG avidity, making the delineated tumor volume small. Out of the study population, 5 patients had MTV < 1 ml. Their primary tumor average SUV was < 4.0.

DISCUSSION:

Targeting the tumor using PET/CT images has refined the radiotherapy planning process far more than depending on the anatomical information from CT alone. Because the pathologic T-stage is not representative of the three-dimensional tumor volume, it can be expected that tumor burden, *measured by a three-dimensional volumetric method*, may be more reliable for the assessment of tumor extent, and serve as a better independent prognostic factor than pT stage[18].

The tumor volume, *although labor-intensive*, can be measured by CT and MRI, and found to correlate well with the treatment outcomes in some head and neck cancers[20, 21]. In PET/CT, the high tumor to background ratio *(contrast resolution)* makes it easier to measure MTV [22].

Different methods for contouring the PET volumes have been proposed but hampered by the difficulty of pathological validation of these methods[11, 12]. Tumor geometry, tissue retraction and tumor heterogeneity are the main obstacles for full pathological volume estimation[15].

In this work, the best contouring method was selected based on the best correlation between the maximum axial diameter in the pathology specimen and the corresponding diameter obtained from different contouring methods. The absolute threshold based on SUVmax 3 gave the best correlation for the primary tumor, whereas Baek et al. have previously found that absolute threshold (SUVmax 3.5) could predict the pathological volume in two groups of oral cavity cancer patients *(with and without dental artifacts)*. It was reported that dental artifacts might increase the uptake in CT corrected images and cause elevation of the SUV[23]. That might partially explain why our threshold for volume assessment was less. In addition, the

number of patients with locally advanced tumor *(n =10)* in their study was far less than in the current study. It worth noting that a detailed description of the pathological methods used to overcome tissue retraction was not described in that work.

Seitz et al. prospectively used a cut-off value of 3.5 to delineate the tumor in 66 patients with oropharyngeal and oral cavity SCC. The pathological volume was determined from visualization of gross tumor infiltration in the fresh specimens, which were collected en-bloc in the operation room and were placed in a polystyrene cast marked longitudinally in the three dimensions and filled with gelatin solution in order to avoid shrinkage of the specimen. They found no differences between PET/CT and MRI regarding the diagnostic performance[24]. It is known that higher thresholds will result in smaller volumes, that may explain the higher SUV cut-off value especially if we know that their study included only 20 patients with advanced local disease. Whether or not the application of different threshold for each cancer stage will give better correlation with the pathologic specimen needs further evaluation. Furthermore, Daisne et al compared CT, MRI, and FDG PET for delineation of tumor volume in pharyngolaryngeal SCC, with the results validated by surgical specimen fixed by non-retratction methods. They indicated that FDG PET was the most accurate modality for measuring tumor volume[25] They developed a customized home-made segmentation algorithm to delineate the tumor volume automatically based on the measured signal-to-noise ratio [26].Their methods may make it difficult to compare their work to others.

In conclusion, thresholding method with absolute SUV value of 3.0 might represent an optimum correlation with the pathologic specimens from oral cancers. However, further validation of these results using non-retractile volumetric pathologic fixation methods is warranted.

Acknowledgements

This work was supported in part by a grant-in-aid for FDG PET research in oral cancer from the Chang Gung Memorial Hospital - Linkou (CMRPG370062).

REFERENCES:

1. Mignogna MD, Fedele S, Lo Russo L. The World Cancer Report and the burden of oral cancer. *Eur J Cancer Prev*;**13**:139-42; 2004.

2. Petersen PE. *The World Oral Health Report 2003: Continuous improvement of oral health in the 21st century - the approach of the WHO Global Oral Health Programme.* Geneva;2003.

3. Pfister DG, Ang KK, Brizel D, Burtness BA, Cmelak AJ, Colevas AD, et al. NCCN Clinical Practice Guidelines in Oncology. Head and Neck Cancers.V.2.2010. 2010; http://www.nccn.org/professionals/physician_gls/PDF/head-and-neck.pdf. Accessed 26 December 2010; 2010.

4. Townsend DW, Beyer T. A combined PET/CT scanner: the path to true image fusion. *The British journal of radiology*;**75 Spec No**:S24-30;2002.

5. Delbeke D, Coleman RE, Guiberteau MJ, Brown ML, Royal HD, Siegel BA, et al. Procedure guideline for tumor imaging with 18F-FDG PET/CT 1.0. *J Nucl Med*;**47**:885-952006;.

6. Keyes JW, Jr. SUV: standard uptake or silly useless value? *J Nucl Med*;**36**:1836-9; 1995.

7. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. *J Nucl Med*;**50 Suppl 1**:122S-50S2009;.

8. Soret M, Bacharach SL, Buvat I. Partial-volume effect in PET tumor imaging. *J Nucl Med*;**48**:932-45; 2007.

9. Shah NP, Workman RB, Coleman RE. PET and PET/CT in Head and Neck Cancer. In: Workman RB, Coleman RE, eds. *PET/CT essentials for clinical practice*. New York, NY: Springer;:104-28; 2006.

10. Boellaard R, Krak NC, Hoekstra OS, Lammertsma AA. Effects of noise, image resolution, and ROI definition on the accuracy of standard uptake values: a simulation study. *J Nucl Med*;**45**:1519-27; 2004.

11. Zaidi H, El Naqa I. PET-guided delineation of radiation therapy treatment volumes: a survey of image segmentation techniques. *Eur J Nucl Med Mol Imaging*;**37**:2165-87; 2010.

12. Zaidi H, Vees H, Wissmeyer M. Molecular PET/CT imaging-guided radiation therapy treatment planning. *Acad Radiol*;**16**:1108-33; 2009.

13. Ashamalla H, Guirgius A, Bieniek E, Rafla S, Evola A, Goswami G, et al. The impact of positron emission tomography/computed tomography in edge delineation of gross tumor volume for head and neck cancers. *International journal of radiation oncology, biology, physics*;**68**:388-95; 2007.

14. Lin S, Han B, Yu L, Shan D, Wang R, Ning X. Comparison of PET-CT images with the histopathological picture of a resectable primary tumor for delineating GTV in nonsmall cell lung cancer. *Nuclear medicine communications*;**32**:479-85; 2011.

15. Schinagl DA, Vogel WV, Hoffmann AL, van Dalen JA, Oyen WJ, Kaanders JH. Comparison of five segmentation tools for 18F-fluoro-deoxy-glucose-positron emission tomography-based target volume definition in head and neck cancer. *Int J Radiat Oncol Biol Phys*;**69**:1282-9; 2007.

16. Black QC, Grills IS, Kestin LL, Wong CY, Wong JW, Martinez AA, et al. Defining a radiotherapy target with positron emission tomography. *International journal of radiation oncology, biology, physics*;**60**:1272-822004;.

17. Kiffer JD, Berlangieri SU, Scott AM, Quong G, Feigen M, Schumer W, et al. The contribution of 18F-fluoro-2-deoxy-glucose positron emission tomographic imaging to radiotherapy planning in lung cancer. *Lung Cancer*;**19**:167-77; 1998.

18. Nestle U, Kremp S, Schaefer-Schuler A, Sebastian-Welsch C, Hellwig D, Rube C, et al. Comparison of different methods for delineation of 18F-FDG PET-positive tissue for target volume definition in radiotherapy of patients with non-Small cell lung cancer. *J Nucl Med*;**46**:1342-8; 2005.

19. Hong R, Halama J, Bova D, Sethi A, Emami B. Correlation of PET standard uptake value and CT window-level thresholds for target delineation in CT-based radiation treatment planning. *Int J Radiat Oncol Biol Phys*;**67**:720-6; 2007.

20. Mancuso AA, Mukherji SK, Schmalfuss I, Mendenhall W, Parsons J, Pameijer F, et al. Preradiotherapy computed tomography as a predictor of local control in supraglottic carcinoma. *J Clin Oncol*;**17**:631-7; 1999.

21. Chong VF, Zhou JY, Khoo JB, Chan KL, Huang J. Correlation between MR imaging-derived nasopharyngeal carcinoma tumor volume and TNM system. *Int J Radiat Oncol Biol Phys*;**64**:72-6; 2006.

22. La TH, Filion EJ, Turnbull BB, Chu JN, Lee P, Nguyen K, et al. Metabolic tumor volume predicts for recurrence and death in head-and-neck cancer. *Int J Radiat Oncol Biol Phys*;**74**:1335-41; 2009.

23. Baek CH, Chung MK, Son YI, Choi JY, Kim HJ, Yim YJ, et al. Tumor volume assessment by 18F-FDG PET/CT in patients with oral cavity cancer with dental artifacts on CT or MR images. *J Nucl Med*;**49**:1422-8; 2008.

24. Seitz O, Chambron-Pinho N, Middendorp M, Sader R, Mack M, Vogl TJ, et al. 18F-Fluorodeoxyglucose- PET/CT to evaluate tumor, nodal disease, and gross tumor volume of oropharyngeal and oral cavity cancer: comparison with MR imaging and validation with surgical specimen. *Neuroradiology*; **51**:677-86; 2009.

25. Daisne JF, Duprez T, Weynand B, Lonneux M, Hamoir M, Reychler H, et al. Tumor volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging, and FDG PET and validation with surgical specimen. *Radiology*; **233**:93-100; 2004.

26. Daisne JF, Sibomana M, Bol A, Doumont T, Lonneux M, Gregoire V. Tri-dimensional automatic segmentation of PET volumes based on measured source-to-background ratios: influence of reconstruction algorithms. *Radiother Oncol*;**69**:247-50; 2003.