Predictive value of PET/CT based metabolic information in the modern 3D based radiotherapy treatment of head and neck cancer patients – single institute study

**Zsolt Cselik[1,2] MD, PhD,
Zoltán Tóth[2,8] MD,
András Kedves[2,3,6] Msc,
Dávid Sipos[2,3,6] MSc,
Omar Freihat[2] Msc,
Tímea Vecsera[3],
Gábor Lukács[2,4] MD, PhD,
Miklós Emri[5] MD, PhD,
Gábor Bajzik[2,6] MD, PhD,
Janaki Hadjiev[6] MD, PhD,
Imre Repa[2,6] MD, PhD,
Mariann Moizs[6] MD, PhD,
Árpád Kovács[2,3,7] MD, PhD**

1. Oncoradiology, Csolnoky Ferenc County Hospital, Veszprém, Hungary
2. Doctoral School of Health Sciences, University of Pécs, Pécs, Hungary
3. Department of Medical Imaging, Faculty of Health Sciences, University of Pécs, Pécs, Hungary
4. Department of Oncology, "Moritz Kaposi" Teaching Hospital, Kaposvár, Hungary
5. Department of Medical Imaging, Faculty of Health Sciences, University of Debrecen, Debrecen, Hungary
6. Dr. József Baka Diagnostic, Radiation Oncology, Research and Teaching Center, "Moritz Kaposi" Teaching Hospital, Kaposvár, Hungary
7. Department of Oncoradiology, Faculty of Medicine, University of Debrecen, Hungary
8. MEDICOPUS Healthcare Provider and Public Nonprofit Ltd., Somogy County Moritz Kaposi Teaching Hospital, Kaposvár, Hungary

Keywords: PET/CT - Predictive value - SUV - MTV - TLG

Corresponding author:
Árpád Kovács MD,
Doctoral School of Health Sciences, University of Pécs,
P.O. Box: 7621,Vorosmarty 4, Pecs, Hungary
Cell phone: +36308292790
kovacs.arpad1979@gmail.com

Received:
11 August 2020
Accepted revised:
11 November 2020

Abstract

Objective: The aim of the study was to evaluate the predictive value of pretreatment positron emission tomography (PET) standardized uptake value (SUVmax), standardized uptake value corrected for lean body mass (SULpeak) value, metabolic tumour volume (MTV) and total lesion glycolysis (TLG) parameters of the primary tumour assessed with PET/computed tomography (CT) in the clinical outcome in patients diagnosed with histopathologically confirmed head and neck squamous cell carcinoma. **Materials and Methods:** Retrospective evaluation was performed using PET/CT image datasets of 52 histologically proven head and neck cancer patients in 4 weeks' prior receiving definitive chemo-radiotherapy (CRT). Positron emission tomography /CT was performed before the CRT and 12 weeks after it for response evaluation. Image data was used for target volume delineation and for specify SUVmax, SULpeak, MTV and TLG parameters of the primary tumour. According to the results of the therapeutic response evaluation two patient subgroups were created in relation to the presence or absence of viable tumour. Metabolic data from pre-treatment PET/CT and therapeutic response were correlated using Kruskal-Wallis test. **Results:** After completion of the CRT in 24/52 (46%) cases viable residual tumour was detected on restaging PET/CT, while in 28/52 (54%) patients showed complete remission. For the therapeutic success prediction assessment, we could not find any significant correlation with pre-treatment SUVmax and SULpeak values (P>0.44, P>0.33). Total lesion glycolysis provided nearly significant difference (P=0.052) and MTV had shown significant difference (P=0.001) between the two patient subgroups statistically. **Conclusion:** Simple metabolic data (SUVmax and SULpeak) from pretreatment fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT were unable to predict therapeutic response, while volumetric information containing MTV and TLG parameters proved to be more useful, thus their inclusion to risk stratification may also have additional value.

Hell J Nucl Med 2020; 23(3): 290-295 *Epub ahead of print: 14 December 2020* *Published online: 28 December 2020*

Introduction

The incidence of head and neck cancers (HNC) is growing worldwide. The natural behavior of these tumors is early invasion into soft tissues, glands, organs and lymph nodes of the head and neck region [1]. At least 75% of these cancers related to use of alcohol and tobacco [2]. Head and neck squamous cell carcinomas (HNSCC) are the fifth most common cancer types in the world and reports for 90% of head and neck cancers and 3%-5% of all malignancies [3].

Clinical staging of these patients mostly used for estimate the prognosis and guide therapy according to the American Joint Committee on Cancer (AJCC) [4]. Nowadays, the main components of the staging process are the physical examination, endoscopy, contrast enhanced computed tomography (CT) [5]. Contrast enhanced and native magnetic resonance imaging (MRI) is also performed to evaluate the size of the primary tumor [6]. These medical imaging methods mentioned above are usually used for the characterization of nodal and distant metastasis [7]. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography combined with computed tomography (PET/CT) allows quantifying the metabolic activity of a tumor (glycolysis) and has become an important modality at several aspects in oncology.

Prognostic values of metabolic parameters measured by ^{18}F-FDG PET/CT remain to be determined [8]. In ^{18}F-FDG PET/CT the most commonly used semi-quantitative parameter is the standardized uptake value (SUV), known as a significant factor for prognosis and treatment guidance in many malignancies [9]. Maximum SUV is a value that shows maximum ^{18}F-FDG accumulation in the cells, which is mostly proven as a predictor for the

aggressiveness of most cancer types [10]. Fluorine-18-FDG PET/CT can improve risk prediction and shows prognostic value as a biomarker of HNCs but the opinion is diverged in the literature between the prognostic values and the effect on the prognosis of the biomarker [11]. Standard values were widely studied among the researchers and for volumetric parameters have not been established yet. There is still the question of which parameter can be associated with better prediction in patients with head and neck cancer [12].

The main goal of our retrospective study was to assess whether the SUVmax and lean body mass corrected peak SUV (SULpeak), metabolic tumour volume (MTV) and total lesion glycolysis (TLG) had a predictive value on the clinical outcomes of the HNC cancer patients receiving definitive chemo-radiotherapy.

Materials and Methods

Patients

Between October 2014 and May 2017, 52 pathologically confirmed, locally advanced HNC patients were enrolled into our study. All patients underwent 3D, ^{18}F-FDG PET/CT fusion based definitive chemo-radiotherapy (with weekly administered cisplatin per protocol) up to 70Gy in Health Center Department of Oncoradiology of Kaposvar University. Second primary malignancy, recurrent tumors found on PET/CT were defined as exclusion criteria. All patients had pre-treatment staging (during the planning process in 4 weeks prior to treatment) and post-treatment (12 weeks after the treatment) PET/CT for the short term follow-up. In accordance to the 7th AJCC staging system, 16 patients had stage I disease, 13 patients had stage II, 14 patients had stage III and 9 patients had stage IV. Forty patients suffered from pharyngeal tumor (5 patients' epipharyngeal, 16 patients' mesopharyngeal, 19 patient's hypopharyngeal). In the laryngeal area there were 6 patients with supraglottic, 4 patients with glottic and 2 patients with subglottic tumors. The epidemiological, the tumors specific and the response to therapy data are summarized in Table 1.

PET/CT imaging

Examinations were performed using Siemens Biograph Truepoint 64 PET/CT (Siemens, Erlangen, Germany). The patients were required to fast for at least 6 hours before intravenous administration of 4MBq/kg activity of ^{18}F-FDG. Blood glucose level was checked before tracer injection to ensure euglycemia. Positron emission tomography/CT was performed after 65 (±10) minutes of uptake period. Images were obtained in treatment position using RT immobilization aids and covering the area from the vertex to the level of the proximal thighs in supine position.

First helical CT was acquired (120kV, 60mAs) without intravenous contrast agent and used for PET attenuation correction as well. Six-nine bed position PET emission scan was acquired for 180 seconds per frame. Iterative ordered subset expectation maximization (OSEM) PET image reconstruction algorithm was used with 168×168 imaging matrix, 3 iterations and 8 subsets, and 5mm Gaussian filtering settings. Positron emission tomography data was corrected for scatter, random coincidences and attenuation using the CT data. All patients underwent staging PET/CT and imaging data was used for radiotherapy target volume delineation. The imaging was repeated after the completion of chemo-radiotherapy (CRT) for therapeutic response assessment.

Table 1. *Values are presented as number of patients (%) unless otherwise indicated. CR is the complete remission, PR is the partial remission, SD is the stable disease and PD is the progressive disease.*

Characteristics	Value
Number of patients	52
Mean age (year)	59±10 (23-82)
Sex	
Men	47 (88%)
Women	5 (12%)
Localization	
Pharynx	
Epipharynx	5 (10%)
Mesopharynx	16 (31%)
Hypopharynx	19 (36%)
Larynx	
Supraglottic	6 (11)
Glottic	4 (8)
Subglottic	2 (4)
Treatment response subgroups	
CR	28 (54%)
PR	19 (36%)
SD	2 (4%)
PD	3 (6%)

(continued)

Treatment response groups	
CR	28 (54%)
NCR	24 (46%)
Initial stage	
I.	16 (31%)
II.	13 (25%)
III.	14 (27%)
IV.	9 (17%)

Image analysis

Metabolic parameters were calculated using dedicated Syngo.via (Siemens, Erlangen, Germany, VB10) multimodality image evaluation and post processing application. Maximum SUV, SULpeak, MTV and TLG data of the head and neck cancers were collected using volume of interest (VOI) technique. The SUVmax represents single voxel activity concentration in a particular lesion with highest uptake. The SULpeak is defined a lean body mass normalized average SUV value measured in a 1cm^3 volume spheric ROI centered around the hottest point in the tumour foci. For MTV and TLG definition relative threshold at 50% of tumour SUVmax was used, as proposed by Deron et al. (2011) [13]. The MTV represents the volume of the above given VOI. Total lesion glycolysis is the product of the VOI average SUV or SUL (SUVmean, SULmean) multiplied by the corresponding MTV.

Clinical evaluation

For evaluation of therapeutic tumors responses based on pre-and post-treatment PET/CT information the PET response criteria in solid tumors (PERCIST) system was used [14]. Two patient groups were created according to the results of the therapeutic response evaluation PET/CT and the clinical follow-up. Furthermore, patient subgroups were set up complete remission (CR) group defined as the absence of viable primary tumors tissue, while non-complete remission (NCR) group defined as the presence of any pernicious proliferations including partial response, stable disease and progressive disease groups [15, 16].

Statistical analysis

For all the statistical analysis, we used in-house developed R-scripts based on the R-software environment for statistical computing (version 3.3.0, 05-03-2016 release; R Foundation for Statistical Computing, Vienna, Austria [17]), extending with ggplot2 and Performance Analytics packages.

We applied quantile plots and Shapiro-Wilk tests [18] to check the normality of the SUVmax, the SULpeak, the TLG and the MTV data. Since these tests showed non-normality distributions in all cases (P=0.0069, P=0.009, P<0.001, P< 0.001, respectively), the identity of the parameter distributions measured in the CR and NCR groups was analyzed by Kruskal-Wallis tests (KWT) [19]. Depending on the results of this analysis, a parameter was considered predictive if the distribution of the two measured values in the two examined groups was different, i.e. the KWT shown P<0.05 value.

Results

A total of 52 patients were enrolled in the study. Patients' characteristics summarized in Table 1. Well-visualized primary lesions were defined at all patients on initial ^{18}F-FDG PET/CT.

The mean SUVmax, SULpeak, TLG and MTV measured on patient's primary tumors were 15±4 (range, 3-21), 12±3 (range, 2-18), 286±182 (range, 4-502), 109±113cm^3 (range, 2-305), respectively (Table 2).

Table 2. *Measured average values in the sub-localizations of head and neck*

	Min				Max				Mean			
	SUV max	**SUL peak**	**TLG**	**MTV**	**SUV max**	**SUL peak**	**TLG**	**MTV**	**SUV max**	**SUL peak**	**TLG**	**MTV**
Epipharynx	2.7	2.2	4.0	2.3	13.8	12.0	502.3	176.7	8.8	6.6	217.6	42.4
Mesopharynx	3.1	2.5	3.7	2.5	9.3	9.3	59.1	13.6	6.5	5.1	9.4	5.7
Hypopharynx	3.1	2.9	25.0	8.6	20.9	18.3	475.5	89.1	10.1	8.4	152.6	29.4
Supraglottic	6.2	4.4	12.7	4.5	10.8	9.2	163.4	37.0	8.3	6.8	80.4	15.3
Glottis	5.7	4.3	15.5	4.4	16.5	13.8	169.6	31.1	9.9	7.7	65.7	15.3
Subglottic	5.7	4.1	22.5	7.0	16.1	12.3	344.3	304.6	8.9	7.1	203.9	47.2

Response analysis

Based on the restaging PET/CT scans CR were achieved in 28/ 52 patients (Figure 1). While viable tumors were observed in 24/52 patients (Figure 2 representing PR case).

Metabolic parameters and outcome

According to the results of KWT we were unable to find statistically significant difference in the SUVmax and SULpeak values of patients achieving complete response and subjects with viable tumor tissue after CRT (P=0.441, P=0.332). TLG values showed nearly significant (P=0.05) difference and MTV proved to be significantly different (P=0.01) between the two different outcome groups (Figure 3).

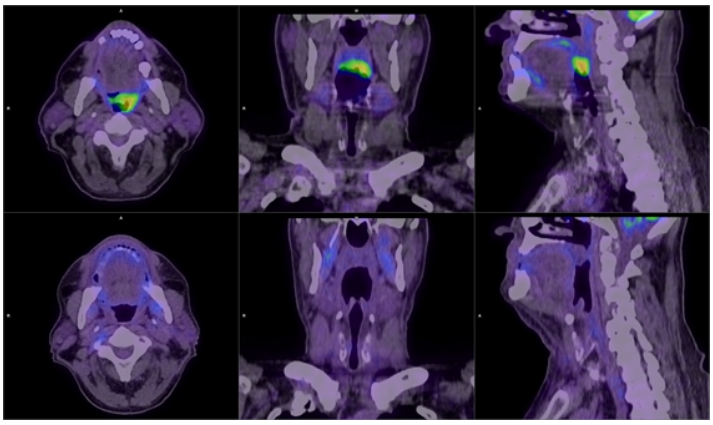

Figure 1. Complete remission (CR): (upper-line) axial, coronal and sagittal PET/CT images show the mesopharynx tumor spreaded over the midline, pre-treatment SUVmax:6,3. Post-treatment (lower-line) axial, coronal and sagittal PET/CT images show Complete Remission (CR); without any pathologic ^{18}F-FDG accumulation on the observed volume.

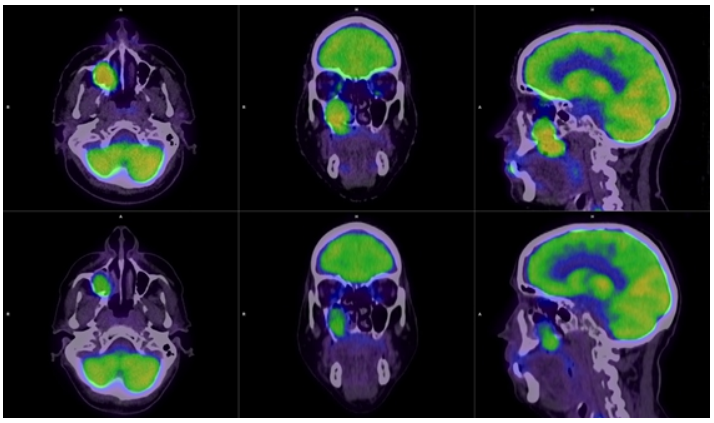

Figure 2. Partial remission (PR): pre-treatment (upper-line) axial, coronal and sagittal PET/CT images show maxillary sinuous tumor penetrated to the bone; pre-treatment SUVmax 7.8. Post-treatment (lower-line) axial, coronal and sagittal PET/CT images show a decrease in SUVmax to 5.1.

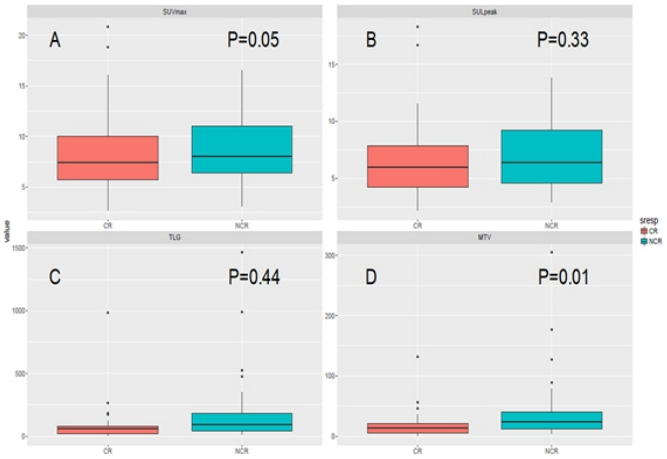

Figure 3. The figure demonstrates the 4 parameter distributions of complete remission (CR) and non-complete remission (NCR) groups (A: maximum standardized uptake value [SUVmax], B: the peak standardized uptake value corrected for lean body mass [SULpeak], C: total lesion glycolysis [TLG] D: metabolic tumor volume [MTV]). The population differences represented by P values

Discussion

The modern complex oncological treatment of the loco-regionally advanced HNSCC patients is radiotherapy usually combined with chemotherapy and/or surgical resection [20]. Approximately two third of head and neck cancer patients are diagnosed with advanced stage disease. If nodal or distant metastases occurred, the 5-year survival decreases to approximately 45% and 35%, respectively [21]. The overall prognosis of HNC remains bad disregard the combined treatment modalities. After the first 2-years the overall loco-regional recurrence may occur in up to 40% of locally advanced head and neck patients [22]. Due to the anatomical features of the head and neck region, organ preservation is important to maintain functions and to minimize aesthetic changes [23]. Hoffman et al. (2012) raised attention about the neoadjuvant treatment strategies for tumor reduction before surgery. Also added a point of the efficacy of CRT and neoadjuvant chemotherapy followed by definitive radiotherapy for advanced HNSCC patients [24].

In the daily clinical practice, there is very important need to accurately predict the outcome of possible treatment options. In case of advanced HNSCC patients the high mortality rate and in case of radical resections precise cancer staging is essential as it allows clinicians to select the relevant treatment strategies which can predict the prognosis of the patients [25]. Therefore, the identification of potential prognostic indicators of these treatments is essential [12].

Fluorine-18-FDG PET/CT proved an essential functional imaging modality for staging, radiotherapy planning and monitoring response in patients with head and neck carcinomas and allows to quantify the metabolic activity of the tumor [26]. The volumetric parameters measured by ^{18}F-FDG PET/CT can provide valuable information regarding the total tumor burden and could be served as prognostic factors. However, studies showed controversial results in defining which parameters are the best in predicting prognosis [27].

The most commonly used functional biomarker to assess tumor activity is SUVmax. It represents maximum ^{18}F-FDG uptake in tumor cells, but it shows only the highest intensity of ^{18}F-FDG uptake and cannot reflect the metabolic activity of the whole tumor [28].

Although SUVmax proposed a possible index for predicting survival and treatment response, several studies reported that SUVmax was not a significant independent prognostic factor for survival [29-32]. Based on our results in the therapeutic response prediction we were unable to find any correlation with pre-treatment SUVmax and SULpeak values (P=0.44, P=0.33).

The accuracy of SUV measurement is altered by numerous physical, biological, technical factors. The use of different PET/CT imaging acquisition and reconstruction parameters can significantly alter SUV quantification. The use of SULpeak value is proposed by PERCIST criteria to overcome some of these limitations.

Volume-based measurements such as MTV and TLG could indicate total volume and total activity of the metabolically active tumor cells. These parameters seemed to be potential prognostic markers and more accurate in survival prediction. Chan et al. (2011) in their study showed that the TLG had higher predictive value than MTV and SUV in overall survival and DFS due its combination of anatomical and biological data [33]. However, it's still not clear which parameter is better for predicting outcomes [29].

Several studies noted that MTV is an adverse prognostic factor for overall survival, independent of other established indicators. Sager et al. (2014) have found that MTV on pretreatment PET could be a potential predictor of short-term outcome and a prognostic factor for DFS in patients with HNC treated after surgery or chemo-radiotherapy [29]. Moreover, Abgral et al. (2014) have also found that MTV of PET/CT in multivariate survival analysis is a potential independent predicting factor for event-free survival and overall survival [34]. Other researchers suggest that both volumetric parameters (TLG, MTV) could be useful and reliable prognostic predictors in survival in head and neck cancer patients [27, 30, 31]. Likewise, Lee et al. (2012) demonstrated that both MTV and TLG were significant prognostic factors on a univariate survival analysis. They suggested that MTV as an independent prognostic factor for survival in addition to pN stage [35]. Many other studies argued that TLG was a more valuable parameter for predicting prognosis and long-term survival than MTV and SUV [22]. The results of Moon et al. (2013) indicates that TLG is a better predictor for overall survival as it was an important independent prognostic factor on multivariate survival analysis [12]. Others pointed out that TLG was the superior prognostic factor and is better in treatment response prediction [14, 29]. Our results also confirm that TLG and MTV can add valuable information on prognosis and survival, it supports the Pak et al. (2014) finding which argued that patients who have higher risk of death and adverse events have high MTV or TLG [36]. Same result on the role of MTV and TLG in prognosis and survival has been investigated by Hsieh et al. (2018) when their study proved that MTV and TLG are independent predictors for overall survival and locoregional progression-free survival [37]. Both parameters provided statistically sig-nificant differences (MTV [P=0.05], TLG [P=0.01]), however MTV proved to be better in predicting treatment response. Finally, although our results are preliminary, we are working in gathering data and information from follow-up which will help the therapeutic experts to improve the decision-making process (e.g. Subgroup analysis) for obtaining the best tailored personal healthcare.

The heterogeneity of available literature data may be explained by the use of different PET acquisition and reconstruction protocols, and diverse volume delineation methods as well, not to mention biological disease heterogeneity. For image segmentation absolute, relative, adjusted SUV cut-off value and gradient based approaches are also evaluated. The use of different image segmentation methods obviously results in variable volumes. The MTV and TLG measurement methods are not well standardized as optimal widely accessible approach is still not available. Consensus recommendations would be required for MTV and TLG measurements to perform proper systematic multicenter evaluation

In conclusion, based on our results, the pretreatment SUVmax and SULpeak values were unable to predict thera-

peutic response in our patients' group but the volumetric information containing MTV and TLG parameters proved to be more useful as prognostic values in patients with HNSCC. Although MTV had shown more significant difference than TLG, both showed significant results in predicting clinical outcome. Thus, their inclusion to risk stratification may have an additional value in predicting the treatment outcomes and response rates, better than simple SUV parameters.

The authors declare that they have no conflicts of interest.

Bibliography

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; 55: 74-108.
2. Gandini S, Botteri E, Iodice S et al. Tobacco smoking and cancer: a meta-analysis. *Int J Cancer* 2008; 122: 155-64.
3. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. *Lancet* 2008; 37: 1695e709.
4. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010; 17: 1471-4.
5. de Bree R, Deurloo EE, Snow GB, Leemans CR. Screening for distant metastases in patients with head and neck cancer. *Laryngoscope* 2000; 110: 397-401.
6. Deng W, Luo L, Lin X et al. Head and neck cancer tumor segmentation using support vector machine in dynamic contrast-enhanced MRI. *Contrast Media Mol Imaging* 2017; 8612519.
7. Zhu L, Wang N. ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography as a diagnostic tool in patients with cervical nodal metastases of unknown primary site: a meta-analysis. *Surg Oncol* 2013; 22: 190-4.
8. Kikuchi M, Shinohara S, Nakamoto Y et al. Sequential FDG-PET/CT after neoadjuvant chemotherapy is a predictor of histopathologic response in patients with head and neck squamous cell carcinoma. *Mol Imaging Biol* 2011; 13: 368-77.
9. Moon SH, Choi JY, Lee HJ et al. Prognostic value of volume-based positron emission tomography/computed tomography in patients with nasopharyngeal carcinoma treated with concurrent chemoradiotherapy. *Clin Exp Otorhinolaryngol* 2015; 8: 142-8.
10. Saleh Farghaly HR, Mohamed Sayed MH, Nasr HA, Abdelaziz Maklad AM. Dual time point fluorodeoxyglucose positron emission tomography/computed tomography in differentiation between malignant and benign lesions in cancer patients. Does it always work? *Indian J Nucl Med* 2015; 30: 314-9.
11. Rosko A, Birkeland A, Shuman A et al. Positron emission tomography-CT prediction of occult nodal metastasis in recurrent laryngeal cancer. *Head Neck* 2017; 39: 980-7.
12. Moon SH, Choi JY, Lee HJ et al. Prognostic value of ^{18}F-FDG PET/CT in patients with squamous cell carcinoma of the tonsil: comparisons of volume-based metabolic parameters. *Head Neck* 2013; 35: 15-22.
13. Deron P, Mertens K, Goethals I et al. Metabolic tumour volume. Prognostic value in locally advanced squamous cell carcinoma of the head and neck. *AAA Nuklearmedizin* 2011; 5 0(4): 141-6.
14. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. *J Nucl Med* 2009; 50 Suppl 1: 122S–50S.
15. Nishimura G, Komatsu M, Hata M et al. Predictive markers, including total lesion glycolysis, for the response of lymph node(s) metastasis from head and neck squamous cell carcinoma treated by chemoradiotherapy: adaptive thresholding method applied to primary tumors and metastatic lymph nodes. *Int J Clin Oncol* 2016; 21: 224-30.
16. Han EJ, O JH, Yoon H et al. FDG PET/CT response in diffuse large B-cell lymphoma: Reader variability and association with clinical outcome. *Medicine (Baltimore)* 2016; 95: e4983.
17. Wilk MB, Gnanadesikan R. Probability plotting methods for the analysis of data. *Biometrika* 1968; 55: 1-17.
18. Shapiro SS, Wilk MB. An analysis of variance test for normality (complete samples). *Biometrika* 1965; 52: 591-611.
19. Kruskal WH, Wallis AA. Use of ranks in one-criterion variance analysis. *J Am Stat Assoc* 1952; 47: 583-621.
20. Gugić J, Strojan P. Squamous cell carcinoma of the head and neck in the elderly. *Rep Pract Oncol Radiother* 2013; 18: 16-25.
21. Ryu IS, Roh JL, Kim JS et al. Impact of ^{18}F-FDG PET/CT staging on management and prognostic stratification in head and neck squamous cell carcinoma: A prospective observational study. *Eur J Cancer* 2016; 63: 88-96.
22. Chajon E, Lafond C, Louvel G et al. Salivary gland-sparing other than parotid-sparing in definitive head-and-neck intensity-modulated radiotherapy does not seem to jeopardize local control. *Radiat Oncol* 2013; 8: 132.
23. Yeh SA. Radiotherapy for head and neck cancer. *Semin Plast Surg* 2010; 24: 127-36.
24. Hoffmann TK. Systemic therapy strategies for head-neck carcinomas: Current status. GMS *Curr Top Otorhinolaryngol Head Neck Surg* 2012; 11: Doc03.
25. Chen YJ, Rath T, Mohan S. PET-computed tomography in head and neck cancer: Current evidence and future directions. *Magn Reson Imaging Clin N Am* 2018; 26: 37-49.
26. Castelli J, De Bari B, Depeursinge A et al. Overview of the predictive value of quantitative ^{18}F-FDG PET in head and neck cancer treated with chemoradiotherapy. *Crit Rev Oncol Hematol* 2016; 108: 40-51.
27. Moon SH, Choi JY, Lee HJ et al. Prognostic value of volume-based positron emission tomography/computed tomography in patients with nasopharyngeal carcinoma treated with concurrent chemoradiotherapy. *Clin Exp Otorhinolaryngol* 2015; 8: 142-8.
28. Kim JW, Oh JS, Roh JL et al. Prognostic significance of standardized uptake value and metabolic tumour volume on ^{18}F-FDG PET/CT in oropharyngeal squamous cell carcinoma. *Eur J Nucl Med Mol Imaging* 2015; 42: 1353-61.
29. Sager S, Asa S, Yilmaz M et al. Prognostic significance and predictive performance of volume-based parameters of F-18 FDG PET/CT in squamous cell head and neck cancers. *J Cancer Res Ther* 2014; 10: 922-6.
30. Kim BS, Pak K, Yi KI et al. Prognostic value of tumoral heterogeneity and volumetric parameters as measured by F18-FDG PET/CT in sinonasal cancer. *Eur Arch Otorhinolaryngol* 2016; 274: 1437-43.
31. Ryu IS, Kim JS, Roh JL et al. Prognostic significance of preoperative metabolic tumour volume and total lesion glycolysis measured by ^{18}F-FDG PET/CT in squamous cell carcinoma of the oral cavity. *Eur J Nucl Med Mol Imaging* 2013; 41: 452-61.
32. Ryu IS, Kim JS, Roh JL et al. Prognostic value of preoperative metabolic tumor volume and total lesion glycolysis measured by ^{18}F-FDG PET/CT in salivary gland carcinomas. *J Nucl Med* 2013; 54: 1032-8.
33. Chan SC, Chang JT, Lin CY et al. Clinical utility of ^{18}F-FDG PET parameters in patients with advanced nasopharyngeal carcinoma: Predictive role for different survival endpoints and impact on prognostic stratification. *Nucl Med Commun* 2011; 32: 989-96.
34. Abgral R, Keromnes N, Robin P et al. Prognostic value of volumetric parameters measured by ^{18}F-FDG PET/CT in patients with head and neck squamous cell carcinoma. *Eur J Nucl Med Mol Imaging* 2014; 41: 659-67.
35. Lee SJ, Choi JY, Lee HJ et al. Prognostic value of volume-based ^{18}F-Fluorodeoxyglucose PET/CT parameters in patients with clinically node-negative oral tongue squamous cell carcinoma. *Korean J Radiol* 2012; 13: 752-9.
36. Pak K, Cheon GJ, Nam HY et al. Prognostic value of metabolic tumor volume and total lesion glycolysis in head and neck cancer: a systematic review and meta-analysis. *J Nucl Med* 2014; 55: 884-90.
37. Hsieh HY, Liu YC, Lin JW, Lin JC. Prognostic effects of the metabolic tumor volume and total lesion glycolysis in patients with advanced squamous cell carcinoma of head and neck. *Ther Radiol Oncol* 2018; 2: 5.