ORIGINAL

Definition of gross tumor volume with FDG-18F PET-CT in patients with head and neck cancer: comparison of different delineation methods

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Abstract

Objective: Besides the high sensitivity and specificity of positron emission tomography (PET) for head and neck tumors, there is still a lack of consensus about how to use this method in radiotherapy planning. The aim of this study is to compare different gross tumor volume (GTV) obtained with PET images in comparison to the size of the target volume generated with CT scan alone, for treated and untreated head and neck lesions. **Methods:** Sixty lesions in fifty patients with head and neck squamous cell carcinoma were included in the study. Delineation of the GTV was achieved using computed tomography (CT) images alone (GTV-CT) and PET-CT images with the visual assessment method (GTVPET-CT) and standard uptake value (SUV) thresholds of 40, 50, 60 and 75 percent (GTV40%, GTV50%, GTV60%, GTV75%, respectively). Correlations were measured by the Spearman test and the Friedman test was used to verify differences between GTVs. **Results:** For all lesions (treated and untreated), only the GTVPET-CT showed a strong correlation with GTV-CT. For only the untreated lesions, GTVPET-CT and GTV75% showed a strong correlation with GTV-CT. The GTV50%, GTV60% and GTV75% showed statistically significant difference in relation to GTV-CT, while GTVPET-CT and GTV40% were similar to GTV-CT. **Conclusion:** The use of PET-CT changes the volume of the final target in head and neck tumors, depending on the methodology used to calculate the GTV. The results presented here showed that the GTV40% and the GTVPET-CT are those who are closer to the target volumes delineated by conventional CT.

Keywords: head and neck neoplasmas; positron-emission tomography; radiotherapy.

INTRODUCTION

Head and neck tumors are usually treated with radiotherapy, either alone or in combination with other therapeutics modalities[1-2]. Recent clinical data have demonstrated efficacy in local disease control with progressive reduction of morbidity and side effects. These results are related to the introduction of higher standards to design therapeutic fields of irradiation that are based upon the better definition of the anatomical structures with the computed tomography (CT) scanner images and physical data processing in the planning workstation[2-4].

Since the introduction of the clinical use of positron emission tomography (PET) with fluorodeoxyglucose (18F-FDG), the metabolic cell activity image became feasible, and after the introduction of a combined equipment of CT and PET, direct correlation between anatomy and function also became possible. At present, PET-CT with 18F-FDG is considered as guidance for therapy response control and to evaluate locally lesion extension and metastatic or occult lesion finding in head and neck tumors. Several different groups had dedicated efforts to study the use of PET-CT in radiation oncology planning where a sensitivity of 98.5 % and specificity of 96.0% had been reported for head and neck tumors[5-7].

Besides the high clinical sensitivity and specificity of the method, there is still a lack of consensus about how to use the PET-CT images in the planning workstation. This mainly happens because the metabolic activity is mathematically expressed as standard uptake values (SUV) and there are no defined threshold value for tumor and non-tumor uptake and also because metabolic 18F-FDG PET images does not show precise anatomic limits. These facts seem to have encouraged experiments with different delineating methods that include the use of qualitative image, fixed or floating SUV threshold values and several other variations, but yet no consensus was achieved[8-19].

Considering the emerging need to accurately understand how each of these methods perform in the clinical environment, we decided to study the relationships of the

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different size of gross tumor volumes (GTV) obtained with PET-CT images, in comparison to the actual size of the target volume generated with CT scan alone, for treated and untreated head and neck lesions.

METHODS

We selected 50 consecutive positive 18F-FDG PET-CT scans performed from April 2006 to April 2009 obtained from our routine head and neck oncology patient archives. All patients had a histological diagnosis of squamous cell carcinoma and no history of recent radiotherapy or chemotherapy treatment (at least 45 days).

Sixty different lesions from these patients were considered as possible target volumes. Delineation of the GTV was achieved using PET-CT images with the visual assessment method (GTVPET-CT) and SUV thresholds of 40, 50, 60 and 75 percent (GTV40%, GTV50%, GTV60%, GTV75%, respectively), and also using unenhanced CT image alone (GTV-CT), as a standard for comparison (Figure 1). The comparison of GTV values was performed for all lesions (treated and untreated) and separately for the untreated lesions.

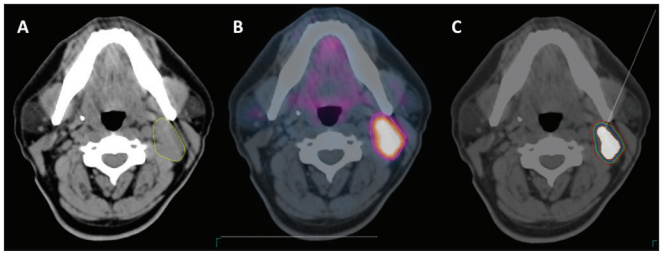

Figure 1. Comparison of the gross tumor volume (GTV) with different delineation methods on a left cervical adenomegaly. A: Axial unenhanced CT showing the GTV-CT (yellow ROI); B: Axial PET-CT showing the GTVPET-CT (pink ROI) measured by the visual assessment method. C: Axial PET-CT showing the GVT40% (red ROI), GTV50% (green ROI), GTV60% (blue ROI) and GTV 75% (white ROI), measured by the threshold method.

Whole body PET-CT was performed 90 minutes after intravenous administration of 0.154 mCi/Kg of 18F-FDG with the patient resting. Images were acquired in a Gemini Dual dedicated PET-CT (Phillips Medical Systems) with a 3-minute bed position time and the patient positioned in supine with arms in down extended position. All tumor volume design was performed in the workstation SYNTEGRA (Phillips Medical Systems) by the radiation oncologist and nuclear medicine staff. The SUV thresholds obtained from the studies were used as borders for lesion drawing either for 40, 50, 60, 75 percent of the maximum SUV value for each lesion and the final delineation and volume were calculated to each of them.

Statistical descriptive analysis was performed and Kolmogorov-Smirnov test was used to evaluate the distribution of the variables. Due to non-normality distribution, the Spearman test was applied. Correlations values of ≤ 0.25 were considered as weak; 0.25 to 0.50 as regular; 0.50 a 0.75 as moderated and ≥ 0.75 as strong correlation[20]. The Friedman test was used to verify differences between GTV40%, GTV50%, GTV60%, GTV75%, GTVPET-CT and GTV-CT, after that a post-hoc Dunn test was used to verify statistically significant differences. The statistical significance level adopted was 5% and the Statistical Package for Social Science - SPSS for Windows, version 17.0 and Graph Pad 3was used for data analysis and processing.

RESULTS

Most patients were male (n = 37, 74%) and mean age was 54.39 years, ranging from 31 to 81 years. The staging determined according to the TNM system[21] was stage II in 12%, III in 32% and IV in 56% of patients. The SUV values ranged from 2.19 to 21.61, with a mean of 6.99 and a median of 6.15.

According to tumor location, 20 were from the oropharynx, 11 from the nasopharyngeal posterior wall, 7 from the larynx, 5 from the hypopharynx, 4 from the nasal cavity/sinuses and 3 from the oral cavity.

Of the 60 lesions evaluated, 42% were primary tumors and 58% were metastatic sites. Thirty percent of the patients had not undergone any previous treatment, 36% underwent combined surgery, chemotherapy and radiotherapy, 16% chemotherapy and radiotherapy, 6% surgery and radiotherapy, 4% surgery and chemotherapy, 4% chemotherapy alone, 2% radiotherapy alone and 2% surgery alone.

Table 1 shows that GTV40%, GTV50%, GTV60%, GTV75% and GTVPET-CT had good correlation with the GTV-CT for all lesions and for the untreated lesions. For all lesions, GTVPET-CT showed a strong correlation with GTV-CT, while the other variables showed only moderate correlation. For the untreated lesions, GTVPET-CT and GTV75% showed a strong correlation with GTV-CT, while the other variables showed only moderate correlation.

Table 1. Correlation of GTV40%, GTV50%, GTV60%, GTV75% and GTVPET-CT with the GTV-CT in all lesions (n = 60) and in the untreated lesions (n = 20).

	All lesions			Untreated Lesions		
Variable	n	Rho	*p*	n	Rho	*p*
GTV 40%	60	0.66	< 0.001	20	0.68	< 0.05
GTV 50%	60	0.68	< 0.001	20	0.72	< 0.05
GTV 60%	60	0.64	< 0.001	20	0.61	< 0.05
GTV 75%	60	0.55	< 0.001	20	0.76	< 0.05
GTV PET-CT	60	0.79	< 0.001	20	0.91	< 0.05

Tables 2 and 3 show the distribution of the differences of the GTV40%, GTV50%, GTV60%, GTV75% and GTVPET-CT with the GTV-CT for all lesions and for the untreated lesions, respectively. In both populations, the lowest median values were observed for the difference between GTV40% and GTVPET-CT with the GTV-CT.

Table 2. Descriptive statistics of the differences of GTV40%, GTV50%, GTV60%, GTV75% and GTVPET-CT with the GTV-CT for all lesions (n = 60).

Variable	n	Minimum	P25	Median	P75	Maximum
GTVCT-GTV40%	60	-22.06	-4.58	3.41	11.31	66.52
GTVCT-GTV50%	60	-4.92	0.71	6.88	16.64	100.97
GTVCT-GTV60%	60	-1.12	3.17	10.91	22.76	117.11
GTVCT-GTV75%	60	0.99	5.51	14.52	27.49	125.34
GTVCT-GTVPET-CT	60	-11.00	0.5	4.48	9.64	50.99

Table 3. Descriptive statistics of the differences of GTV40%, GTV50%, GTV60%, GTV75% and GTVPET-CT with the GTV-CT for untreated lesions (n = 20).

Variable	n	Minimum	P25	Median	P75	Maximum
GTVCT-GTV40%	20	-8.88	0.30	7.37	15.36	66.52
GTVCT-GTV50%	20	-3.19	4.31	10.17	24.26	70.50
GTVCT-GTV60%	20	0.34	5.18	14.29	30.51	73.35
GTVCT-GTV75%	20	3.33	6.84	19.90	36.65	76.31
GTVCT-GTVPET-CT	20	0.47	2.73	6.36	14.98	35.65

Table 4 shows the comparison between GTV40%, GTV50%, GTV60%, GTV75% and GTVPET-CT with the GTV-CT through the Dunn's multiple comparison test for all lesions and for the untreated lesions. For both groups, the GTV50%, GTV60% and GTV75% showed statistically significant difference in relation to GTV-CT. On the other hand, GTVPET-CT and GTV40% did not show statistically significant difference in relation to GTV-CT.

Table 4. Comparison between GTV40%, GTV50%, GTV60%, GTV75% and GTVPET-CT and the GTV-CT in all lesions (n = 60) and in the untreated lesions (n = 20).

Comparison	All lesions	Untreated lesions
	*p**	*p**
GTV40% *vs.* GTV-CT	> 0.05	> 0.05
GTV50% *vs.* GTV-CT	< 0.001	< 0.001
GTV60% *vs.* GTV-CT	< 0.001	< 0.001
GTV75% *vs.* GTV-CT	< 0.001	< 0.001
GTVPET-CT *vs.* GTV-CT	> 0.05	> 0.05

* Dunn's multiple comparison test.

DISCUSSION

In this study, we tried to address the influence of metabolic information from PET-CT with 18F-FDG on the definition of target volumes for radiotherapy planning in patients with head and neck tumors. The GTV-CT, because it is currently considered the gold standard for planning, was used as a reference for comparing the metabolic GTVs new standards introduced with the advent of functional imaging of PET-CT with 18F-FDG, which are the GTVs determined by the threshold method and also the GTVPET-CT determined by the visual qualitative method.

The lesions we studied were separated into two groups, the first comprised the total number of lesions (treated and untreated) and the second only the untreated lesions. Most of the studies to date on this topic have been limited to untreated lesions[16,22-24] and therefore technically simpler to be delineated. Our purpose by including those patients previously treated in our sample is associated with the need to evaluate these tools in patients with anatomic distortion after surgery or previous chemotherapy and/or radiotherapy, which represents the majority of the population we observe in our institution.

The sample of our study was similar to previous studies on this theme, composed predominantly by males, with SCC, stages III and IV, and with the usual distribution of lesions for this pathology[16,22-24]. When analyzing the values of SUV, we observed that our values were mildly reduced when compared to previous studies[16], which may be associated with the inclusion of patients submitted to previous radiotherapy and/or chemotherapy without surgery, thus contributing to reduced levels of metabolism and SUV.

Most studies of patients with head and neck tumors choose the method of threshold, setting the design in 40% of SUV[9,13,25] and 50% of SUV[11]. The value of 40%, initially applied to cases of non-small cell lung cancer, was established after the introduction of simulators in clinical practice. Therefore, based on the above studies, we adopted the threshold values of 40% and 50%, values of 60% and 75% were defined empirically by the absence of information on these data, and the qualitative visual method that is more commonly used in radiotherapy planning.

Our results suggested that, in most cases, when the set threshold value is equal to or greater than 50%, there is a potentially reduced and possibly insufficient coverage of the tumor tissue displayed CT, regardless of the lesions have been submitted to previous therapeutic interventions or not.

Based on the results of this study, the values of GTV40% and GTVPET-CT do not have a statistically significant difference compared with the GTV-CT. Thus, it is potentially applicable and desirable to use the threshold value of 40% of the maximum SUV to automatically delineate the planning, which could possibly help to reduce the uncertainties associated with changes in the methodology of the qualitative visual method.

Due to the behavior GTV40% and GTVPET-CT does not change, regardless of the clinical indication for radiotherapy planning, this interesting tool tested opens the

possibility to be used in the untreated lesions on staging, as well as in all the treated and non-treated lesions in the daily oncology practice.

In conclusion, the use of PET-CT with 18F-FDG changes the volume of the final target in head and neck tumors, depending on the methodology used to calculate the GTV. The results presented here showed that the GTV40% and the GTVPET-CT are those who are closer to the target volumes delineated by conventional CT. Values of GTV40% proved to be potentially applicable to automatically delineate the planning and possibly help to reduce the uncertainties associated with changes in the methodology of the qualitative visual method.

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