Published in final edited form as:

Eur J Radiol. 2016 February ; 85(2): 319–323. doi:10.1016/j.ejrad.2015.11.039.

Is there a role for PET/CT parameters to differentiate thyroid cartilage invasion from penetration?

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Abstract

Background—Assessment of thyroid cartilage invasion (tumor extension through inner cortex) and thyroid cartilage penetration (tumor involving both the inner and outer cortices of thyroid cartilage) may be challenging with CT (Computed Tomography) and MR imaging (Magnetic Resonance Imaging). Positron Emission Tomography/Computed Tomography (PET/CT) is a non invasive imaging modality that provides both anatomic and metabolic information. Quantitative data obtained from PET/CT, also known as PET/CT parameters, include maximum, mean or peak standardized uptake values (SUVmax, SUVmean, SUVpeak), metabolic tumor volume (MTV), total lesion glycolysis (TLG), standardized added metabolic activity (SAM) and normalized standardized added metabolic activity (NSAM). Our aim was to examine if FDG PET/CT parameters could differentiate thyroid cartilage invasion from penetration.

Methods—50 patients who underwent PET/CT before laryngectomy for squamous cell carcinoma of the larynx, had SUVmax, SUVmean, SUVpeak, TLG, MTV, SAM and NSAM calculated on a dedicated workstation. Univariate and multivariate analysis was performed. ROC analysis was used to determine the ability of PET/CT parameters to predict pathologically proven thyroid cartilage invasion or penetration.

Results—Of the 50 patients, 50% (25/50 patients) had history of prior radiation therapy. Among the previously irradiated group, 24% had thyroid cartilage invasion and penetration. 8% of the patients in this group had thyroid cartilage invasion only. Among the non-irradiated group, 76%

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Conflicts of interest
None.

had thyroid cartilage invasion and penetration, 8% had thyroid cartilage invasion without penetration. ROC analysis revealed that none of the PET/CT parameters had enough power to predict thyroid cartilage penetration, but TLG, MTV and SAM had enough power to predict thyroid cartilage invasion in non-irradiated patients. TLG, MTV, SAM and NSAM had enough power to predict thyroid cartilage invasion and penetration in irradiated group.

Conclusion—TLG, MTV and SAM have enough power to predict thyroid cartilage invasion and penetration in irradiated patients. PET/CT parameters do not have enough potential to differentiate thyroid cartilage invasion from penetration.

Keywords

Larynx; Positron Emission Tomography; Thyroid Cartilage; Head and neck squamous cell carcinoma

Introduction

Since the US Department of Veterans Affairs (VA) laryngeal study group and the radiation therapy oncology (RTOG) 91-11 trials, there has been significant change in the management of T3 and T4a laryngeal squamous cell carcinoma (SCCa) [1-3]. Extent thyroid cartilage involvement is a defining factor between T3 and T4a stages. Laryngeal SCCa with involvement of only inner cortex of the thyroid cartilage (thyroid cartilage invasion) is staged as T3 and those involving both inner and outer cortices of the thyroid cartilage (thyroid cartilage penetration) are staged as T4a [1-3]. Currently American Society of Clinical Oncology and the National Comprehensive Cancer Network expert panels recommend initial laryngectomy for patients with T4a laryngeal carcinoma. T3 laryngeal SCCa can be treated with radiation therapy as initial treatment strategy.

Before the VA and RTOG 91-11 trials, the primary question for the patient with advanced laryngeal carcinoma was whether the patient was operable [2]. Identification of imaging findings such as thyroid cartilage invasion, penetration, or extralaryngeal spread were not important, as the management was total laryngectomy, regardless of degree of cartilage involvement [2]. As a result of these trials, the impact of thyroid cartilage invasion (T3) versus penetration (T4a) has been recognized as important, as cartilage penetration is usually treated surgically [1-3]. 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG PET/CT) imaging has been increasingly used in the assessment head and neck SCCa [4], as it provides both anatomical and functional information. There are a variety of parameters that can be acquired from quantitative analysis of FDG PET/CT. PET/CT parameters can be used as biomarkers that may have prognostic and diagnostic value [4].

Anatomic imaging alone, computed tomography (CT) and magnetic resonance imaging (MRI), has become extremely important in clinical decisions about whether to proceed with radiation therapy (RT) or total laryngectomy. The differentiation between thyroid cartilage invasion versus penetration can be difficult, even with the most advanced imaging technique. However, the myriad of metabolic markers available with PET/CT are rarely used to direct

treatment. Our goal, therefore was to examine if FDG PET/CT parameters could impact treatment planning by differentiating thyroid cartilage invasion from penetration.

Methods and materials

Patients

After institutional review board approval and waiving for informed consent for this retrospective study we performed a database review of the Department of Pathology to identify patients who had undergone total laryngectomy for SCCa of the larynx between November 2002 and April 2014. Fifty patients were identified who had preoperative PET/CT performed, total laryngectomy, and pathologic examination to determine cartilage invasion or penetration.

FDG-PET/CT Protocol

All PET/CT studies were performed using one of 4 PET/CT systems (GE Discovery 690 Elite, 600, ST, or LS; General Electric, Milwaukee, Wis). Patients fasted at least 4 hours before the scan, and were imaged approximately 60 minutes after radiotracer injection. Patients were instructed not to talk during uptake time. Scans were obtained from skull vertex to mid thigh with arms down. All PET data was reconstructed with and without CT-based attenuation correction. The emission scan lasted for 2-4 minutes for each bed position.

Image Analysis

All PET/CT studies were retrieved from the electronic archival system and reviewed on a MIMvista workstation (software version 6.1; MIM Software Inc) by two board certified radiologists (ATK, ASC), with subspecialty training in Nuclear Radiology and Neuroradiology, and in Neuroradiology with expertise in head and neck imaging, respectively. PET/CT images were reviewed in multiple planes. Volume of Interest (VOI_{PET}) was determined as the volume of hypermetabolic FDG uptake using a gradient technique from commercially available software (PETedge; MIM Software, Inc.; Cleveland, Ohio).

The imaging biomarker measurements performed included maximum standardized uptake value (SUV max), mean standardized uptake value (SUV mean), peak standardized uptake value (SUV peak), metabolic tumor volume (MTV), total lesion glycolysis (TLG), standardized added metabolic activity (SAM) and normalized SAM (NSAM). All SUVs in this study were normalized to body weight. After the primary tumor was segmented, SUV max, SUV mean, SUV peak, MTV and TLG were automatically calculated by the MIMvista software.

SUV max reflects the highest pixel in a volume of interest (VOI) [4]. Metabolic tumor volume (MTV), another parameter which gained interest in recent years [4,5], is the volume of visually positive FDG activity [4,5].

SUV mean reflects the average SUV of all the voxels in VOI. SUV peak is the local average of a 1 ml spherical volume centered on SUV max. SUV peak has been proposed to be less effected by image noise and a more reproducible parameter compared to SUV max [4]. TLG is the product of MTV and SUV mean, incorporating both tumor size and functionality [4].

Both SUV max and SUV peak are prone to volume averaging, which could be challenging in the assessment of small tumors [4,6,7]. SUV mean, TLG and MTV will vary with the method used to determine the VOI [4].

A recently reported measurement, SAM tries to avoid partial volume effects and seeks to identify only the metabolic activity above background, corresponding to the tumor uptake [8]. However SAM is also impacted from the scanner calibration, injected dose of radiotracer and patient's body weight [4,8]. To avoid these limitations, Mertens et al [8] also introduced NSAM (SAM/mean background).

To calculate SAM the VOI_{PET} was determined as noted above. A second VOI (VOI_{SAM}) acquired by expanding VOI_{PET} by 3mm in three dimensions. VOI_{SAM} contains all of the counts due to the tumor but also includes some counts from surrounding tissue. A third VOI (VOI_{BKG}) obtained by expanding VOI_{SAM} , again by 3 mm, excluding other structures with high activity. Average SUV in the volume between VOI_{SAM} and VOI_{BKG} was calculated and used to subtract the SUVs that would be present in VOI_{SAM} in the absence of tumor (**Figure 1, 2**). Thus SAM represents the total SUVs above background for the tumor. Normalized SAM (NSAM) is calculated as $SAM / (\text{Average normal tissue SUV})$.

Statistical Analysis

The purpose of the project was to determine association between PET analysis with thyroid cartilage invasion or penetration. The outcome variables were SUVmax, SUVmean, SUVpeak, TLG, MTV, SAM and NSAM. Age, gender, T stage at presentation, N stage at presentation, recurrence after radiotherapy (RT recurrence), thyroid cartilage invasion, thyroid cartilage penetration are covariates that are potentially associated with the outcome variables. Age and the outcome variables were considered as continuous variables. The others are considered as the categorical variables. The mean and standard deviation are presented for the continuous variables and frequencies and percentages are presented for the categorical variables.

Chi-square test or Fisher exact test was employed to test if there was an association between the characteristics of patients and history of radiation therapy. Two-sample T test was employed to test for any difference of age between non-irradiated patients and irradiated patients.

Generalized linear model was employed for univariate and multivariate analyses. Log transformation is applied for the outcome variables of SUVmax, SUVmean, SUVpeak, TLG, MTV, SAM and NSAM to fit the model better since the distributions of these variables are highly skewed. History of radiation therapy and thyroid cartilage invasion were forced in the model due to the purpose of the project. The other covariates that are significant in the univariate analyses were also put in the model for the model selection. AIC (*Akaike information criterion*) criterion was used for the model selection.

The predictive discriminatory powers on thyroid cartilage penetration or thyroid cartilage invasion related to PET parameters (SUVmax, SUVmean, SUVpeak, TLG, MTV, SAM and NSAM) were analyzed with receiver operating characteristics (ROC) analysis. Their abilities

to predict thyroid cartilage invasion or penetration status were determined by using ROC curves and measuring the area under the curve (AUC). Whether the AUCs of ROC curves were different from 0.5 (which means no discrimination ability) are tested with Chi-square tests. The cutoff values in the ROC curves were estimated in order to obtain specific sensitivity (such as 90%), specificity (such as 90%). The optimal cut-point was determined by the Youden index, the maximum difference between sensitivity and 1-specificity. The significance level for the analyses was 0.05. SAS 9.3 was employed for the data management and analyses.

Results

Patient characteristics

Fifty patients met the eligibility and inclusion criteria. Patient demographics and characteristics between patients without prior radiation therapy and patients who recurred after radiation therapy are listed in **Table 1**.

Twenty-two patients were scanned on the GE Discovery LS, 8/50 on the GE Discovery ST in 2D mode, 5/50 patients were scanned on the GE Discovery 690 Elite in 3D mode, and 15/50 on the GE Discovery 600 in 3D mode. The mean patient blood glucose level was 99.02 (SD±21.8) mg/dl. Patients were injected with a mean of 14.51 (SD±1.84) mCi of 18F-FDG.

Univariate/multivariate analysis

Thyroid cartilage invasion and penetration were each associated statistically significantly with elevated PET/CT parameters in univariate analysis. In the multivariate analysis, only prior history of radiation therapy and thyroid cartilage invasion status were associated significantly with PET/CT parameters. After adjusting the effect of prior history of radiation therapy, thyroid cartilage invasion has statistically significantly high TLG, MTV, SAM and NSAM.

ROC analysis

ROC analysis performed for both irradiated and non-irradiated laryngeal carcinoma patients. ROC analysis of irradiated patients showed that only TLG, MTV, SAM and NSAM have significant power to predict thyroid cartilage invasion and penetration respectively (**Tables 2 and 3**). ROC analysis of non-irradiated group showed that none of the PET/CT parameter has significant power to predict thyroid cartilage penetration, while, TLG, MTV, and SAM have significant power to predict thyroid cartilage invasion.

Discussion

As identification of thyroid cartilage invasion or penetration currently changes the management of laryngeal SCCa, determination of this often subtle but very important detail has become important. Different imaging modalities have been tested for accuracy for this purpose. Computed tomography (CT), which has been the 'work horse' of head and neck carcinoma imaging, showed sensitivity and specificity for thyroid cartilage penetration as

72% and 84%, respectively [1], but had an 18.5% false positive rate for thyroid cartilage penetration [3]. MRI initially appeared more promising to identify thyroid cartilage invasion, however presence of perichondral edema, which may appear similar to invasion, may also result in false positives [3]. Recently Becker et al [9] introduced new MRI criteria to improve differentiation of neoplastic cartilage invasion versus malignancy related inflammatory changes [1,9] but there is still limited information about accuracy of MRI interpretation for thyroid cartilage invasion, penetration and/or extralaryngeal spread [1].

In a recent and promising study, Kats et al [3] recommended incorporation of gross tumor volume (GTV) assessment from CT into the diagnostic formula to improve prediction rate of thyroid cartilage invasion. The study did not differentiate thyroid cartilage invasion from penetration. This analysis revealed promising results among RT-naïve patients using a cut off of 50 cm³ with sensitivity of 47%, specificity of 94%, PPV 78% and NPV of 80% in detecting thyroid cartilage penetration in patients with advanced laryngeal carcinoma [3]. However GTVs calculated by using CT and MR images are labor and time intensive, and have high inter, or intraobserver variability [10].

Daisne et al [10] compared GTVs calculated at CT and MRI and FDG PET/CT with pathological specimens. GTVs at FDG/PET CT were smaller and found to be more accurate than those at CT and MRI [10]. Calculation of GTV as metabolic tumor volume (MTV) from FDG PET/CT has been a very promising PET/CT parameter to evaluate tumor volume and functionality together [5].

In recent years FDG PET/CT gained significant importance in staging and restaging of head and neck SCCa [4,5]. FDG PET/CT not only offers anatomical information but also functional information [4,5]. Quantitative assessment of the functional information provides a variety of different PET/CT parameters.

This is the first study, to our knowledge, assessing the role of PET/CT parameters in identification of thyroid cartilage invasion or penetration. Our results showed none of the PET/CT parameters had enough power to predict thyroid cartilage penetration in non-irradiated patients. TLG, MTV and SAM had enough power to predict thyroid cartilage invasion in this group. TLG, MTV, SAM and NSAM had power to predict thyroid cartilage invasion and penetration in irradiated patients. In previously irradiated patients, it is difficult to differentiate thyroid cartilage invasion and penetration from post radiation changes by CT. Recent study by Kats et al also showed that this is still a difficult task by gross tumor volume (GTV) evaluation as well. Hence, PET/CT parameters may play a role in identifying patients with thyroid cartilage invasion/penetration in previously irradiated patients.

PET/CT parameters did not show potential to differentiate between thyroid cartilage invasion and penetration in either group. Our study is limited due to relatively small patient population for each of the separate groups. Our group with thyroid cartilage invasion included patients who had thyroid cartilage penetration. We had only 4 cases with thyroid cartilage invasion only, two were in non-irradiated group and 2 were in irradiated group.

In conclusion, Although PET/CT parameters do not have potential to differentiate thyroid cartilage invasion from penetration, TLG, MTV, SAM and NSAM have enough power to

predict thyroid cartilage invasion and penetration in irradiated patients. Rarely, a patient may be a candidate for re-irradiation, and these metabolic parameters may help in this treatment decision. Unfortunately, most patients who have been radiated are not candidates for anything other than a total laryngectomy, so our results will have limited clinical applicability. This could be important in cases where differentiation of thyroid cartilage involvement from post radiation changes is difficult.

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Figure 1.

67 year old male, previously irradiated. T4a transglottic laryngeal carcinoma with pathologically proven thyroid cartilage penetration. Axial fused PET/CT (1A) shows the location and extent of the metabolic activity of the tumor. Sagittal and coronal PET/CT images (1B, 1C) show the primary VOI (red) and two outer VOIs (light blue and dark blue). SUV max, SUV mean, MTV, and TLG were calculated from VOI_{PET} (defined by a gradient method using the PET uptake, red contour). SUV peak was centered on the voxel defined by SUV max. SAM was calculated as the total SUVs from VOI_{SAM} less the normal tissue SUVs calculated from the volume between VOI_{SAM} (light blue contour) and VOI_{BKG} (dark blue contour).

Figure 2. 62 year old female, previously irradiated. T3 transglottic laryngeal carcinoma with pathologically proven thyroid cartilage invasion. Axial fused PET/CT (2A) shows the location and extent of the metabolic activity of the tumor. Sagittal and coronal PET/CT images (2B, 2C) show the primary VOI (red) and two outer VOIs (light blue and dark blue).

Table 1

Descriptive statistics

Variable	Level	N (%) = 50
age65	<65	28 (56.0)
	>=65	22 (44.0)
Sex	Female	13 (26.0)
	Male	37 (74.0)
Variable	Level	N (%) = 50
Path Tstage	T1-T2 (including Tx)	9 (18.0)
	T3-T4	41 (82.0)
Path N stage	N0	31 (62.0)
	N1-N2 (including Nx)	19 (38.0)
Primary location	Glottic	21 (42.0)
	Supraglottic/Subglottic/transglottic	29 (58.0)
t.cart.penetration	no	25 (50.0)
	yes	25 (50.0)
t.cart.invasion	no	21 (42.0)
	yes	29 (58.0)
Rthistory	no	25 (50.0)
	yes	25 (50.0)
Age	Mean	63.58
	Median	62.50
	Minimum	42.00
	Maximum	91.00
	Std Dev	9.83
	Missing	0.00

Table 2

The cutoff values of PET parameters to predict invasion when achieving 90% sensitivity, 90% specificity and maximum sum of sensitivity and specificity as well as prediction power in term of area under curve (AUC) and p-value in the receiver operating characteristics (ROC) analysis comparison AUC=0.5.

Variables	90% sensitivity	90% specificity	Maximum sum of sensitivity and specificity	AUC	P value
SUV max	Spe=47% SUV max=7.75	Sen=37.5% SUV max=16.2	Sen=100% Spe=47 % SUV max=7.7	0.684	0.093
SUV mean	Spe=41% SUV mean=4.3	Sen=25% SUV mean=8.8	Sen=100% Spe=41 % SUV mean=4.6	0.640	0.224
SUV peak	Spe=59% SUV peak =6.05	Sen=38% SUV peak =12.6	Sen=100% Spe= 59% SUV peak=6.1	0.735	0.021
TLG	Spe=59% TLG =23.6	Sen=50% TLG =117.5	Sen=100% Spe= 59% TLG=23.4	0.809	0.0005
MTV	Spe=59% MTV=5.2	Sen=50% MTV=18.3	Sen=100% Spe= 59% MTV=5.03	0.816	0.0003
SAM	Spe=59% SAM=22.0	Sen=50% SAM=89.0	Sen=100% Spe= 59% SAM=21.08	0.805	0.0006
N SAM	Spe=65% N SAM=11.9	Sen=50% N SAM=50.3	Sen=100% Spe=65 % N SAM=11.9	0.838	<0.0001

Table 3

The values of PET parameters to predict penetration when achieving 90% sensitivity, 90% specificity and maximum sum of sensitivity and specificity as well as prediction power in term of area under curve (AUC) and p-value in the receiver operating characteristics (ROC) analysis comparison AUC=0.5.

Variables	90% sensitivity	90% specificity	Maximum sum of sensitivity and specificity	AUC	P value
SUV max	Spe=58% SUV max=8.8	Sen=0% SUV max=19.5	Sen=100% Spe= 58% SUV max=8.64	0.667	0.131
SUV mean	Spe=37% SUV mean=4.6	Sen=0% SUV mean=10.1	Sen=100% Spe=37% SUV mean=4.6	0.605	0.368
SUV peak	Spe=53% SUV peak =6.0	Sen=17% SUV peak =15.6	Sen=100% Spe= 53% SUV peak=6.1	0.693	0.071
TLG	Spe=53% TLG =23.2	Sen=50% TLG =120.6	Sen=100% Spe=53 % TLG=23.4	0.798	0.003
MTV	Spe=53% MTV=5.2	Sen=50% MTV=19.6	Sen=100% Spe= 53% MTV=5.03	0.816	0.001
SAM	Spe=58% SAM=26.9	Sen=33% SAM=178.5	Sen=100% Spe= 58% SAM=23.9	0.803	0.001
N SAM	Spe=64% N SAM=14.0	Sen=50% N SAM=52.1	Sen=100% Spe=64 % N SAM=12.0	0.825	0.0003