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¹⁸F-FDG PET/CT Metabolic Tumor Volume and intra-tumoral heterogeneity in pancreatic adenocarcinomas: Impact of Dual-Time-Point and Segmentation Methods

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Abstract

Objectives—We aimed to determine the consistency of quantitative PET measurements of metabolic tumor volume (MTV) and intra-tumoral heterogeneity index for primary untreated pancreatic adenocarcinomas, when using dual-time-point ¹⁸F-FDG PET/CT imaging.

Methods—This is an Institutional Review Board approved, retrospective study including 71 patients with pancreatic adenocarcinoma, who underwent dual-time-point ¹⁸F-FDG PET/CT imaging, at ~1h (early) and ~2h (delayed), post injection. Automated gradient-based and 50% SUV_{max}-threshold segmentation methods were used to assess the primary tumor MTV, and metabolic intra-tumoral heterogeneity index, calculated as the area under Cumulative SUV-volume histograms (AUC-CSH), with lower AUC-CSH indexes corresponding to higher degrees of tumor heterogeneity. We defined that more than a $\pm 10\%$ change in MTV or AUC-CSH, compared to baseline, as clinically significant.

Results—71 FDG-avid pancreatic tumors were identified, with an average tumor diameter of 3.4 ± 0.9 cm (range, 1.5 to 6.4 cm). MTV values remained consistent between early and delayed imaging when using the gradient PET segmentation method ($p=0.086$), whereas statistically significant change was seen when using 50% SUV_{max}-threshold segmentation ($p < 0.001$). A decrease in more than 10% change in MTV (% MTV) was observed in 70.4% (50/71) tumors, and 7.0% (5/71) of the tumors showed an increase more than 10 % MTV, when using the 50% SUV_{max}-threshold segmentation. AUC-CSH indexes showed statistically significant differences between early and delayed time points ($p < 0.001$), when using the gradient segmentation. AUC-CSH index decreased 10% in 40.8% (29/71) of the tumors. AUC-CSH index remained stable

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between early and delayed when using the 50% SUV_{max} -threshold segmentation ($p=0.148$) with % of change of less than 10% for all tumors.

Conclusion—Metabolic Tumor Volume was relatively stable between early and delayed time points when PET gradient segmentation was used but changed >10% in 77.4% of the tumors at delayed time point when threshold segmentation was used. The tumor heterogeneity index (AUC-CSH) changed >10% in 40.8% of tumors at delayed imaging, when gradient segmentation was used but remained stable when threshold segmentation was used. It is important to standardize uptake time and segmentation methods to use FDG PET metabolic tumor volume and heterogeneity index as imaging biomarkers.

Keywords

^{18}F -FDG-PET/CT; dual-time-point; metabolic tumor volume (MTV); intra-tumoral heterogeneity; pancreatic adenocarcinoma

INTRODUCTION

Pancreatic cancer is well-known for being the five most lethal malignancies in the world, with over 330,000 deaths worldwide ¹. In developed countries, its annual mortality rate closely equals its incidence at 8.3 versus 8.6 per 100,000, respectively, thereby reflecting a short survival time, generally less than 1 year ¹. Pancreatic cancer is already advanced at the time of diagnosis in the majority of cases, and only 10–20% of patients will be considered for curative surgery ^{2,3}, while more than 50% of patients will present with metastatic disease and could only be treated with palliative chemotherapy ⁴. Among the patients who undergo surgical resection, the 5 year survival rate is about 15%–40% ^{5,6}.

As a standard of care, patients with suspected pancreatic lesions are scanned with ^{18}F -FDG PET/CT at one hour post-injection; however it is unclear if this particular timing allows for optimal imaging of pancreatic cancer. ^{18}F -FDG uptake continues to rise over time in malignant tumors, even after several hours post-injection, while this is rare for benign lesions ^{7,8}. At the same time, a longer distribution time allows for improvement of blood pool and urinary tract clearance of FDG, and lowers background activity. Therefore, delayed scanning, in addition to the usual standard 1 hour post-injection scan, may provide additional valuable information for tumor staging and patient prognosis ⁹. Dual time point FDG-PET has been shown to differentiate between malignant and benign processes of several malignant tumors ¹⁰, increasing the diagnostic sensitivity and specificity for head and neck cancers, breast cancer, and malignant lung lesions ¹¹. Other studies have demonstrated the value in grading tumors, such as breast cancers ¹², and gliomas ¹³ using dual time point imaging.

The most widely used PET-derived parameter to measure tracer accumulation in PET is the maximum standardized uptake value (SUV_{max}), which quantifies tumor glucose metabolic uptake ^{14,15}. Recently, studies have supported the use of volumetric parameters such as metabolic tumor volume (MTV) as a potential marker for predicting outcome, and for radiation therapy planning in patients with resectable pancreatic cancer ^{16–19}. Furthermore, recent interest has raised in the development of new imaging strategies to assess for intra-

tumoral heterogeneity^{20,21}. To adopt new PET metrics into the clinical practice, such as metabolic tumor volume and intra-tumor heterogeneity index, it is important to determine its reproducibility. MTV have been previously shown to have low inter-observer variability^{22,23}. Although the impact of dual time point SUV measurements has been evaluated in various malignant tumors, there is little knowledge about the consistency of volumetric PET parameters, or intra-tumoral heterogeneity when using two time points imaging. The consistency of intra-tumoral heterogeneity over time has not been previously studied and assessing the consistency of MTV measurements over time in patients is limited²².

Our study aimed to evaluate the consistency of both volumetric PET metrics and quantitative index of intra-tumoral heterogeneity in patients with newly diagnosed pancreatic adenocarcinomas using dual-time-point FDG-PET imaging.

MATERIAL AND METHODS

We conducted a retrospective study including 71 patients (mean age 67 ± 9 yo, range 48 to 88 yo), biopsy-proven newly diagnosed pancreatic adenocarcinoma, who underwent a baseline ^{18}F -FDG PET/CT staging using dual time point imaging at 1 h and at 2 h after intravenous FDG injection. This was an Institutional review board approved, HIPAA-compliant, PET/CT imaging study, and patients' informed consents were waived. None of the patients had surgery, radiation therapy or systemic chemotherapy before being scanned with ^{18}F -FDG PET/CT. Patients with uncontrolled diabetes, active inflammation or second primary malignancy were excluded. The demographic patients' characteristics are detailed in Table 1.

PET/CT Protocol

Patients were instructed to fast for at least 4 hours before scanning and their weight, height, and blood glucose levels were recorded at the time of the scan. The mean blood glucose level was 113.7 mg/dL (range, 50–193 mg/dL), with an average injected dose of 558.7 MBq (range, 310.8–925 MBq). Patients were scanned from the base of the skull to mid thighs with a second PET/CT acquisition of the upper abdomen using 2 fields of view to include the entire pancreas. Patient was asked to void the bladder between scans. The time interval between the ^{18}F -FDG injection and the first and second scans were 64.2 ± 0.25 minutes (range, 56.1–85.3 minutes), and 118 ± 0.4 min (range, 94–151 minutes), respectively.

Patients were scanned using a 64-MDCT lutetium oxyorthosilicate crystal scanner (Discovery VCT, General Electric Medical Systems, Waukesha, Wis, U.S), in 3D acquisition mode with 4.15 minutes per bed position. The images were reconstructed using the ordered subset expectation maximization algorithm, with 128×128 matrix, two iterations, 21 subsets, 3-mm post-reconstruction Gaussian filter, and standard Z filter, 4.7-mm pixel, and 3.27-mm slice thickness. PET data were reconstructed with and without CT-based attenuation using an unenhanced CT for attenuation correction and anatomical co-registration. CT parameters were 50 cm axial dynamic FOV, weight-based, 20–200 mA, 120–140 kVp, 3.75-mm slice thickness, pitch of 0.984, 0.5-second gantry rotation speed and 512×512 matrix²⁴.

Image Analysis

An experienced nuclear medicine physician reviewed the PET/CT images using a MIM workstation (MIM Software, version 5.2). Axial, coronal, and sagittal PET, CT and fused PET/CT images were used for the identification of the primary pancreatic lesion. The automated semi-quantitative PET parameters included the maximum SUV (SUV_{max}), reflecting a maximum single-pixel uptake value adjusted for lean body mass, the peak SUV (SUV_{peak}) calculated using an automated computed maximal average SUV in a 1.0 cm^3 spherical volume within the tumor²⁵, the metabolic tumor volume (MTV) expressed as tumor volume with FDG uptake, and the tumor glycolytic activity (TLG) representing the tumor metabolic volume multiplied by average SUVs of included voxels²⁶. For each lesion, SUV_{max} , SUV_{mean} , and SUV_{peak} , MTV and TLG were measured using two validated PET segmentation methods: a gradient-based and a 50% SUV_{max} -threshold.

The gradient-based segmentation was performed using an edge-detection tool that generated an automated volume of interest (VOI) within the lesion, outlined in axial, transverse and sagittal views by placing the cursor in the center of the lesion and dragging it out until the three orthogonal guiding lines reached the boundaries of the FDG-avid lesion, avoiding for normal adjacent structures. For the threshold segmentation technique, a 50% SUV_{max} -threshold was applied using a spherical VOI, predefined by MIM software tool, which was placed over the lesion, adjusting to include the entire FDG-avid tumor, avoiding normal adjacent structures. Once the reader verified drawn boundaries in all three orthogonal planes, segmentation of the obtained volume was performed²⁴.

The quantitative index of intra-tumoral metabolic heterogeneity (AUC-CSH index) was calculated as the area under the curve (AUC) of a Cumulative SUV-volume histogram (CSH) obtained by plotting the percent volume greater than the percentage of SUV_{max} (calculated for gradient-based and for 50% SUV_{max} -threshold); with lower AUC corresponding to higher degrees of heterogeneity²⁷. Early and delayed time points AUC-CSH indexes were extracted from MIM software for the two PET segmentation methods.

Statistical Methods

Descriptive values were expressed as the mean ($\pm$ SD) or median [25th, 75th range], if data were not normally distributed. The change in the SUV_{max} [Retention index (RI)] was calculated from the 1h early scan and the 2 h delayed scan according to the following formula: $RI = (\text{delayed } SUV_{max} - \text{early } SUV_{max}) / (\text{early } SUV_{max}) \times 100$. The relative percentages of change between early and delayed values for the other quantitative PET parameters, i.e. for SUV_{peak} , MTV and TLG, and AUC-CSH index were also calculated as: $[(\text{delayed (value)} - \text{early (value)}) / \text{early (value)}] \times 100$. We defined more than $\pm 10\%$ of change, compared to baseline, as clinically significant. Independent Student's t-test was performed to compare normal variables, otherwise, non-parametric tests including Wilcoxon's signed-rank test for paired data was used to compare MTV, SUV_{max} , SUV_{peak} , TLG, and AUC-CSH index. Pearson correlation coefficients were performed to examine the strengths of association between the two PET segmentation variables: PET-gradient and 50% SUV_{max} -threshold methods. Correlations values closer to ± 1 were representative of

perfect degree of association. Statistical analyses were conducted using the SPSS software (version 15.0, SPSS Inc).

RESULTS

Patient Characteristics

A total of 71 patients with biopsy-proven newly diagnosed pancreatic adenocarcinoma were investigated in the present study. One FDG-avid pancreatic tumor was identified in each patient. Tumor sizes, measured on the non-contrast CT, ranged from 1.5 to 6.4 cm, with a median size of 3.5 ± 0.9 cm. There were 15 patients with stage II, 34 patients with stage III, and 22 patients with stage IV pancreatic adenocarcinoma. Patients' clinical characteristics are described in Table 1.

SUV_{max} and SUV_{peak}

The pancreatic tumors demonstrated increased FDG avidity at delayed time points as compared to the early time points, except for four cases where the tumor uptake remained stable. SUV_{max} statistically increased from early to delayed time points (SUV_{max} 5.6 ± 2.7 [range, 2.1 to 15.8] vs 7.0 ± 2.7 [range, 2.5–15.9] (paired t-test, $p < 0.001$). An increase in SUV_{max} was seen in 94.4% (67/71) of the tumors with a retention index (RI) of $26.8 \pm 17.8\%$ (range 0.3% to 88.5%); this increase metabolic uptake was greater than 10% in 56 tumors, and greater than 20% in 41 tumors. The remainder 5.6% (4/71) of the tumors showed stability ($< 10\%$ increase) in the delayed time point SUV_{max}. Statistically significant increase was seen between early and delayed SUV_{peak} (4.5 ± 2.1 vs 5.3 ± 2.4 , $p < 0.0001$).

Metabolic Tumor Volume

MTV measurements were found to be consistent over time when using the PET gradient segmentation method (30.8 ± 20.8 ml vs 29.5 ± 20.2 ml; $p = 0.086$). By contrast, when using 50% SUV_{max}-threshold PET delineation method, average MTV values were significantly different between early and delayed scans (18.9 ± 13.0 ml vs 14.1 ± 8.8 ml) ($P < 0.001$, paired t test).

By using PET gradient segmentation method, MTV values remained stable between early and delayed time points for 76% of the tumors ($< 10\%$ of MTV), and a clinically significant increase of MTV was seen in 11.3% of the tumors (8/71), and a decreased in

MTV was observed in 12.6% (9/71) of the tumors. By using the 50% SUV_{max}-threshold segmentation method, 70.4% of the tumors (50/71) showed a clinically significant reduction in % MTV [figure 1]. These tumors had increase in SUV_{max} at delayed time point. About 7% (5/71) tumors showed clinically significant increase in MTV values, which had stable or slightly decrease in SUV_{max} at delayed time point. The remainder 22.5% tumors (16/71) showed stable ($\pm 10\%$) MTV values at delayed time point.

Metabolic Intra-tumor Heterogeneity

When the gradient PET segmentation methodology was applied, statistically significant difference was seen among intra-tumoral heterogeneity indexes between early and delayed time points (AUC-CSH of 0.562 ± 0.095 [range 0.35–0.73] vs 0.519 ± 0.089 [range 0.29–

0.72]; ($p < 0.0001$, paired t test). Stable metabolic intra-tumoral heterogeneity values were seen between early and delayed FDG-PET imaging time points when using 50% SUV_{max} -threshold; early AUC-CSH of 0.646 ± 0.028 [range 0.57–0.71] vs delayed AUC-CSH of 0.642 ± 0.027 [range 0.57–0.74] ($P = 0.148$, paired t test).

By using PET gradient segmentation method, variability in the % AUC-CSH was observed over time in 43.6% (31/71) of the tumors with decreased % AUC-CSH of greater than 10% in 29/71 tumors [figure 2], and increased % AUC-CSH of more than 10% in 2 tumors; the rest of the intra-tumoral heterogeneity indexes remained stable over time. We also subgrouped the tumors in three categories (tumors with stable MTV, with increase in MTV and with decrease in MTV over time) and no significant changes were seen between the three categories with regard to early ($p = 0.267$), or delayed AUC-CSH heterogeneity index ($p = 0.996$), or % change in AUC-CSH (% AUC-CSH) ($p = 0.051$) or tumor size ($p = 0.25$).

By using 50% SUV_{max} -threshold segmentation method, there was no increased or decreased clinically significant % AUC-CSH over time, being the percentage of change less than 10% for all tumors. Statistically significant % AUC-CSH index ($p = 0.003$) was seen between the three groups with stable MTV, increase in MTV or decreased in MTV at delayed time point. No significant changes were seen between the 3 groups with regard to early ($p = 0.199$), or delayed ($p = 0.15$) AUC-CSH heterogeneity index or tumor size ($p = 0.810$).

Negative correlation was seen between AUC-CSH indexes and MTV values for either early, or delayed time points ($r_{early} = -0.50$, and $r_{delayed} = -0.52$) using the PET gradient segmentation; meaning that tumors presenting larger metabolic volumes were more heterogeneous (i.e. lower AUC-CSH indexes). There was no correlation between MTV and AUC-CSH values when using 50% SUV_{max} -threshold PET segmentation method for either early ($r = -0.09$) or delayed ($r = -0.2$) time points.

Correlation between the two segmentation methods

Moderate but significant correlations were found between PET gradient-based and 50% SUV_{max} -threshold segmentation methods, for early and delayed time points, for MTV measurement ($r_{early} = 0.64$, and $r_{delayed} = 0.60$), and for AUC-CSH values ($r_{early} = 0.68$, and $r_{delayed} = 0.58$), and excellent correlation was seen for SUV_{max} ($r = 1$) and TLG measurements ($r_{early} = 0.82$, and $r_{delayed} = 0.76$).

DISCUSSION

The purpose of the current study was to assess the consistency of metabolic tumor volume and intra-tumoral heterogeneity when using dual-time-point ^{18}F -FDG PET/CT imaging in 71 newly diagnosed pancreatic adenocarcinoma tumors. Two different automated PET segmentation methods were used to compare the different PET metrics.

As expected from other publications, the FDG avidity increased over time in 94% of the pancreatic tumors. The average values of SUV_{max} , and SUV_{peak} were found to be significantly higher at delayed time points within the tumors ($p = 0.009$ and $p < 0.0001$,

respectively). Delayed-phase or dual-time-point after a single injection of 18F-FDG PET/CT has been proposed for differential diagnosis of a variety of malignancies, based on the theory that 18F-FDG uptake increases over time in malignant lesions, in contrast to stable or decreasing 18F-FDG uptake in benign lesions²⁸. Nakamoto et al investigated the role of dual-time-point FDG-PET imaging in differentiating between malignant and benign pancreatic lesions, reporting that dual time point PET scan 2 hours after FDG injection provided a higher sensitivity, specificity, and accuracy compared to those for single time point images²⁹.

MTV values were found to remain consistent over time when using the PET gradient segmentation method. These results are concordant with a recent publication in the setting of a different population with non-small cell lung cancer (NSCLC), where investigators found that MTV of the primary NSCLC tumor did not significantly changed between 1 and 2 h after 18F-FDG injection by using gradient-based delineation²². Furthermore, we evaluated the effect of dual-time-point in MTV measurements by using another segmentation method, the 50% SUV_{max} -threshold delineation, and we found that early and delayed average MTV values were significantly different ($p < 0.001$), with most of the tumors (70.4%) showing a decreased of MTV of more than 10%. This tendency of decreased of MTV over time by using the threshold delineation was related to the increased of FDG avidity over time, since tumors with significant smaller MTV values at delayed time points were the ones with increased in FDG avidity over time, and the tumors with stable or increased in MTV values at delayed time points were the ones with stable or slightly decreased SUV_{max} values over time.

We also compared both segmentation methods for early and delayed PET values: an excellent correlation was found between the two methods for SUV_{max} measurements, and good correlations for MTV and AUC-CSH values. These two methods of segmentation have been previously compared using dynamic imaging by Chen et al. concluding that tumor volumes delineated by gradient method significantly correlated with those delineated by 40% SUV_{max} -threshold method, in patients with head and neck cancer³⁰. Hatt et al found large discrepancies in image based determination of NSCLC tumor volumes according to the methodology used for tumor delineation²³. Another study using a single time point PET image found that the gradient method outperformed the threshold method in terms of accuracy and robustness³¹. Therefore, the gradient segmentation method may be more reliable for the assessment of MTV measurements over time.

In this study, we addressed the consistency of intra-tumoral metabolic heterogeneity indexes (AUC-CSH index) when using dual-time-point, and different segmentation methods. By using the PET gradient segmentation, the AUC-CSH indexes were different between the two scans. When applying the 50% SUV_{max} -threshold segmentation method, the heterogeneity indexes remained stable, probably related to the fact that by using a threshold we are only including the part of the tumor (pixels-volume) with the 50% maximum uptake, excluding areas with low FDG uptake, i.e. we are considering only a smaller volume of interest in the tumor where the heterogeneity is not changing over time. To our knowledge, this is the first manuscript assessing the impact of dual-time-point together with different segmentation approaches on AUC-CSH indexes. Previously, Van Velden et al³² assessed the test-retest

variability at a single time point, using various PET quantitative uptake heterogeneity measurements, including AUC-CSH, in 27 patients with colorectal carcinoma, concluding that there was a high reproducibility and reliability (intra-class correlation coefficients of 0.97) and low test-retest variability (10 %) for AUC-CSH values. Hall et al ²³ investigated the impact of two different tumor delineation methods (manual and thresholding PET) on a single-time point uptake heterogeneity, which was estimated using the coefficient of variation (COV), defined as the ratio between the standard deviation of SUV values and the mean SUV value within the MTV. Highly correlation was found between COV values for the two delineation methods ($r=0.98$ $p<0.0001$). However, COV is a simple parameter that provides a global measure of heterogeneity and may not be informative of the spatial distribution of the heterogeneity, potentially yielding the same value for very different heterogeneous distributions ²³.

To date, most of the publications have focused on evaluating different metabolic heterogeneity factors using different approaches for tumor volume delineation ^{33,34}. With the growing interest of texture features and tumor heterogeneity in patient's survival outcome prediction ³⁵ and in monitoring treatment response in the future ³⁶, the impact of PET segmentation and scan time are important factors to be considered

Our present study has some limitations. This is a retrospective, single-center study, using one reader and one tumor type (pancreatic tumor). We used one single heterogeneity parameter obtained by the cumulative SUV volume histogram ²⁷. Furthermore, metabolic heterogeneity using 18F-FDG PET imaging can be represented by other methods, such as textural features and elliptic solid mathematical model with homogeneous density ³⁷⁻³⁹. It would be important to investigate the impact of uptake time on multiple heterogeneity indices.

CONCLUSIONS

The PET segmentation method and the scan time impacted on the consistency of MTV and AUC-CSH measurements. When using dual-time-point 18F-FDG-PET/CT imaging in patients with pancreatic adenocarcinoma, MTV showed consistency between early and delayed imaging by PET gradient segmentation method, whereas 50% SUV_{max} -threshold delineation method produced statistically significant lower MTV values at delayed time points, which corresponded to the tumors that showed increase in FDG uptake over time. AUC-CSH index changed over time when using gradient-based delineation, and remained stable when using the 50% SUV_{max} -threshold, likely related to the fact that we are restricting the assessment of the tumor heterogeneity to a smaller volume of interest. It is important to standardize uptake time and segmentation methods when using PET metabolic tumor volume and heterogeneity index as imaging biomarkers for therapy response and patient outcome predictions.

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Figure 1. PET images at early and delayed time points in axial, sagittal, and coronal projections, illustrating the pancreatic metabolic tumor volume (MTV) using gradient-based PET (in yellow) and 50% SUV_{max} -threshold (in blue) segmentations. When using gradient segmentation, MTV remains stable between early (44.7 ml) and delayed (43.3 ml) time points, whereas MTV decreased when using 50% SUV_{max} -threshold from 24.6 ml to 12.1 ml.

Figure 2.

Early and delayed fused PET/CT (1) and PET (2) images in axial (A1, A2), sagittal (B1, B2) and coronal (C1, C2) projections demonstrated a large $3.6 \times 3.9 \times 4.2$ cm FDG-avid pancreatic tumor within the body of the pancreas. Early images (at ~ 1 h p.i.) shows a metabolic tumor uptake with SUV_{max} of 9.2, metabolic tumor volume (MTV) of 56.24 ml (by gradient-based PET segmentation – in blue) and 5.8 ml (by 50% SUV_{max} -threshold segmentation – in yellow), and a heterogeneity index (AUC-CSH) of 0.356 (by gradient-based) and 0.621 (by 50% SUV_{max} -threshold). On delayed (at ~ 2 h p.i.) images, SUV_{max} increases to 15.6; MTV remains stable with gradient-based delineation (57.4 ml) and decreased with 50% SUV_{max} -threshold (1.7 ml). AUC-CSH indexes remained stable with 50% SUV_{max} -threshold (0.597) and decreased with gradient-based segmentation (0.291).

Table 1

Patients' Demographics

Patient Characteristics	n	%
Age		
40–50 y	3	4.2
51–70 y	43	60.6
>70 y	25	35.2
Sex		
Female	29	40.8
Male	42	59.2
Location of the tumor		
Head of the pancreas	49	69.0
Body of the pancreas	12	16.9
Tail of the pancreas	10	14.1
Tumor Stage		
Stage I	0	0
Stage II	15	21.1
Stage III	34	47.9
Stage IV	22	31
Resectable tumor		
No	52	73.2
Yes	13	18.3
Borderline	6	8.5
Outcome		
Alive	14	19.7
Dead	57	80.3