Original Article

Impact of tumour region of interest delineation method for mid-treatment FDG-PET response prediction in head and neck squamous cell carcinoma undergoing radiotherapy

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Background: The aim of this study was to evaluate the impact of tumour region of interest (ROI) delineation method on mid-treatment ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) response prediction in mucosal head and neck squamous cell carcinoma during radiotherapy.

Methods: A total of 52 patients undergoing definitive radiotherapy with or without systemic therapy from two prospective imaging biomarker studies were analysed. FDG-PET was performed at baseline and during radiotherapy (week 3). Primary tumour was delineated using a fixed SUV 2.5 threshold (MTV2.5), relative threshold (MTV40%) and a gradient based segmentation method (PET Edge). PET parameters SUV_{max}, SUV_{mean}, metabolic tumour volume (MTV) and total lesion glycolysis (TLG) were calculated using different ROI methods. Absolute and relative change (Δ) in PET parameters were correlated to 2-year locoregional recurrence. Strength of correlation was tested using receiver operator characteristic analysis using area under the curve (AUC). Response was categorized using optimal cut-off (OC) values. Correlation and agreement between different ROI methods was determined using Bland-Altman analysis.

Results: A significant difference in SUV_{mean}, MTV and TLG values were noted between ROI delineation methods. When measuring relative change at week 3, a greater agreement was seen between PET Edge and MTV2.5 methods with average difference in ΔSUV_{max}, ΔSUV_{mean}, ΔMTV and ΔTLG of 0.0%, 3.6%, 10.3% and 13.6% respectively. A total of 12 patients (22.2%) experienced locoregional recurrence. ΔMTV using PET Edge was the best predictor of locoregional recurrence (AUC =0.761, 95% CI: 0.573–0.948, P=0.001; OC Δ>50%). The corresponding 2-year locoregional recurrence rate was 7% *vs.* 35%, P=0.001.

Conclusions: Our findings suggest that it is preferable to use gradient based method to assess volumetric tumour response during radiotherapy and offers advantage in predicting treatment outcomes compared with threshold-based methods. This finding requires further validation and can assist in future response-adaptive clinical trials.

Keywords: ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET); delineation; head and neck; mid-treatment; response

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Introduction

Definitive radiotherapy is a standard treatment for mucosal head and neck squamous cell carcinoma (HNSCC). Following treatment, up to 15–50% of patients still experience locoregional recurrence within the first 2 years (1,2). The treatment is also associated with significant toxicities impacting on quality of life. Hence, there is a need for personalised response adaptation by escalation or de-escalation of treatment based on risk of recurrence.

Studies have attempted to prognosticate treatment response based on anatomical changes in tumour volumes measured using mid-treatment computed tomography (CT) scans (3). Changes in functional imaging has been shown to precede anatomical changes in the tumour during treatment (4). ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) provides an non-invasive method to characterise tumour biology (5). Several studies have shown FDG-PET performed during radiotherapy can be used as an early treatment response biomarker to predict recurrence in head and neck squamous cell carcinoma (6-9). These studies show relative change in volumetric FDG-PET parameters such as metabolic tumour volume (MTV) and total lesion glycolysis (TLG) to be optimal measures for response prediction (6,8,9). However, a critical factor on the derived FDG-PET parameters is the dependence on tumour region of interest (ROI) delineation method employed (5,10-15). Currently, there is considerable heterogeneity and a lack of consensus in the use of ROI delineation methodology in different published studies in head and neck squamous cell carcinoma (16,17). Fixed threshold PET metabolic volume segmentation method is the most commonly used method to derive PET metabolic volumes to provide prognostic biomarkers and to predict treatment outcomes in pre-treatment setting for head and neck cancer. In a meta-analysis of the prognostic value of pre-therapeutic MTV and TLG in head and neck cancer, nine of 13 studies used a fixed threshold, and eight of those used SUV cut off of 2.5 (8). They found a higher correlation to clinical outcomes using SUV cut off value of 2.5 (HR: 3.2 *vs.* 2.8).

Each method is expected to provide different quantitative measures depending on tumour size, shape, heterogeneity, tumour avidity and background FDG-PET avidity (10,15,18). Mid-treatment FDG-PET assessment during radiotherapy is further complicated by influence of treatment related inflammation and changing tumour morphology especially in complex anatomical head and neck regions (17). The data is much more limited to support the optimal PET segmentation method to be employed during radiotherapy to predict treatment outcomes, with most using threshold method (fixed, relative, background or adaptive) and/or qualitative (16). The data is lacking on the comparative effectiveness with gradient based segmentation method, despite its potential advantage over the threshold-based method in mid-treatment setting where the tumour tends to be smaller and with lower metabolic activity.

There are currently no studies that have explored the influence of different tumour ROI delineation methods in mid-treatment response assessment in head and neck squamous cell carcinoma. The additional value of mid-treatment FDG-PET over anatomical tumour volume change has also not been shown in this patient population.

Our hypothesis is that it is feasible to use gradient based method to assess metabolic PET tumour response during radiotherapy and choice of ROI delineation method can result in significantly different FDG-PET parameters extracted from baseline and mid-treatment FDG-PET imaging. We aim to measure the agreement in FDG-PET parameters extracted from baseline and week 3 FDG-PET using different ROI delineation methodology. We also aim to find the optimal tumour ROI delineation method for treatment response prediction in HNSCC by correlating resulting quantitative FDG-PET parameters to locoregional clinical outcomes. We present the following article in accordance with the STARD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-798/rc).

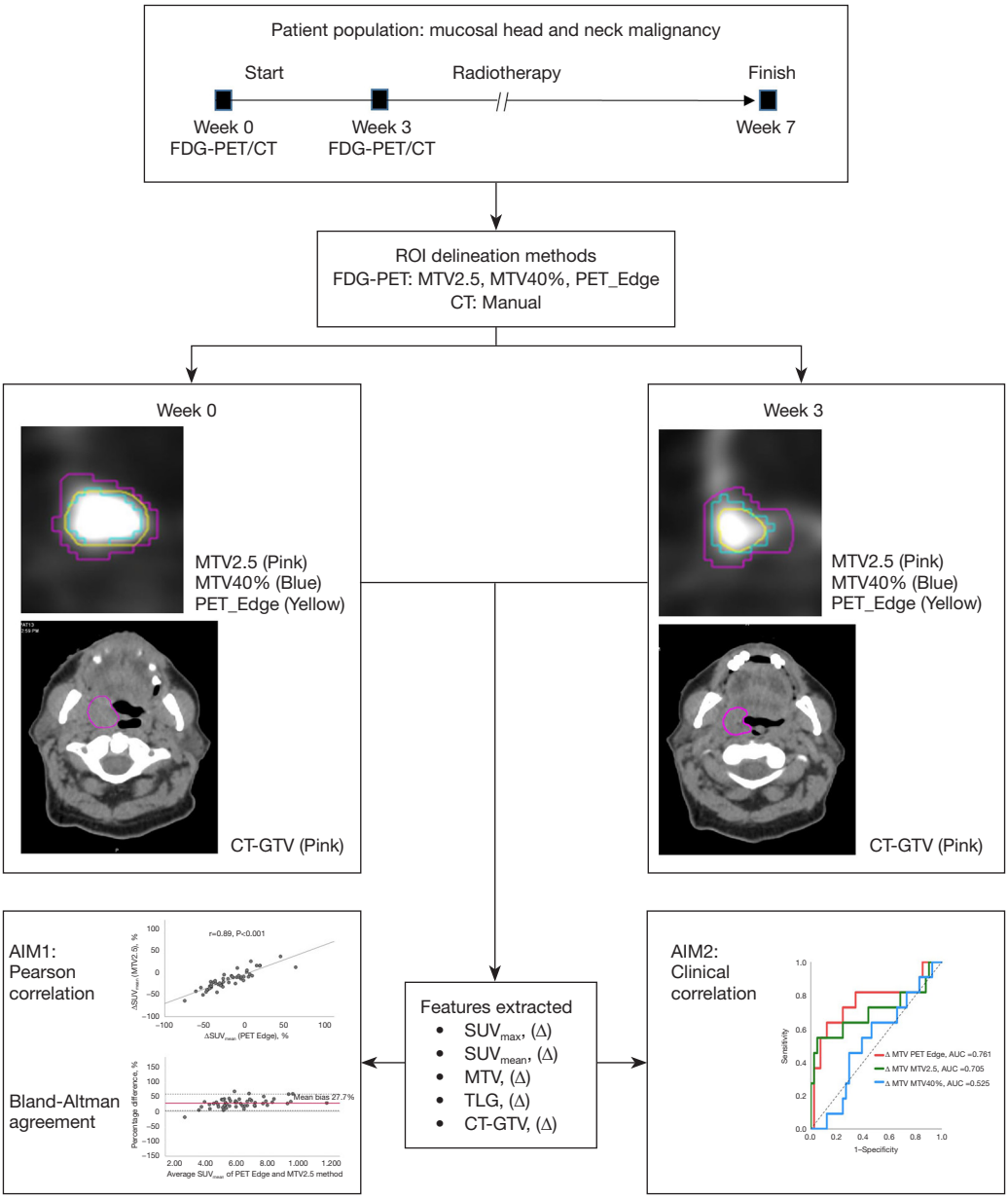

Figure 1 Flow diagram. FDG-PET, ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography; CT, computed tomography; MTV, metabolic tumour volume; GTV, gross tumour volume; TLG, total lesion glycolysis; ROI, region of interest; SUV, standardized uptake value; AUC, area under the curve.

Methods

Study design

Patients with newly diagnosed, biopsy-proven, non-metastatic mucosal head and neck squamous cell carcinoma treated with definitive radiotherapy with or without concurrent systemic therapy from two separate prospective quantitative imaging biomarker studies were evaluated (*Figure 1*) (19,20). Patients less than 18 years old, with previous radiotherapy in the head and neck region or contraindications to MRI or FDG-PET were excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the South Western Sydney Local Health District research

ethics committee and informed consent was taken from all individual participants. Trial ID ACTRN12616000534482, ANZCTR.

All patients were evaluated and reviewed by a multidisciplinary team consisting of radiation oncologists, medical oncologists, surgeons and radiologists. Patients were treated using an IMRT simultaneous integrated boost technique using daily image guidance over 35 fractions. Patients were treated at two tertiary hospitals from 2014 to 2019. Radiotherapy treatment volumes were defined using latest consensus international guidelines and underwent a stringent peer review process (21). All patients underwent radiotherapy to the primary site and bilateral neck.

All patients underwent FDG-PET before (week 0) and during (week 3) radiotherapy. Week 3 time-point was chosen based on previous published series from our institution and other centres (6,22-24). Week 3 time point is also early enough during radiotherapy to allow sufficient time for treatment adaptation in future clinical trials. Treatment response was evaluated with post-treatment FDG-PET and clinical examination including nasoendoscopy. Recurrences were confirmed histologically or via imaging following discussion at a multidisciplinary head and neck meeting.

The primary outcome for the study was 2-year locoregional recurrence measured from time of diagnosis. A 2-year time point was chosen because the vast majority of locoregional recurrences occur within this period (25).

PET/CT acquisition

PET studies were acquired in radiotherapy treatment position on a GE DiscoveryTM MI 5-ring digital positron emission tomography (PET)-CT (GE Healthcare, Waukesha, MI). Patients received 2.2 MBq/kg of ^{18}F-FDG after at least 4 h of fasting. The average blood sugar level was 5.7±1.2 mmol/L (range, 3.3–9.6 mmol/L). The staging and all sequential posttreatment scans were performed on the same scanner with the same acquisition and reconstruction protocols. The PET studies were acquired in three-dimensional (3D) mode with the patient lying on a radiotherapy flat-bed insert for a total acquisition time of 1.5–2.5 min per bed position adjusted according to the patient weight, from vertex to proximal femora at about 1-hour post injection. Transmission scans and attenuation corrections were obtained using 128-slice GE CT, using helical mode without the use of a contrast medium. The PET images were reconstructed using a GE VUE Point FX (Time of Flight) algorithm into a 256×256 matrix size with a slice thickness of 3.75 to 4.0 mm. The PET images were reconstructed using GE VUE Point FX (Time of Flight) algorithm into a 256×256 matrix size with a slice thickness of 3.75 to 4.0 mm. CT images were acquired at 3.75 to 5 mm slice thickness and reconstructed to a transaxial matrix size of 512×512. The current (30–40 mAs) and voltage (120–140 kV) were varied according to the patient weight. The baseline and mid-treatment scans were performed on the same scanner with the same acquisition and reconstruction protocols.

Image analysis

Primary region of interest (ROI) was the primary tumour. All PET images were viewed and had ROIs delineated using MIM Software (MIM Software Inc.; Beachwood, OH).

The primary tumours were volumetrically delineated by a radiation oncologist (YT) in consensus with a nuclear medicine physician (PL) on FDG-PET imaging and another radiation oncologist (ML) on CT imaging at baseline and week 3 mid-treatment who were blinded to clinical outcomes.

To explore the effect of various delineation methods on metabolic PET parameters, a tumour region of interest (ROI) was delineated using three commonly utilized semi-automated methods; a fixed SUV threshold, a relative threshold and a gradient based method (6,7,12,13). The fixed SUV threshold involved applying an isocontour of SUV =2.5 ('MTV2.5'), this cut-off was chosen based on previous published literature (6,8,12,13,22). MTV2.5 was delineated using SUV threshold of 2.5 as the lowest limit of the segmentation criteria within a spherical volume of interest containing the tumor. The spherical volume was chosen to visually include the entire tumour and manual adjustments were only rarely allowed to exclude obvious non-involved regions of FDG-PET uptake. For relative threshold method, a 40% of maximum standardized uptake value ('MTV40%') was chosen based on a large prospective study and multiple previous clinical series (7,13,14,18,26-29). MTV40% delineated all voxels with SUV values above or equal to 40% of the maximum SUV within the same spherical volume of interest containing the tumor. A semi-automatic gradient based method involved applying a 'PET Edge' tool of the MIM software, this has been shown to closely approximate manual segmentation and pathological tumour volume (30,31). PET Edge gradient method calculates spatial derivatives along tumor radii then defines the tumor edge based on derivative levels and

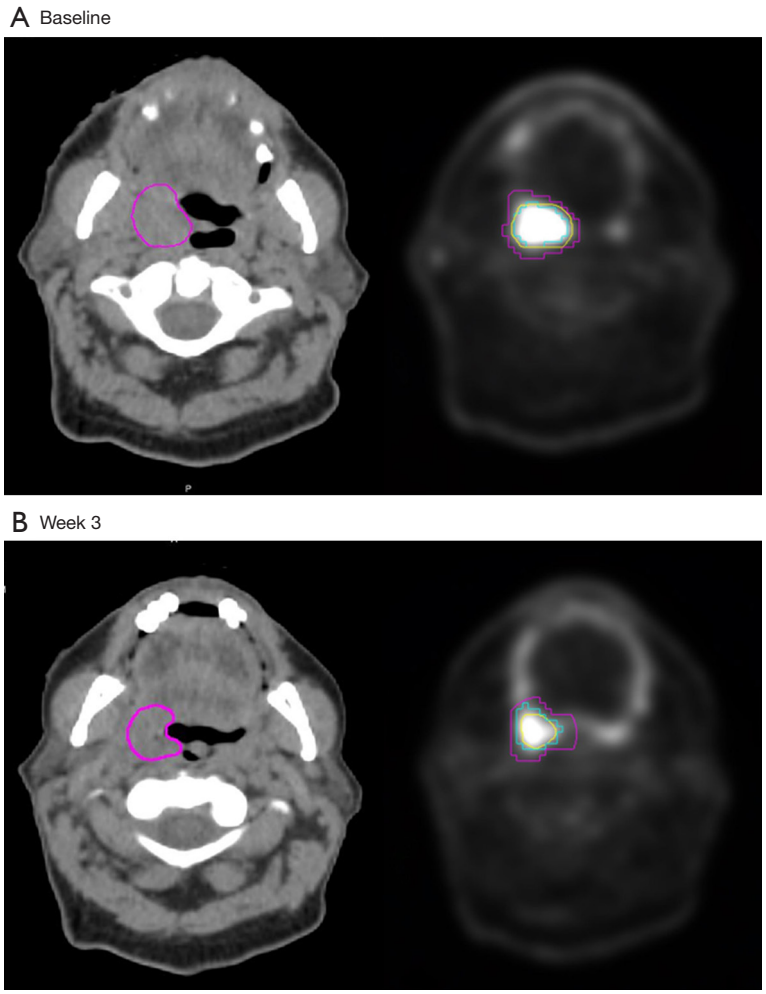

Figure 2 CT tumour (GTV) and FDG-PET MTV delineated using different region-of-interest segmentation methods; CT in red, PET Edge in yellow, MTV2.5 in pink, MTV40% in blue. (A) Baseline; (B) week 3. Resulting percentage change in tumour volumes for this patient at week 3 were –25.7% (CT), –76.2% (PET Edge), –41.9% (MTV2.5), and –25.0% (MTV40%). CT, computed tomography; FDG-PET, ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography; MTV, metabolic tumour volume; GTV, gross tumour volume.

continuity of the tumor edge (32). PET Edge method was used as described previously by Werner-Wasik *et al.* (33). In brief, the method involved the clinician selecting the image slice where the tumour appears the largest, then placing a starting point near the center of the tumour. The clinician then drags out from the center of the lesion; spatial gradients are calculated along each axis interactively and the length of an axis is restricted when a large spatial gradient is calculated along that axis approximating the boundaries of the tumour. Following release of the mouse button the edges of the structure are automatically calculated and outlined volumetrically. Tumour volume was also manually delineated on CT images (CT-GTV) to compare the change in anatomical CT volumes to FDG-PET tumour volumes. An example of different delineated ROIs are provided in *Figure 2*.

DICOM images containing ROIs were subsequently analysed using open-source PyRadiomics software (v2.2.0) (34). Four metabolic parameters; the maximum SUV uptake (SUV_{max}), and volumetric parameters mean SUV uptake (SUV_{mean}), MTV and tumour lesion glycolysis (TLG = SUV_{mean} × MTV) were measured for all three ROI delineation methods at both time points.

Percentage change (Δ) in FDG-PET imaging parameters from baseline was calculated, defined as Δ = [(week 3 – week 0)/week 0] × 100%.

Statistical analysis

Due to non-normal data distribution, PET parameter values from different ROI delineation methods were compared using the Wilcoxon signed-rank test.

Correlation between the delineation methods for absolute PET parameter values at baseline and relative change at week 3 were estimated using Pearson coefficients test. The level of agreement between different ROI delineation methods was determined using Bland-Altman analysis.

The absolute value and change (Δ) in parameters were compared to locoregional recurrence using Mann-Whitney U test. For parameters with predictive value, receiver operator characteristic (ROC) analysis was performed using area under the curve (AUC) as an index of accuracy to differentiate between multiple predictive parameters. Optimal cut-off values for analysis were derived from the ROC curves aiming for best sensitivity and specificity by applying the Youden index (35). Locoregional recurrence-free survival (LRFS) curves were estimated using Kaplan-Meier analysis and compared using the log-rank (Mantel-Cox) test.

The data were analyzed using SPSS statistical software (Version 24.0; IBM Corp, Armonk, NY, USA). Statistical significance was considered as P<0.05.

Results

A total of 54 patients underwent week 0 pre-treatment FDG-PET. Two patients did not undergo week 3 mid-treatment FDG-PET resulting in 52 patients who were available for subsequent analysis. Patient and tumour details are summarised in *Table 1*. The median follow up was 31.2 months (range, 4–68 months). A total of 12 patients (22.2%) experienced locoregional recurrence.

A significant difference in week 0 and relative change in SUV_{mean}, MTV and TLG values were noted between different ROI delineation methods (Wilcoxon signed rank test, P<0.05). The largest week 0 MTVs and TLGs were obtained using MTV2.5 method (mean: 17.9 mL, 106.5 g), compared to PET Edge (mean: 10.5 mL, 79.9 g) and MTV40% (mean: 7.8 mL, 64.9 g). The largest change in ΔMTV and ΔTLG at week 3 was noted using the PET Edge method, –47.9% and –58.0% respectively. Change in CT-GTV volume at week 3 was only –25.3% in comparison (*Table 2*). Box plots of PET parameters at week 0 and their relative change for the three ROI delineation methods are shown in *Figure 3*.

For week 0 FDG-PET parameters, good or excellent correlation was found between delineation methods for SUV_{max}, SUV_{mean}, MTV and TLG (r>0.81, range: 0.87–1.00, P<0.05; Figure S1). When measuring agreement for FDG-PET parameter values at week 0, a greater agreement was seen between PET Edge and MTV40% methods (Figure S2). On average, the difference in week 0 SUV_{max}, SUV_{mean}, MTV and TLG values measured using PET Edge and MTV40% methods were 0.0%, 2.9%, 2.2% and 1.2% respectively.

For relative change (Δ) in FDG-PET parameters at week 3, good correlation was found for ΔSUV_{mean} (r>0.89, range: 0.89–0.94, P<0.05; Figure S1). Only moderate to poor correlation was noted for ΔMTV and ΔTLG between different ROI delineation methods (r<0.68, range: 0.17–0.68, P<0.05). When measuring agreement for relative change in FDG-PET parameter values at week 3, a greater agreement was seen between PET Edge and MTV2.5 methods (Figure S2). On average, the difference in ΔSUV_{max}, ΔSUV_{mean}, ΔMTV, ΔTLG values measured using PET Edge and MTV2.5 methods were 0.0%, 3.6%, 10.3% and 13.6% respectively.

Change in CT-GTV did not correlate to locoregional recurrence. No baseline FDG-PET parameters correlated to locoregional recurrence. Only relative change (Δ) in volumetric FDG-PET parameters, MTV and closely related TLG measured using PET Edge and MTV2.5 methods correlated to locoregional recurrence (*Table 3*). Relative change (Δ) in FDG-PET parameters had a stronger correlation to locoregional recurrence than absolute values.

Relative change in MTV at week 3 (ΔMTV) measured using PET Edge was the best predictor of locoregional recurrence (AUC =0.761, 95% CI: 0.573–0.948, P=0.001; *Figure 4*). In patients with locoregional recurrence, a significant difference in ΔMTV measured using PET Edge was noted compared to those without locoregional recurrence (–55.4% *vs.* –19.8%, P=0.008). Optimal cut-off of ΔMTV calculated using PET Edge for predicting local recurrence was <50.4% drop in MTV; resulting in sensitivity of 82% (9/11; 95% CI: 74–89%), specificity of 66% (27/41; 95% CI: 62–69%) and accuracy of 69% (36/52; 95% CI: 66–72%). A statistically significant difference was found on Kaplan-Meier survival analysis based on primary tumour ΔMTV optimal cut-off value. The corresponding 2-year locoregional recurrence rate was 7% *vs.* 35%, P=0.001 (log rank). Comparison of tumour volumes measured using three FDG-PET ROI delineation methods

Table 1 Patient demographics

Characteristics	Patients (n=52)	Nil LRR (n=40)	LRR (n=12)	P value
Age at diagnosis (years)	62±9.4	61±9.9	66±6.4	0.038
Gender				0.487
Male	48 [89]	38 [79]	10 [21]	
Female	6 [11]	4 [67]	2 [33]	
Smoker				0.934
No	14 [26]	11 [79]	3 [21]	
Yes	40 [74]	31 [78]	9 [23]	
Alcohol intake				0.327
Nil	13 [24]	11 [85]	2 [15]	
<1 SD/day	16 [30]	11 [69]	5 [31]	
1–3 SD/day	7 [13]	7 [100]	0 [0]	
>3 SD/day	11 [20]	7 [64]	4 [36]	
Ex-heavy (3 SD/day)	7 [13]	6 [86]	1 [14]	
Primary tumour site				0.086
Tonsil	19 [35]	16 [84]	3 [16]	
Base of tongue	14 [26]	13 [93]	1 [7]	
Soft palate	4 [7]	4 [100]	0 [0]	
PPW	4 [7]	3 [75]	1 [25]	
Larynx	6 [11]	3 [50]	3 [50]	
Hypopharynx	7 [13]	3 [43]	4 [57]	
TNM stage				0.861
Stage 2	6 [11]	5 [83]	1 [17]	
Stage 3	13 [24]	9 [69]	4 [31]	
Stage 4a	31 [57]	25 [81]	6 [19]	
Stage 4b	4 [7]	3 [75]	1 [25]	
T stage				0.558
T1	4 [7]	3 [75]	1 [25]	
T2	22 [41]	19 [86]	3 [14]	
T3	23 [43]	17 [74]	6 [26]	
T4	5 [9]	3 [60]	2 [40]	
Grade				0.037
Well differentiated	2 [4]	1 [50]	1 [50]	
Mod differentiated	9 [17]	4 [44]	5 [56]	
Poor differentiated	18 [33]	15 [83]	3 [17]	
Unknown	25 [46]	22 [88]	3 [12]	

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	Patients (n=52)	Nil LRR (n=40)	LRR (n=12)	P value
P16 status				0.693
Negative	6 [11]	5 [83]	1 [17]	
Positive	20 [37]	17 [85]	3 [15]	
Unknown/NA	28 [52]	20 [71]	8 [29]	

Continuous variables are presented in mean ± standard deviation and compared using Mann-Whitney U test. Categorical data are presented as numbers [%] and compared using Chi-square (χ^2) test. LRR, locoregional recurrence; PPW, posterior pharyngeal wall; N/A, not applicable.

Table 2 Mean value and standard deviation of FDG-PET parameters at baseline and relative change at week 3 based on three region-of-interest delineation methods (PET Edge, MTV2.5, MTV40%)

Delineation method	Baseline				Change at week 3			
	SUV_{max}	SUV_{mean}	MTV	TLG	ΔSUV_{max}	ΔSUV_{mean}	ΔMTV	ΔTLG
PET Edge	13.06±4.80	7.13±2.19	10.53±11.64	79.86±92.20	−31.8%±25%	−20.6%±27%	−47.9%±35%	−58.0%±34%
MTV2.5	13.06±4.80	5.30±1.33	17.86±14.22	106.49±109.60	−31.8%±25%	−16.9%±20%	−37.5%±50%	−44.4%±55%
MTV40%	13.06±4.80	7.56±2.96	7.83±6.88	64.93±70.86	−31.6%±26%	−30.4%±25%	−2.9%±52%	−29.3%±41%
CT GTV volume	–	–	14.57±12.55	–	–	–	−25.3%±20%	–

Data are presented in mean ± standard deviation; Δ parameter = (week 3 − baseline)/baseline × 100%. MTV, metabolic tumour volume; TLG, total lesion glycolysis; GTV, gross tumour volume; FDG-PET, ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography.

and CT (CT-GTV) stratified by locoregional recurrence status are shown in *Figure 5*.

Discussion

Our study is the first to explore the impact of ROI delineation method in mid-treatment FDG-PET response prediction in HNSCC. We identified PET Edge, a gradient based method performed best for mid-treatment response assessment in our patient population. Our data suggests that change in MTV measured at week 3 is a better predictor for treatment response compared to other PET derived parameters or CT based tumour volume. We demonstrated that impact of different ROI methods on extracted features were magnified when utilising mid-treatment imaging. Our results aid in the design and analysis of future FDG-PET guided response-adaptive radiotherapy clinical trials in HNSCC.

Patients in our study had their primary tumour delineated at baseline and week 3 mid-treatment using three commonly utilised semi-automated ROI delineation methods which have previously shown to be reproducible and with predictive capability in HNSCC (6,22,23). Semi-automated methods have the advantage of improving interobserver variability and reduce time required for delineation. However, each method has individual limitations depending on tumour size, uptake, tumour heterogeneity and background FDG uptake dependent on tumour site.

Our results are consistent with previous studies utilising baseline FDG-PET that have shown significant differences in metabolic PET parameters extracted from different ROI delineation methods (10,14). We found that MTV and TLG values were largest using MTV2.5 method and smallest using MTV40% method. However, only limited studies have measured the level of agreement of metabolic PET parameters values between the different ROI methods on baseline imaging in HNSCC (12,14). We found that on baseline imaging good agreement was found only between PET Edge and MTV40% method, with a mean % bias of <3%. These results are consistent with study by Guezennec *et al.*, who analysed 43 HNSCC tumour MTV on baseline FDG-PET using three ROI delineation methods including PET Edge and MTV40%. They also found that MTV volumes were larger using PET Edge method with reasonable agreement between PET Edge and MTV40% derived MTV volumes (14). Head and mucosal

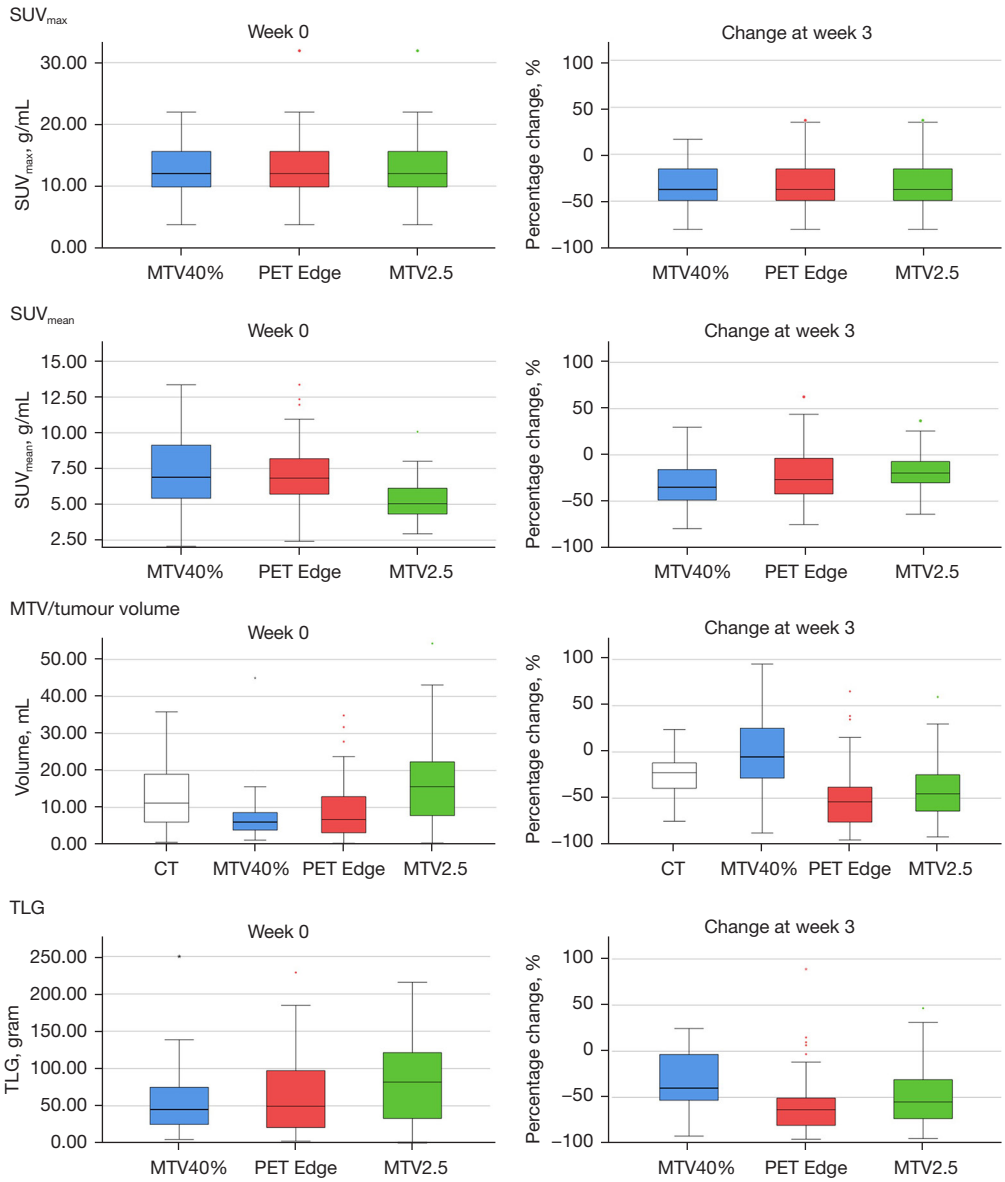

Figure 3 Box plots of FDG-PET parameters at week 0 and relative change at week 3 based on three region-of-interest delineation methodology (PET Edge, MTV40%, MTV2.5) and CT tumour volume. FDG-PET, ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography; MTV, metabolic tumour volume; CT, computed tomography; TLG, total lesion glycolysis.

sites have a background level of low grade FDG uptake that can overestimate the true primary tumour size when using absolute SUV measure such as MTV2.5, hence resulting in poor agreement with other methods (13).

Tumour delineation on mid-treatment FDG-PET imaging is further complicated by inflammation and reducing tumour uptake as a result of radiotherapy response. There are currently no studies that have measured the impact of different ROI delineation method on extracted parameters from mid-treatment imaging in HNSCC. We found the impact of ROI delineation method were amplified when measuring change in metabolic PET parameters as evidenced by worse agreement in relative change in values compared to baseline values. Even though the tumour volume calculated by MTV2.5 were consistently larger then PET Edge on mid-treatment imaging, the

Table 3 Comparison of primary tumour PET parameters measured using different delineation methods (PET Edge, MTV2.5, MTV40%) and CT tumour volumes between patient with locoregional recurrence *vs.* nil LRR

Timepoint	Parameter	Nil LRR (mean ± SD)	LRR (mean ± SD)	P value*	ROC (AUC)
PET Edge					
Week 0	SUV_{max}	12.6±4.0	14.7±6.8	0.261	
	SUV_{mean}	7.0±2.1	7.5±2.5	0.270	
	MTV	10.0±11.9	12.4±10.9	0.466	
	TLG	71.3±87.2	110.0±130.0	0.492	
Change at week 3 (%)	ΔSUV_{max}	−34.5%±23.2%	−21.7%±31.5%	0.155	
	ΔSUV_{mean}	−22.1%±23.1%	−14.8%±36.8%	0.553	
	ΔMTV	−55.4%±29.7%	−19.8%±41.8%	0.008†	0.761
	ΔTLG	−64.9%±29.7%	−32.1%±39.8%	0.010†	0.756
MTV2.5					
Week 0	SUV_{max}	12.6±4.0	14.7±6.8	0.261	
	SUV_{mean}	5.2±1.1	5.7±1.8	0.298	
	MTV	17.2±13.8	20.3±16.1	0.693	
	TLG	97.1±95.1	139.2±150.6	0.533	
Change at week 3 (%)	ΔSUV_{max}	−34.5%±23.2%	−21.7%±31.5%	0.155	
	ΔSUV_{mean}	−17.7%±18.6%	−13.9%±25.0%	0.388	
	ΔMTV	−48.0%±24.6%	1.8%±89.7%	0.038†	0.705
	ΔTLG	−55.8%±26.1%	−1.6%±102.2%	0.043†	0.701
MTV40%					
Week 0	SUV_{max}	12.6±4.0	14.7±6.8	0.261	
	SUV_{mean}	7.3±2.6	8.5±3.9	0.289	
	MTV	7.8±7.3	8.0±5.6	0.787	
	TLG	60.0±66.0	82.2±86.7	0.533	
Change at week 3 (%)	ΔSUV_{max}	−34.5%±23.2%	−21.7%±31.5%	0.161	
	ΔSUV_{mean}	−32.8%±22.2%	−21.5%±33.9%	0.222	
	ΔMTV	4.0%±57.0%	−1.1%±34.4%	0.797	
	ΔTLG	−32.7%±41.2%	−19.2%±41.3%	0.175	
CT					
Week 0	GTV	13.9±11.8	18.4±15.8	0.519	
Change (%)	ΔGTV	−28.1%±18.2%	−14.9%±25.3%	0.071	

*, parameters compared to locoregional recurrence status using Mann-Whitney U test, Δ parameter = (week 3 − week 0)/week 0 × 100%. †, significant (P<0.05), Mann-Whitney U test. Units: SUV_{max} (g/mL), SUV_{mean} (g/mL), MTV (mL), TLG (g), GTV (mL). ROC, receiver operator characteristics; AUC, area under the curve; MTV, metabolic tumour volume; TLG, total lesion glycolysis; GTV, gross tumour volume; LRR, nil locoregional recurrence.

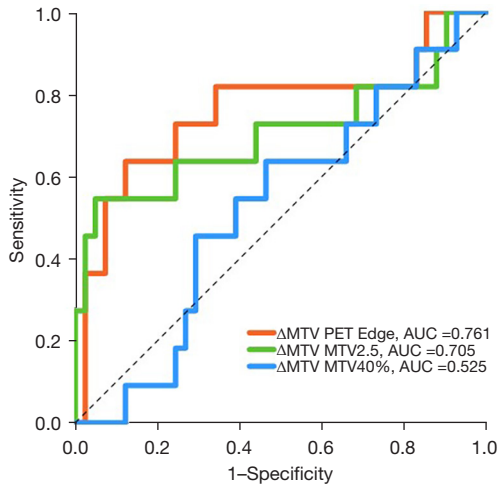

Figure 4 Receiver operator characteristic curves for change in MTV at week 3 measured using different region-of-interest delineation methods (PET Edge, MTV2.5, MTV40%) when correlated to locoregional recurrence at 2 years. Strongest correlation was shown for change in MTV measured using PET Edge method (AUC =0.761). MTV, metabolic tumour volume; PET, positron emission tomography; AUC, area under the curve.

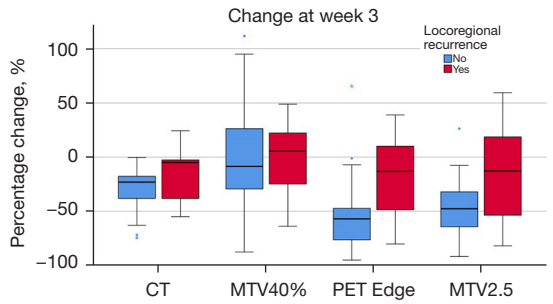

Figure 5 Relative change in tumour volume at week 3 derived on FDG-PET using three region-of-interest delineation methods (PET Edge, MTV2.5, MTV40%) and CT (CT-GTV) stratified by locoregional recurrence status. Figure showing the significant difference in volume when measured using PET Edge and MTV2.5. FDG-PET, ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography; GTV, gross tumour volume; MTV, metabolic tumour volume.

relative change from baseline were moderately similar. Hence, only a moderate agreement in change in metabolic PET parameters between PET Edge and MTV2.5 method was found, with a mean % bias of <15%. This is likely explained by a limitation of the MTV40% method on the absolute value of SUVmax from which it is derived. In patients with good treatment response, if week 3 tumour SUV_{max} approaches background uptake of irradiated mucosa the true tumour volume can be vastly overestimated using the MTV40% method. This is consistent with a small study containing 10 patients by Edet-Sanson *et al.*, which measured the influence of different delineation methods including MTV40%, manual delineation and 'adaptive threshold' method on calculated tumour volume (MTV) from baseline and weekly mid-treatment FDG-PET in non-small cell lung cancer (27). Using extensive imaging during treatment, they were able to show that MTV calculated using different delineation methods magnified as treatment progressed. They found that MTV40% delineation method was not useful in delineating tumour beyond week 1 mid-treatment based on visual interpretation of the volume due to background treatment related inflammation (27). The study by Edet-Sanson *et al.* did not perform a gradient based method for comparison and they did not correlate their findings to treatment outcome for its value in response prediction.

Currently the optimal ROI method for tumour delineation in HNSCC is unknown (17,36). Studies that have utilised mid-treatment FDG-PET changes for prediction of clinical outcomes have used varying ROI delineation methodology resulting in differing predictive parameters (6,22,23,37). We found that change in FDG-PET parameters (ΔMTV and ΔTLG) at week 3 during radiotherapy measured using PET Edge and MTV2.5 predicted for clinical response. Based on our data, change in MTV (ΔMTV) measured using PET Edge had the strongest correlation to locoregional tumour control. Based on our data, a greater percentage decrease in MTV (Δ>50.4%) was highly predictive of tumour control. Our results confirm findings from previous studies that changes in FDG-PET metabolic parameters are better treatment response markers compared to absolute values (22,23). Studies by Min *et al.* and Pollom *et al.* have shown that ΔTLG from mid-treatment FDG-PET can predict clinical outcomes (23). The studies utilised differing methodologies to delineate the MTV and hence limits direct comparison. In our study, absolute or change in SUV_{max} and SUV_{mean} did not correlate to clinical outcome, this is consistent with previous studies (6,23). No FDG-PET parameters measured using MTV40% correlated to clinical outcome. It is likely that gradient based method outperformed other methods in our population because it was more accurate at differentiating tumour margins from changes to surrounding inflamed tissue during radiotherapy, hence has higher correlation

to clinical outcomes (38). To date, this is the first study in HNSCC that has attempted to identify the optimal ROI delineation method for mid-treatment response assessment.

When comparing the tumour volume changes during treatment on FDG-PET and CT; we found greater reduction in tumour volume measured using PET Edge method (–48%) and MTV2.5 (–38%), compared to CT-GTV (–25%). Therefore, our results confirm findings from previous studies that show that metabolic changes on FDG-PET precede anatomical changes measured on CT (39,40). We also found that anatomical CT based primary tumour volume changes did not correlate to locoregional recurrence. Study by Kabarriti *et al.* measured CT based primary and nodal volumes at week 3 during radiotherapy in 96 oropharyngeal cancer patients (3). They found a similar reduction in CT based tumour volume (19%) to our study. However, they found that a greater than 19% reduction in total tumour volume was an independent predictor for locoregional recurrence. The differing results could be due to larger number of included patients in their study and inclusion of nodal tumour volume measurements. A potential limitation of using CT based imaging biomarkers it the low reproducibility due to significant inter-observer variability in manual target delineation in a complex anatomic site of head and neck malignancies. Due to treatment related changes this variability has been shown to further increase when utilising mid-treatment CT images (41). Semi-automated PET based tumour delineation are reproducible and have greater clinically applicability as an imaging biomarker in future response-adaptive clinical trials.

Strengths of our study include the number of patients and reproducible methodology employed for response assessment. Patients in our study were prospectively recruited, underwent standardised imaging protocol and had consensus based ROI delineation. We also correlated CT and FDG-PET based tumour volumes to locoregional clinical outcomes which remains a gold-standard for response assessment. There are a few limitations of our study. Ours was a single institutional study with serial imaging undertaken on the same PET machine. Cross facility standardisation of SUV values is required to translate and validate our results in prospective multicentre trials. The heterogeneities can be minimised through phantom calibrations, but inherent limitations remain taking into account different PET scanners with different sensitivities and blurred edge due to partial volume effects, acquisition and reconstruction protocols. We believe that parameters measuring relative change from baseline using serial PET imaging if done on the same PET scanner provides auto-normalisation of measurements compared to using a single static value. In this respect, the use of relative reduction as treatment response criteria would facilitate more reproducible, readily accessible and interpretable predictive imaging biomarkers to facilitate future multicentre trials for image guided adaptive therapy. Studies also indicate the importance of timing of mid-treatment imaging on extracted imaging parameters and hence extrapolation of our results to other imaging timepoints should be done with caution (11). Another limitation of the gradient based method used in this study is that it is only available within the MIM Maestro® software. Results from gradient based method used in this study should not be generalized to other gradient based methods without additional comparison. We have also not compared our results with less commonly utilised methods for tumour delineation such as 'background-related' threshold and manual PET contouring methods due to the significant inter-observer variability in implementation in a complex anatomic site such as head and neck.

Conclusions

Our study highlights the critical importance of ROI delineation method choice in mid-treatment response assessment. Our findings suggest that it is feasible to use gradient based method to assess metabolic PET tumour response during radiotherapy and offers advantage in predicting treatment outcomes compared with threshold-based methods.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-798/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-798/coif). MGJ is currently an employee of GenesisCsare and declares institutional research agreements between GenesisCare and Elekta AB, MIM Software Inc., ViewRay Technologies

and Brainlab AB. MGJ declares a licencing agreement with Standard Imaging Inc. During part of his involvement in the study, MGJ was an employee of the Sydney South West Local Health District and was supported by a NSW Cancer Institute Fellowship. He is also supported by an Australian Government NHMRC Leadership Fellowship. MGJ and PK declares that they are supported by an Australian Government NHMRC Leadership Fellowship. PC receives funding from South Western Sydney Local Health District and University of New South Wales. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the South Western Sydney Local Health District research ethics committee and informed consent was taken from all individual participants.

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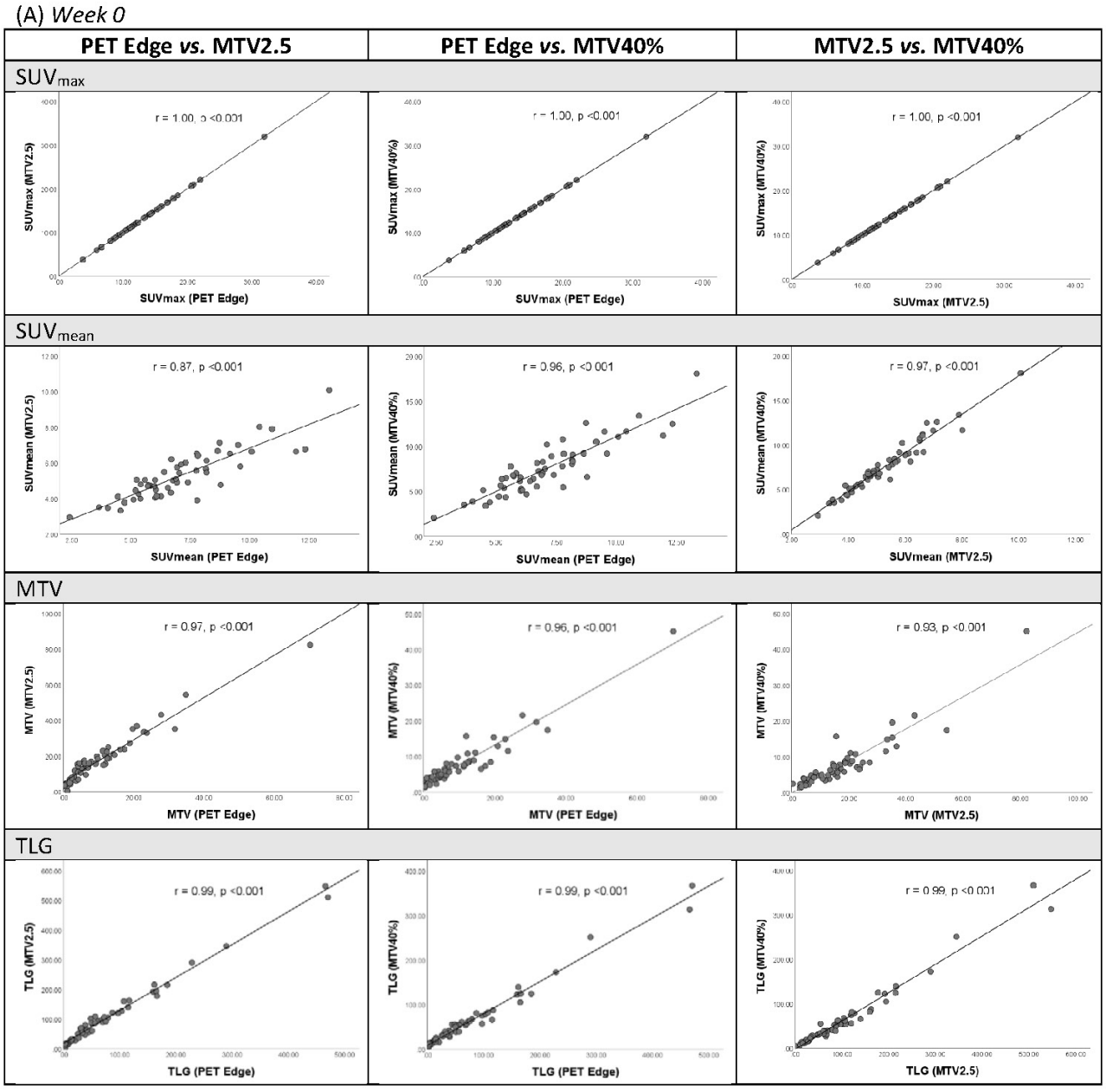
(A) *Week 0*



(B) *Proportional change in values at week 3*

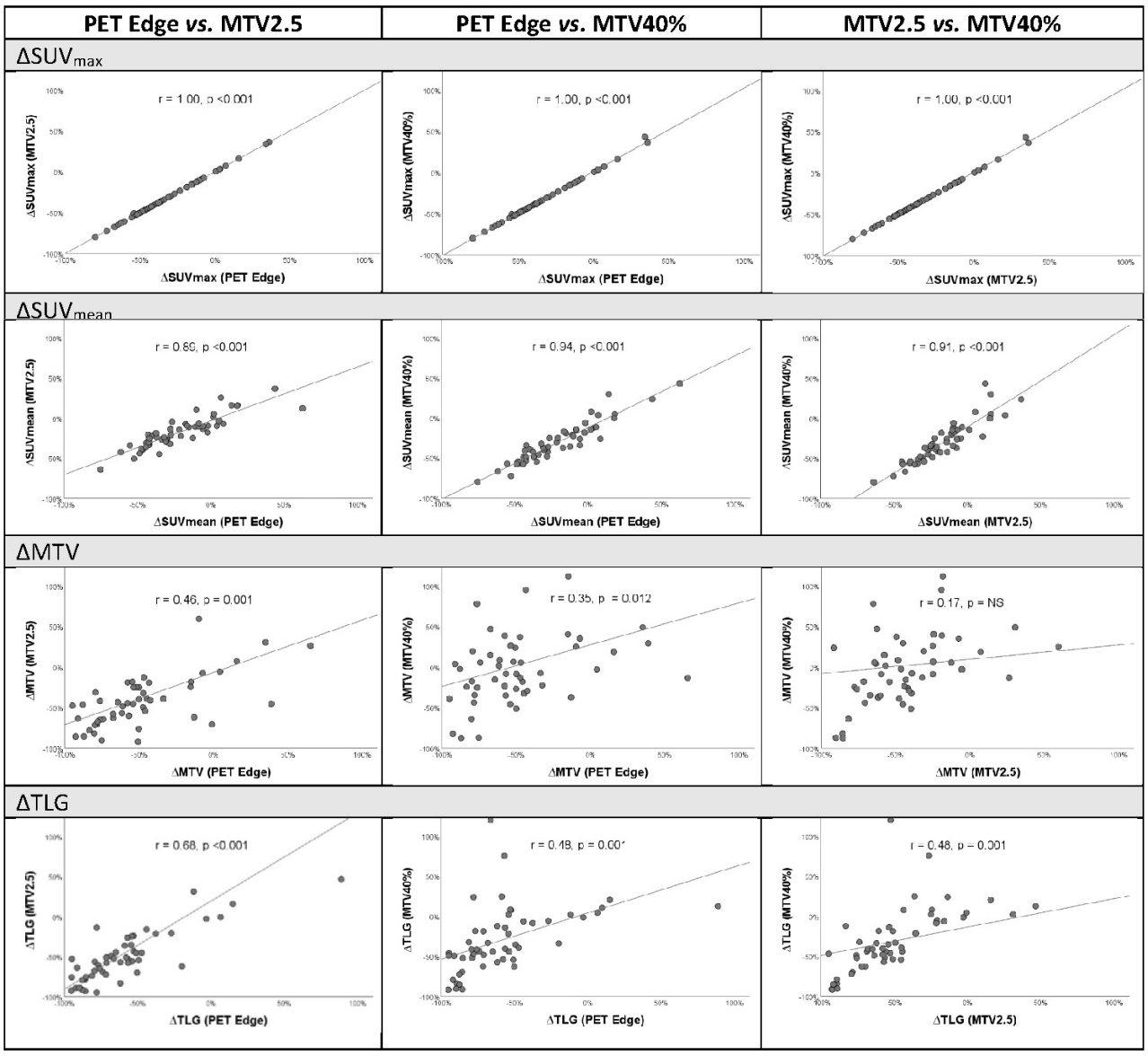
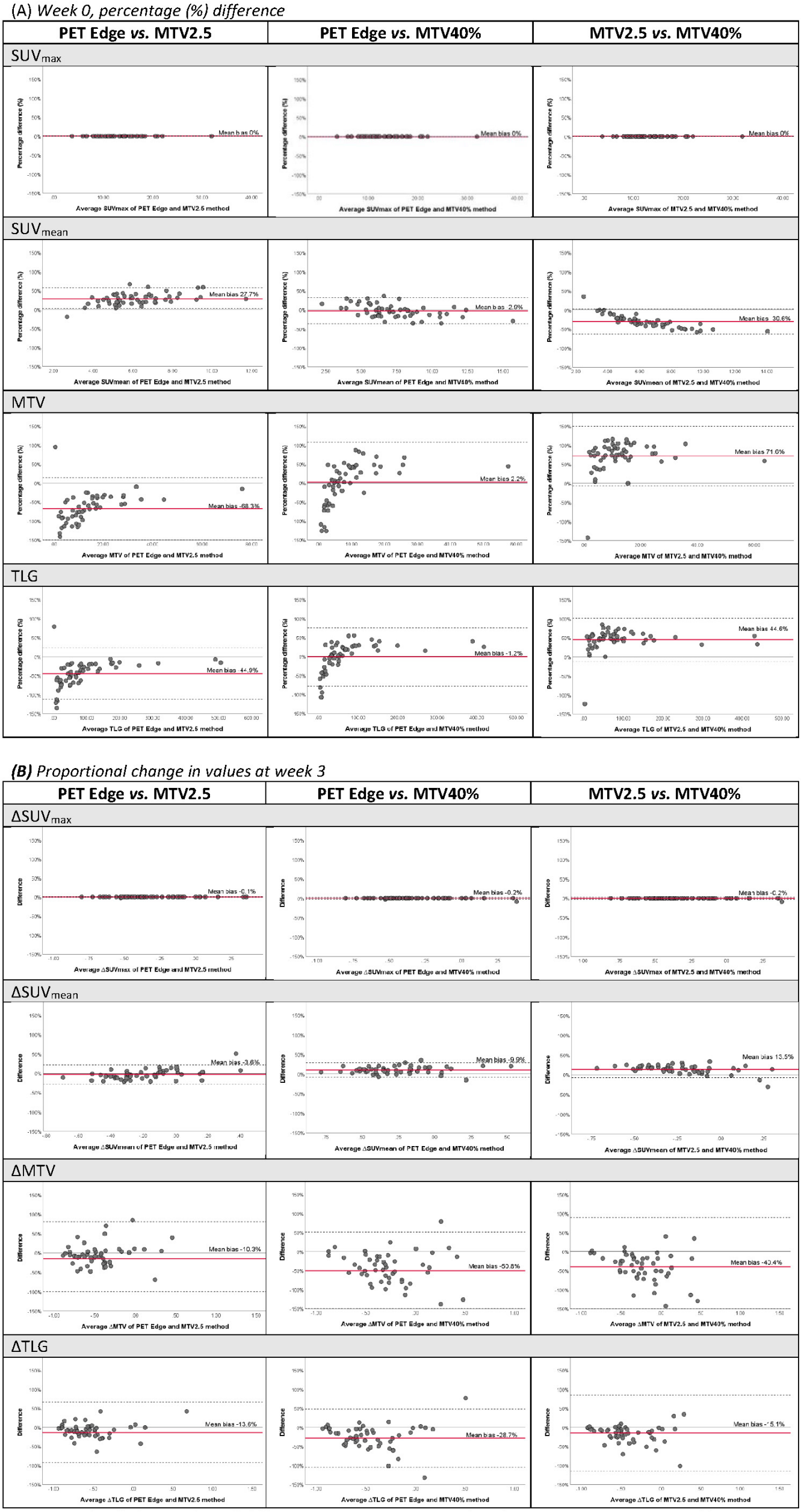


Figure S1 Scatter plot and corresponding Pearson correlation coefficient for PET parameter values (SUV_{max}, SUV_{mean}, MTV, TLG) between three ROI delineation methods (PET Edge, MTV2.5, MTV40%) at week 0 (A) and change at week 3 (B).

https://dx.doi.org/10.21037/qims-22-798

(A) *Week 0, percentage (%) difference*



(B) *Proportional change in values at week 3*

Figure S2 Bland Altman plots of difference in PET parameter values (SUV_{max}, SUV_{mean}, MTV, TLG) between ROI delineation methods (PET Edge *vs.* MTV2.5; PET Edge *vs.* MTV40%; MTV2.5 *vs.* MTV40%) at week 0 (A) and change at week 3 (B).

https://dx.doi.org/10.21037/qims-22-798