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Defining primary anal cancer tumour volume on FDG–PET – an initial assessment of semi–automated methods

Abstract

Purpose

Clinician inexperience, intra–observer and inter–observer variations in tumour definition may affect staging, radiotherapy target definition, and treatment outcomes, particularly in rare cancers. The purpose of this study was to assess the correlation between semi–automated methods of primary anal cancer (AC) definition and our current clinical standard of manual clinician definition using ^{18}F–FDG–PET imaging and to provide recommendations for clinical use.

Methods

All patients referred for chemoradiotherapy for AC between 2012 and 2016 were prospectively enrolled, with all ^{18}F–FDG–PET imaging acquired within one year of chemoradiotherapy collected. Three methods of primary AC definition were performed on all PET datasets. Manual definition by an experienced radiologist was considered the clinical standard for comparison of volume and coincidence (Dice coefficient) in our study. Semi–automated techniques assessed included a gradient–based SUV (SUV–gradient) method and a SUV threshold method with a range of thresholds relative to SUV_{max} (40 (T40), 50 (T50) and 60% (T60)).

Results

Ten patients were enrolled with 33 PET study sets available for analysis. While all methods created contours on pre– and post–treatment scans, manual definition of PET–avid disease was only necessary on 11 of the 33 study sets. SUV–gradient and T40 defined contours were not statistically different in volume to the clinical standard (p = 0.83 & 0.72 respectively). The observed Dice coefficient relative to the manual clinician contours were 0.75 and 0.73 for the SUV–gradient and T40 methods respectively.

Conclusions

It is possible to define gross AC using SUV–based methods, with the SUV–gradient–based method followed by the T40 method most closely correlating with our current clinical standard. The SUV–gradient–based method studied is housed within a proprietary clinical system. A semi–automated approach that uses a vendor neutral T40 method and the clinician's knowledge and skill appears optimal in defining AC. With this approach AC may be defined reliably to enhance efficiencies in radiotherapy and nuclear medicine processes, and to support clinicians in identifying and defining this rare disease.

Trial registration

ANZCTR, ACTRN12620000066987. Registered 28 January 2020–Retrospectively registered, https://www.anzctr.org.au/ACTRN12620000066987.aspx

Keywords: anal cancer, PET, automated, radiotherapy, SUV, target volume

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Abbreviations: AC, anal cancer; PET, positron emission tomography; 18F–FDG, 18F–fluorodeoxyglucose; CT, computed tomography; MRI, magnetic resonance imaging; SUV, standard uptake value; SUVmax, maximum SUV; SUVmin, minimum SUV; SCC, squamous cell carcinoma; CBCT, cone beam CT; IMRT, intensity modulated radiotherapy

Introduction

Anal cancer (AC) is a relatively rare cancer, with an estimated global incidence of 0.53 per 100,000,[1] and increasing rates of incidence.[2,3] Standard management for AC uses a chemoradiotherapy regime implemented following staging procedures.[4,5] Staging of AC employs physical examination and a multi–modality imaging approach, including computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET), in varying combinations and frequency.[6,7] 18F–fluorodeoxyglucose (FDG) PET is the main functional imaging modality employed in cancer disease staging and radiotherapy planning.[8,9] FDG–PET has greater sensitivity in the definition of AC than CT alone, detecting primary AC tumour more often than CT.[10–13] It has also shown to impact on staging and treatment intent in up to 20% of cases when used in addition to CT.[12,14,15] With enhanced sensitivity and less interobserver error, PET offers potential in rare cancers, such as AC, to overcome observer inexperience and reduce intra– and inter–observer variations in tumour definition.

A PET scan is a quantitative imaging modality, with the standard uptake value (SUV) its unit of measurement. It has been suggested that SUV values can be used to quickly and automatically delineate gross disease (high SUV) from normal tissues preventing observer bias innate in manual delineation.[16–18] Inter–observer variability in the definition of radiotherapy treatment volumes can impair disease control and treatment outcomes.[19,20] PET imaging reduces this inter–observer difference, but it does not remove it entirely.[21,22] Manual definition and identification of the tumour edge is dependent on the observer's skills, experience, contouring system and window settings used. By selecting voxels based on their quantitative measure of metabolic activity, radiotherapy target volumes may be more biologically relevant, thus maximising active tumour dose coverage, minimising adjacent normal tissue dose, allowing dose painting across tumour sub–populations and improving treatment outcomes.[23,24]

SUV–based methods of PET–based contouring have been widely investigated using a minimum threshold value derived as a percentage of the maximum SUV (SUVmax) value within the tumour region.[25–28] In this technique, all voxels with an SUV value above the threshold percentage are considered tumour and included within the contour. Thresholds between 15 to 60% of the maximum SUV have been studied across several tumour sites.[29–32] Further techniques have defined tumour based on the gradient of SUV change at the edge of a tumour.[33] These methods utilise complex image interpretation and derivation models to define the relevant PET metabolic borders. Due to this complexity they are often contained within commercial systems.[34,35] Consensus has yet to be reached on the optimal method of SUV–based tumour definition or the SUV value(s) within each method. The optimal method appears likely to be tumour site dependent.

Semi–automated contouring techniques based on SUV may also have benefits in the post–treatment setting for standardising response assessment.[17,36] assessment of AC response to treatment is primarily through assessment of physical changes, primarily tumour size on clinical examination or morphological imaging using CT, MRI or in some cases ultrasound[6,7,36] rather than metabolic changes on PET. The accurate delineation of active metabolic tumour, its size and extent in the presence of local tissue background PET activity is often experience–based and can vary between clinicians.[21,38] Differences in tumour response assessment reporting between observers may alter a patient's treatment and surveillance course, affecting overall outcomes.

We aimed to identify if semi–automated SUV–based techniques of tumour definition, including a range of SUVmax thresholds and a gradient–based tool, are translatable to primary AC definition pre– and post–chemoradiotherapy. We further aimed to quantify which SUV–based contouring method best correlated to manual contours defined by an experienced clinician (our current standard) for potential use in staging, radiotherapy treatment planning and response assessment for patients with AC.

Methods

This prospective study was approved by and conducted in accordance with the Austin Health Research Ethics Committee requirements. Informed consent was obtained from all participants. All patients with histologically proven squamous cell carcinoma (SCC) of the anal canal, consecutively referred for chemoradiotherapy at Austin Health were enrolled into the study between 2012 and 2016. Ten patients in total were enrolled during this time.

Radiotherapy was delivered using an intensity modulated radiotherapy (IMRT) technique. A planned primary tumour dose of 54Gy was delivered five days a week over five to six weeks. All patients received daily pre–treatment imaging using cone beam CT (CBCT), with all shifts actioned via remote couch adjustment with a zero–action threshold. Radiotherapy was completed as prescribed in all but one patient, where treatment ceased at fraction 27 of 30 due to acute toxicity. All patients were reviewed one month following completion of radiotherapy, and thereafter every three to six months by a radiation oncologist with MRI and PET imaging and clinical examination as per standard departmental practice (Figure 1).
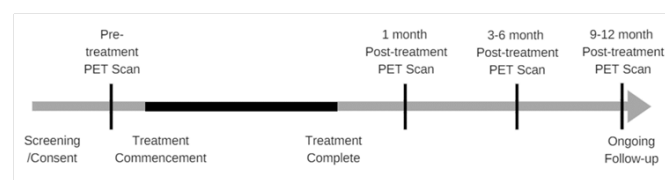

Figure 1 Study timeline schema.

PET imaging

All patients underwent pre–chemoradiotherapy (pre–treatment) whole body 18F–FDG–PET/CT scans as per standard colorectal imaging protocols at our institution. Patients were injected with 250–260Mbq 18F–FDG and images acquired from skull vertex to upper thighs after a 50–90–minute uptake time using a Philips Ingenuity® or Gemini® TF64 PET/CT (Philips Healthcare, Cleveland, OH, USA). CT attenuation correction was applied to images for viewing and analysis. Post–treatment 18F–FDG–PET images were performed with the same parameters as the pre–treatment scan in the same molecular imaging facility. All available post–treatment scans performed within one year, including one–month post–treatment and others as per departmental practice, following a patient's treatment were included in the analysis.

Image fusion

Image study sets were exported to MIM Maestro® version 6.8.3 (MIM Software Inc., Cleveland, Ohio, USA) where pre– and post–treatment PET–CTs were co–registered per patient by a single senior clinical observer based on the low dose CT scans. Registration was completed in two stages. First, whole CT study sets were registered via rigid assisted alignment, with a box–based alignment performed using a region of interest defined around the pelvis from L4 to the pubic symphysis and laterally to cover the medial acetabulum excluding the femoral heads. The resultant fusion was visually inspected in all planes, axial, sagittal and coronal, with respect to the anus and distal rectum and adjusted manually where required due to any relative soft tissue movement or filling.

Contour definition

Primary anal canal tumours were contoured for the purpose of this study according to three methods on each PET study set, as described below. Contours were only produced when visibly identified by the clinician, or where they reached the criteria relative to the SUV of the semi–automated method.

Manual Method: A senior radiologist and nuclear medicine specialist with more than 15 years of experience and knowledge in colorectal PET reporting and contouring, manually contoured the gross tumour extent on all relevant axial slices of each PET scan, pre– and post–treatment using a standard MIM Maestro® window setting.

This method is considered our standard for comparison and analysis. All Manual method contours were independently reviewed and accepted by a senior colorectal Radiation Oncologist. This method replicates the current manual clinical process prior to co–registration with other imaging modalities so as to compare PET–only methods of definition.

SUV–gradient Method: The proprietary gradient–based MIM Maestro® PET Edge® tool, as described by Werner–Wasik et al.,[34] was used by a second senior clinician with 10 years radiotherapy planning and contouring experience on each pre– and post–study set to define gross tumour extent where visible. Where metabolic activity was not clearly identifiable as persistent disease, no contour was produced.

SUV–threshold Method: A series of three contours, T40, T50 and T60, were created for each patient on each available study set by the same single senior clinician as the SUV–gradient method above using the auto–threshold tool within MIM Maestro®.[34] Pre– and post–treatment study sets were fused for each patient. A 3D sphere region of interest (ROI) was placed to surround all visible pre–treatment primary AC PET avid disease while excluding obvious local anatomical structures, such as the bladder. A SUV threshold of 40% (T40), 50% (T50) & 60% (T60) of the SUVmax measured within the pre–treatment ROI for each patient were used to generate contours on each study set for that patient. Any contours produced by semi–automated methods on post–treatment imaging were removed where non–contiguous with, and greater than 0.5cm from the pre–treatment contour for analysis. This step was designed to ensure relative disease response/persistence was measured in absence of background activity within adjacent tissues.

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 7.02 for Windows (GraphPad Software, La Jolla California, USA). Contour descriptors, volume (cc), SUVmax, and SUVmin, were calculated as median values (interquartile ranges). Resultant study contour volumes for each semi–automated method, SUV–gradient and SUV–threshold, were compared for similarity and correlation to the current clinical standard of the clinician, Manual method, for each study set using Dice's coefficient of similarity and Spearman correlation coefficient (rs).Wilcoxon matched–pairs signed rank test was also performed as Shapiro–Wilk normality testing indicated data to be non–Gaussian. A two–tailed p–value of < 0.05 was considered statistically significant.

Results

Ten patients were referred for chemo–radiotherapy between 2012 and 2016 with all recruited for this study. The median age at time of treatment was 60 with a range of 50–74. One patient was replaced in this study due to their inability to complete the required. The T40 method was the closest threshold method in volume to the Manual method 108.6% (p=0.73, rs=0one–month post–treatment study PET imaging. This patient was replaced in the study with the next consecutively referred patient.

A total of 33 prospectively acquired PET study sets (10 pre– and 23 post–treatment) were available for analysis. The number of post–treatment imaging studies was limited by incomplete referral and attendance. Semi–automated methods, SUV–gradient, T40, T50, and T60 produced contours on 15, 25, 18, and 14 study sets respectively, compared to 11 produced by the clinician (Manual method). Figure 2 demonstrates the resultant volumes on one representative patient's study set. For comparative analysis to our clinical standard, Manual method, only the 11 study sets, comprising ten pre–treatment and one post–treatment, were considered. Resultant contour descriptors are summarised in Table 1 and Table 2.
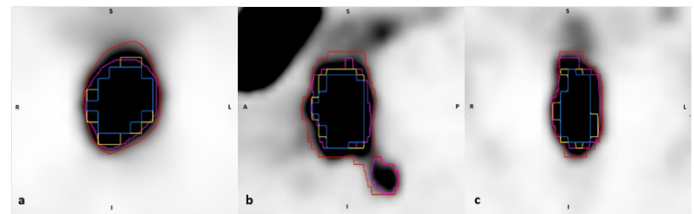
Figure 2 Axial (a), Sagittal (b), and Coronal (c) images demonstrating contour volumes derived from Manual (pink), T40 (red), T50 (yellow), T60 (blue) and SUV-gradient (orange).

The SUV–gradient method contour volumes demonstrated greatest similarity with the Manual method, with a Dice similarity coefficient of 0.75 (Table 1). The SUV–gradient method contour volumes were also closest in volume to the clinician, at 100.7% (p=0.83, rs=0.84) of the clinician's volume.77) (Table 1). SUVmax within our cohort of datasets with Manual method–defined contours (n=11) ranged from 4.65 to 36.1, with a median of 9.25. No semi–automated techniques were statistically different from the Manual method (Table 2). The SUV–gradient method was the only method not significantly different (p=0.64) to the Manual method in SUVmin, (Table 2). The SUVmin can be considered analogous to a SUV threshold.

Table 1 Summary of contour volumes derived by SUV-thresholds 40% (T40), 50% (T50), 60% (T60) of SUV$_{max}$, and SUV-gradient on pre-treatment and post-treatment ^{18}F-FDG-PET study sets from 10 patients with anal cancer. Data presented as median (IQR), with Dice coefficient, Correlation (r$_s$) and p-values based on comparison with corresponding clinician (Manual) volumes

			Datasets with Manual contours				
	Median Volume (cc)	Datasets (N)	Median Volume (cc)	Median Volume as percentage of Manual volume	r$_s$	p-value	Median Dice Coefficient
Manual	6.23 (2.8-20.75)	11	6.23 (2.8-20.75)				
SUV-gradient	6.95 (1.42-16.46)	15	8.87 (2.18-17.62)	100.70 (84.79-124.6)	0.84 (0.48-0.96)	0.83	0.75 (0.65-0.81)

Table continued...

	Median Volume (cc)	Datasets (N)	Datasets with Manual contours				
			Median Volume (cc)	Median Volume as percentage of Manual volume	r_s	p-value	Median Dice Coefficient
T40	3.68 (1.2-8.52)	25	7.94 (3.27-16.0)	108.60 (55.4-174.9)	0.77 (0.30-0.94)	0.72	0.73 (0.63-0.83)
T50	1.89 (0.56-6.62)	18	5.19 (1.79-11.26)	63.90 (43.14-83.31)	0.75 (0.26-0.93)	0.019	0.66 (0.60-0.74)
T60	2.24 (0.57-4.72)	14	3.20 (1.22-16.0)	38.5 (25.87-58.11)	0.82 (0.41-0.95)	0.001	0.56 (0.41-0.71)

Table 2 Median (IQR) SUV values of study contours derived by Manual (clinician), SUV-gradient, T40, T50 and T60 methods. Wilcoxon matched-pairs signed rank test p-values are presented for comparison with the Manual method

	Median SUV_{min}	p-value	Median SUV_{max}	p-value
Manual	1.67 (1.13-1.9)		9.25 (6.15-18.18)	
SUV-gradient	1.46 (0.73-2.63)	0.64	7.68 (6.15-11.78)	>0.99
T40	3.74 (3.01-7.28)	0.002	5.71 (3.37-8.56)	>0.99
T50	4.66 (3.77-9.18)	0.001	7.33 (4.85-11.62)	>0.99
T60	5.59 (3.69-10.95)	0.003	7.78 (5.84-13.38)	>0.99

Discussion

Anal cancer is 18F–FDG–PET avid thus enabling the use of a quantitative PET imaging to define gross tumour extent.[10,11] This study has demonstrated that the SUV–threshold of 40% SUVmax (T40) and the SUV–gradient method delineate primary anal cancer volumes that are most coincident in location and volume with clinician–defined (Manual method) primary AC tumour volumes (Table 1). These methods therefore appear clinically useful semi–automatic methods of primary AC staging and radiotherapy treatment target definition and warrant further evaluation.

Auto–segmentation of tumour volumes, based on quantitative measures of 18F–FDG–PET, have been shown to have reduced inter–observer variability.[21,39] We have shown the potential for a semi–automated SUV–based method to closely replicate clinician–defined, Manual, primary AC contour volumes. Automated methods have previously been shown to improve consistency in tumour staging and radiotherapy target definition,[35,40] and this study shows that we can extend this application to AC definition and treatment. Our small cohort and the length of time to reach this number (four years) is indicative of the rarity of this cancer. While low cohort numbers preclude robust statistical analyses, our results provide confirmation of the potential value of these methods in primary AC definition. Further work is required to validate these results in larger numbers, and to also ensure that the same methods are applicable to nodal disease delineation, as this will impact on the complete radiotherapy treatment planning volumes.[7,41]

The SUV–threshold method identifies all voxels within a ROI exhibiting metabolic activity higher than the threshold SUV value. This may be distinctly different to the metabolically active disease visible to the clinical observer. Using a ROI that is larger than the visible metabolic disease ensures all voxels are assessed

quantitatively to reduce operator selection bias. Tumour volumes defined by the SUV–gradient method utilising the PET Edge® tool are easily influenced by the observer as it requires the user to both decide that there is metabolic activity indicative of disease and then to approximately identify the disease borders to which the tool is then directed to contour. Defining this edge is particularly problematic in tumours with heterogenic activity or those exhibiting large areas of diffuse intermediate activity.[42] Within our cohort, one pre–treatment study set exhibited an extreme (>300%) difference in the T40 and PET Edge® contour volumes compared to the clinician (Figure 3). On further examination of this PET study set, the primary tumour was observed as a clear area of high PET activity surrounded by a large area of diffuse intermediate activity. It is this area of intermediate activity that was contoured by the SUV–based techniques but not by the clinician, who classified it as background activity. Such differences in definition can lead to disparate contour sizes which may impact radiotherapy treatment dose and outcomes, including recurrence and side effects.[42]

The accuracy of these semi–automated techniques may be dependent on several factors inherent in 18F–FDG–PET, including proximity of PET avid 'normal' tissue, patient–specific background tissue metabolic activity, tumour size, inconsistencies in PET scan parameters and image resolution of PET.[8,17,18,43] Relative SUV values account for inter–patient differences in tracer uptake and were used for this reason in this study. Relative SUV values may not be representative of a whole population where datasets have been obtained from a number of imaging facilities. In our study, we have attempted to limit this effect by performing all scans within the same nuclear imaging facility with standard scan protocols. To minimise the influence of background metabolic activity, further work in our cohort could evaluate a background normalisation method, such as that described in the literature to further minimise its influence on tumour definition.[36,42,44,45] Further issues may arise due to the inherent metabolic activity of adjacent pelvic structures such as bladder and proximal rectum. Our methods of ROI definition and contour checking were aimed to minimise these issues of overlap but demonstrate the requirement of an experienced clinical observer in this process, similar to that observed by Ciernik et al.[24]

In the post–treatment setting, too low a SUV threshold may not distinguish between minimal persistent disease and background activity. This has the potential of altering future treatment and surveillance. Using a quantitative method for disease assessment offers a continuum of treatment response classification. Measurable relative response characteristics may provide more definite measures of response that more appropriately relate to long–term clinical outcomes.[46–48] While this may remove the observer from the direct interpretation of disease–positive voxels, they are still required to ensure the ROI is appropriate and resultant volumes relevant.

While the T40 method exhibited a close correlation with the clinician's volumes, it differed most when the clinician's volumes indicated that the primary AC tumour was small (<7cc) (Figure 3). Whether this is an effect of the relatively low image resolution of PET or the SUV–independent methodology underlying the clinician's manual volumes is unclear. Jeraj et al.[8] commented that tumours <5–10mm in size may be under visualised on PET, and our work would suggest that those tumours visualised may be oversized when compared to a clinician (Figure 3). This is of particular importance in the post–treatment setting where persistent or recurrent tumours may be very small (<5mm) and not clearly definable from inherent metabolic activity in local tissue. In our study there was little clinician

information for comparison to semi–automated methods on post–treatment scans as only one patient on one study set was considered to have an incomplete metabolic response by the clinician. Semi–automated methods, however, defined volumes on up to 15 of 23 (65.2%) post–treatment study sets. These semi–automated contour volumes were small ranging from 0.31cc to 2.3cc and again would be difficult to exclude from background activity or sampling issues.[49,50] Whether these are realistic volumes or false positives due to inherent background activity requires long term follow up and comparison with pathological specimen. The SUV–gradient method appeared to be less influenced by tumour size and may be more appropriate for tumours <10cc in size. Removing the clinician from the monitoring process with a fully automated method using relative SUV values without accounting for background metabolic activity may lead to false diagnosis of persistent disease. Should this be acted upon, a patient may receive unnecessary follow–up treatment with associated toxicity and anxiety.

A limitation of the SUV–gradient method used in this study is the proprietary PET Edge® tool as it is only available within the MIM Maestro® software. A software platform independent semi–automated contouring method using a SUV threshold value of 40% of SUVmax would also be appropriate for definition of anal cancer prior to radiotherapy, as we have shown a similar level of correlation (rs=0.77) to the clinician's volumes, as well as in response assessment post–treatment.

Our assumption of the clinician's volumes being the gold standard could be debated when we consider the quantitative nature of PET and the qualitative visual interpretation method that may be employed by the clinician. Semi–automated techniques take advantage of this quantitative information to provide reproducible tumour definition. There does not appear to be a clear consensus as to the most appropriate gold standard and this may be affecting radiotherapy outcomes. Potential biases of the observer, based on their clinical experience, window settings used, and lack of clear delineation guidelines may lead to potential unwanted variations in contours and response assessment between observers. Methods identifying disease on a voxel–based level, such as those studied here, must have a role in tumour definition and surveillance. We have demonstrated the potential of these methods in anal cancer but realise their current limitations. Both T40 and SUV–gradient methods in this study require some degree of user intervention which may lead to inter–observer variability which would need to be quantified in future studies. Developing clear guidelines for these methods would reduce this potential error. Further, the SUV–gradient method uses a proprietary tool which is not readily available across all clinical systems. Complex computer learning algorithms may improve the accuracy in the future through patient–specific adaptive pathways that more closely match, or even exceed, the skilled clinician's volumes.[51–54] For now, the quantitative definition of AC on PET should only be semi–automated, acting as an aide to the clinician in identifying the active tumour border rather than having to contour individual image slices. The clinician can then edit the contours that are based on quantitative voxel data, rather than producing contours based on visual greyness.

In conclusion, a SUV–based method of defining primary AC is capable at producing clinically relevant volumes simply and efficiently. Using a 40% threshold offers a vendor agnostic method of definition that can be employed widely across imaging and radiotherapy departments, and their respective clinical systems. They are currently not a replacement for a skilled clinician, and we suggest that they be used as an aide to tumour definition. Future research in

larger patient cohorts is required to establish the optimal approach, particularly in treatment response assessment and with respect to locoregional lymphatics.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Austin Health Research Ethics Committee, reference number HREC/14/Austin/643, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Trial registration: ACTRN 12620000066987.

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