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Impact of Integrated PET/CT on Variability of Target Volume Delineation in Rectal Cancer

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Several studies have demonstrated substantial variability among individual radiation oncologists in defining target volumes using computed tomography (CT). The objective of this study was to determine the impact of combined positron emission tomography and computed tomography (PET/CT) on inter-observer variability of target volume delineation in rectal cancer. We also compared the relative concordance of two PET imaging tracers, ^{18}F-fluorodeoxyglucose (FDG) and ^{18}F-fluorodeoxythymidine (FLT), against conventional computed tomography (CT). Six consecutive patients with locally advanced rectal cancer were enrolled onto an institutional protocol involving preoperative chemoradiotherapy and correlative studies including FDG- and FLT-PET scans acquired in the treatment position. Using these image data sets, four radiation oncologists independently delineated primary and nodal gross tumor volumes (GTVp and GTVn) for a hypothetical boost treatment. Contours were first defined based on CT alone with observers blinded to the PET images, then based on combined PET/CT. An inter-observer similarity index (SI), ranging from a value of 0 for complete disagreement to 1 for complete agreement of contoured voxels, was calculated for each set of volumes. For primary gross tumor volume (GTVp), the difference in estimated SI between CT and FDG was modest (CT SI = 0.77 vs. FDG SI = 0.81), but statistically significant ($p = 0.013$). The SI difference between CT and FLT for GTVp was also slight (FLT SI = 0.80) and marginally non-significant ($p < 0.082$). For nodal gross tumor volume, (GTVn), SI was significantly lower for CT based volumes with an estimated SI of 0.22 compared to an estimated SI of 0.70 for FDG-PET/CT ($p < 0.0001$) and an estimated SI of 0.70 for FLT-PET/CT ($p < 0.0001$). Boost target volumes in rectal cancer based on combined PET/CT results in lower inter-observer variability compared with CT alone, particularly for nodal disease. The use of FDG and FLT did not appear to be different from this perspective.

Keywords: Rectal cancer; Target definition; FDG-PET; FLT-PET; and Treatment planning.

Introduction

Accurate delineation of tumor extent is a crucial aspect of planning three-dimensional conformal radiation therapy planning, the treatment technique most commonly used for preoperative radiation treatment of rectal cancer. Typically, a CT scan is used for defining the tumor volumes using anatomic information. Commonly, it is difficult to distinguish involved nodes from benign ones as both may have normal appearances. Often, the boundaries between the tumor and normal tissues are obscured by inflammatory changes or artifact, making it difficult to accurately outline the tumor areas on the treatment planning CT. This leads to significant inconsistency in volume delineation among physicians. Several

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Abbreviations: CT, Computed tomography; PET/CT, Positron emission tomography and computed tomography; FDG, ^{18}F-fluorodeoxyglucose; FLT, ^{18}F-fluorodeoxythymidine; EUS, Endoscopic ultrasound; GTVp, Primary gross tumor volume; and GTVn, Nodal gross tumor volume.

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studies have demonstrated a substantial variability among radiation oncologists in defining the target volume using CT images, suggesting that the benefits of conformal treatment planning with high-precision radiotherapy could be offset by this inconsistency in target delineation (1-3).

The development of ^{18}F-fluorodeoxyglucose (FDG)-PET as an indicator of glucose metabolism has revolutionized the use of functional imaging for cancer management. Studies on using FDG-PET for radiation therapy planning of lung (4-6) and head and neck cancers (7-10) have shown promising results. However, the data on the use of FDG-PET for radiation planning in rectal cancers is limited.

FDG is not a highly selective tracer for tumor imaging, and inflammatory lesions are the most common cause of false-positive results for FDG-PET scans (11, 12). A novel tracer ^{18}F-fluorodeoxythymidine (FLT), a thymidine analog, is being investigated as a more selective imaging agent of cellular proliferation. FLT is trapped intracellularly after phosphorylation by the enzyme thymidine kinase (11). The first study in humans showed a significant correlation between FLT standardized uptake values (SUV) and proliferative activity in pulmonary nodules (13). Tumor uptake of FLT in patients with colon and other gastrointestinal tumors has also been demonstrated by PET imaging (14).

We hypothesized that the use of accurately-fused PET/CT imaging study will improve tumor definition for radiation targeting in rectal cancer. The objective of this study was to determine the impact of combined PET/CT on inter-observer variability of target volume delineation in rectal cancer. We also compared the relative impact of the two PET imaging tracers FDG and FLT.

Patients And Methods

Study Population

We applied the current analysis to the imaging studies of six consecutive patients with locally advanced rectal cancer enrolled in an IRB approved protocol at Stanford University School of Medicine between October 2004 and March 2005. The protocol involves preoperative chemoradiotherapy and correlative studies including FDG- and FLT-PET/CT scans acquired in the treatment position. Eligibility criteria for the protocol are histologically confirmed adenocarcinoma of the rectum, endoscopic ultrasound (EUS) evidence of T3 or T4 disease or involvement of regional nodes, age > 18, Karnofsky score > 70, and no prior pelvic or whole abdominal radiotherapy. We analyzed imaging studies performed before the commencement of any form of therapy. The median age was 51.5 years. By EUS staging, all patients had T3 disease, and two had involved perirectal nodes. By FDG-PET, two patients had abnormal pelvic nodes. However, PET was not required for staging purposes according to the therapeutic protocol onto which these patients were enrolled. The patient characteristics are summarized in Table I.

Table I
Patient Characteristics

Case	Stage by EUS	Age	Gender
1	T3N0M0	21	Male
2	T3N0M0	37	Male
3	T3N0M0	55	Female
4	T3N1M0	51	Male
5	T3N1M0	66	Male
6	T3N0M0	52	Male

Imaging Protocols

Combined PET/CT (Discovery ST^{8}, GE Medical Systems, Milwaukee, WI) was performed before the preoperative chemoradiotherapy portion of the treatment. Patients were asked to abstain from eating for six hours prior to the FDG-PET examination, and pre-injection blood glucose levels were checked (range 95-127 mg/dL). Radiolabeled tracer (15 mCi of FDG or 8 mCi of FLT) was injected *via* a peripheral intravenous catheter. The examination was started 45-60 minutes after injection, consisting of a whole body staging scan (6-7 bed positions from the mid-cranium to mid-thigh) followed by a high-resolution scan of the region of interest (2-3 bed positions from the level of the L1 vertebral body to the mid femurs). The latter scans were used for this analysis. The patients were scanned in the treatment position, prone with a belly board. The FDG- and FLT-PET/CT scans were performed at least 24 hours apart from each other. Five of the patients received the FLT-PET/CT scan, while all six had the FDG-PET/CT scan. One patient (Case #6) did not receive an FLT-PET scan because of a technical issue related to FLT synthesis on the day of the scheduled scan.

The CT scan used for treatment planning was acquired first using the multi-slice helical CT portion of the scanner. The acquisition of FDG-PET data was then acquired without repositioning the patient. The PET and CT data sets were transferred to an Eclipse treatment planning workstation (Varian Medical Systems, Palo Alto, CA) where the data sets were fused automatically using DICOM coordinates. Patients were set up in the same position for the FLT-PET acquisition, and fusion of these scans with the treatment planning CT scans was performed manually with the aid of surface fiducial markers visible on both CT and PET.

Volume Delineation

Using these image data sets, four radiation oncologists independently delineated primary and nodal gross tumor volumes (GTVp and GTVn) for a hypothetical boost treatment. Nodal boost volumes were based on individual interpretation of the CT or PET/CT imaging and were not constrained to agree with the reported interpretations of diagnostic studies. Contours were first defined based on CT alone with observers blinded to the PET images, then based on combined FDG- and FLT-PET/CT. Thus, each observer defined six sets of volumes per patient. The initial PET window/level settings were as follows: the display was adjusted such that for FDG-PET the liver intensity was at 10-20% grey level or step 2 on a 10-step color scale, and for FLT-PET the intensity at the soft tissue of the thighs was at less than 10% grey or step 1 on a 10-step color scale. Additional adjustment of window and level settings was then allowed according to the best judgment of each observer. Copies of the diagnostic contrast-enhanced CT, endoscopic ultrasound, and colonoscopy reports were available at the time of target definition. Because on this therapeutic protocol PET was not required as part of the staging evaluation, and because the goal of this analysis was to evaluate the impact of PET-CT based compared to CT based volume delineation, the FDG-PET diagnostic reports were not provided to the observers.

Data Analysis

Inter-observer variability between the four radiation oncologists was then assessed. An inter-observer similarity index (SI), ranging from a value of 0 for complete disagreement to 1 for complete agreement of contoured voxels, was defined as in Equation [1], and is one of a family of similarity metrics used for volume comparisons in this context (15, 16). SI values were calculated pair-wise among the four radiation oncologists, resulting in six novel SI values for each of the six patients. For FLT, there were only five evaluable patients. The SI values for each patient were analyzed using a linear mixed effects model with random effects for patients and for observer pairs; imaging modality was regarded as a fixed effect with three levels (CT, FDG, and FLT). Thus, observations from the same patient were allowed to be correlated; likewise, observations from the same pair of observers were allowed to be correlated. The modeling of these correlations to adjust for possible biases among observers and systemic irregularities in the patients makes this analysis more correct than a paired *t* test, which requires data that are not interdependent. The SAS procedure MIXED was used to obtain estimates of modality while adjusting for the above correlations (SAS Institute, Inc., Cary, NC). All p-values are two-sided.

$$SI = 2 \times [V\,(\text{intersection of A and B}) / (V(A) + V(B))], \quad [1]$$

where V is volume.

Results

Metabolic imaging significantly affected target definition in these rectal cancer cases. As shown in Figure 1, the rectal tumor is not apparent on the CT planning scan (left panel). However, when the PET information is incorporated, the tumor becomes apparent (right panel). Additional examples of how PET information impacts CT planning are shown in Figures 2 and 3. These data are quantitated in Table II. The PET data also altered the initial stage by EUS of several of the patients. The tumor volumes identified by the various imaging modalities are summarized in Table II. The maximum SUV of primary tumors ranged from 16.4-23.6 (mean 20.1) for FDG, and 5.2-17.0 (mean 12.8) for FLT. The maximum SUV of nodes ranged from 3.3-12.3 (mean 8.8) for FDG, and 3.0-5.7 (mean 4.35) for FLT.

With respect to the GTVp, PET/CT tended to have its greatest impact on the definition of the superior/inferior extent of the rectal lesion (Figure 2). Overall, GTVp definition changed substantially and became more consistent with the addition of the PET information. Using a linear mixed effects model to adjust for the interdependent relationships between the SI data, the estimated SI for CT was 0.77, for FDG 0.81 and for FLT 0.80. The increase of 0.04 for FDG

Table II
Tumor volumes identified by the various imaging modalities.

Case	Primary tumor volume (cc) [mean volume (range)]			Nodal tumor volume (cc) [mean volume (range)]		
	CT	FDG-PET	FLT-PET	CT	FDG-PET	FLT-PET
1	103.9 (63.3-127.7)	125.1 (103-152.5)	113.8 (103.7-120)	6.4 (0-24.8)	1.06 (0-4.3)	6.0 (0-17.8)
2	146.1 (125.9-163.7)	171.5 (156.8-182.4)	173.4 (157.7-209.3)	0.49 (0-0.8)	0	0
3	41.8 (39.7-45.1)	39.4 (35.4-45.1)	42.2 (34.3-45.7)	2.3 (0-3.9)	3.4 (0-6.6)	2.2 (0-4.2)
4	50.35 (32.9-62.2)	57.6 (49.7-64.0)	53.6 (39.3-62.5)	3.8 (0.8-9.1)	0.15 (0-0.6)	0
5	64.6 (47.4-89.8)	72.3 (57.6-88.7)	60.6 (53.5-72.7)	1.0 (0.7-1.5)	0	0
6	144.7 (138-156)	178.8 (143-203.6)	N/A	0.84 (0-1.4)	0	N/A

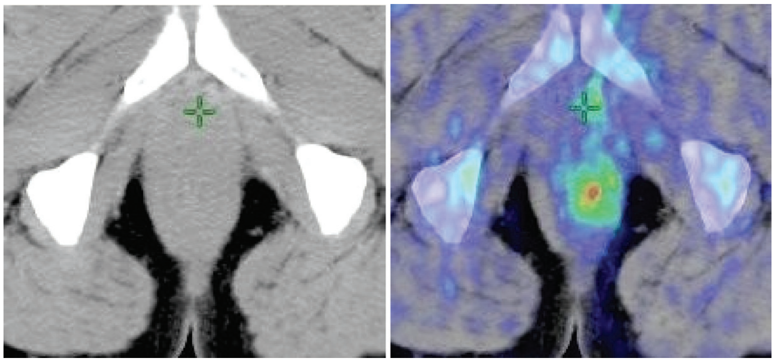

Figure 1: Representative integrated FDG-PET/CT (right) showing uptake in rectal lesion, which is poorly delineated on CT alone (left).

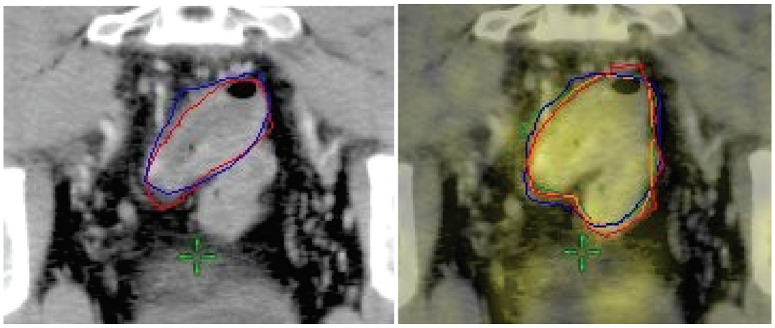

Figure 3: The volume delineation of GTVp shows that two of the four observers outlined GTVp on the axial slice based on CT alone (left). However, all four observers had more consistent tumor delineation based on FDG-PET/CT (right).

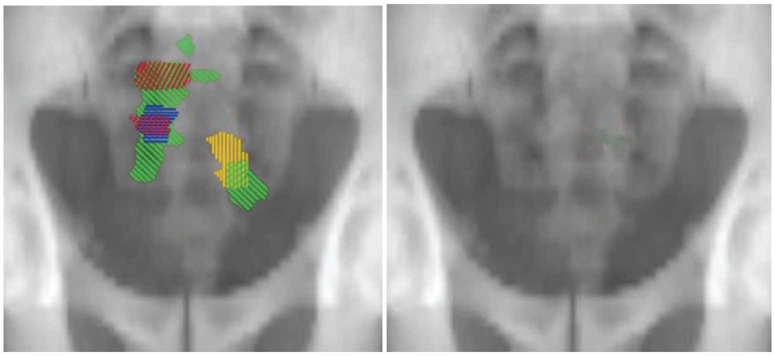

Figure 4: Digitally reconstructed radiograph (DRR) based on CT alone (left) showing GTVn in different colors representing each of the four different observers. The DRR on the right demonstrates the agreement among all the observers that there was no gross nodal disease based on FLT-PET/CT in the same patient.

Table III
Comparison of GTVp PET inter-observer similarity index (SI) to CT scan.

Modality	Estimated SI	Standard Error		95% CI	
CT	0.77	0.03		0.69	0.84
FDG	0.81	0.03		0.75	0.870
FLT	0.80	0.03		0.74	0.86
Inter-modality Difference	SI difference	Standard Error	P-value	95% CI	
FDG-CT	0.04	0.02	0.01	0.01	0.07
FLT-CT	0.03	0.02	0.09	-0.004	0.06
FDG-FLT	0.01	0.02	0.54	-0.02	0.04

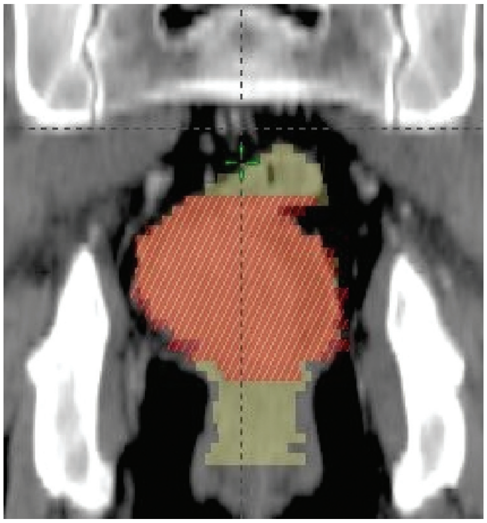

Figure 2: Representative coronal image of CT scan showing how the GTVp definition changed based on CT scan alone (red) and with the addition of integrated FDG-PET/CT (yellow).

over CT was significant ($p = 0.013$), while the increase of 0.03 between CT and FLT was marginally non-significant ($p < 0.082$). The SI difference between FDG and FLT was not significant ($p = 0.54$). Table III summarizes the estimated GTVp SI values and p-values for comparison of the various imaging modalities.

With respect to the GTVn, the estimated SI for CT was 0.22, for FDG 0.70 and for FLT 0.70. Differences between FDG and CT and between FLT and CT were strongly significant ($p < 0.0001$). Table IV summarizes the estimated GTVn SI values and p-values for comparison of the various imaging modalities. The low SI for CT alone reflects the difficulty in interpreting nodal involvement based only on morphology, leading to high variability between the observers (Figure 4). Comparisons between the SI's for FDG-PET/CT and FLT-PET/CT for both GTVp and GTVn were not significant ($p = 0.54$ and 0.98, respectively).

The significant improvement in concordance of tumor volume delineation among the four radiation oncologists using FDG-PET and FLT-PET over standard CT imaging, particularly for nodal disease, may have been impacted by our measurement system. Whereas on CT observers tended to identify abnormal nodes but disagreed on which nodes were abnormal, resulting in low SI scores, on FDG-PET and FLT-PET observers tended to agree on the absence of any abnormal nodes, resulting in several raw SI scores of 1. Neverthe-

Table IV
Comparison of GTVn PET inter-observer similarity index (SI) to CT scan.

Modality	Estimated SI	Standard Error		95% CI	
CT	0.22	0.12		-0.087	0.52
FDG	0.70	0.12		0.47	0.94
FLT	0.70	0.12		0.46	0.94
Inter-modality Difference	**SI difference**	**Standard Error**	**P-value**	**95% CI**	
FDG-CT	0.49	0.07	<.0001	0.35	0.63
FLT-CT	0.49	0.08	<.0001	0.34	0.64
FDG-FLT	0.001	0.08	0.98	-0.15	0.15

less, this does reflect increased consistency of volume delineation based on metabolic imaging.

Discussion

Accurate identification of the tumor volume may result in better tumor control and a higher chance of cure in rectal cancer patients. In addition, it will also help to better differentiate tumor from normal tissues and may result in greater sparing of normal tissues using sophisticated radiation treatment planning techniques. Accurate definition of the tumor volume is particularly important as we apply advancements in image guided radiotherapy (IGRT) techniques to greater clinical use (17). Currently, CT-based volume definition remains the standard for radiation therapy planning for rectal cancer. However, several studies have demonstrated a substantial variability among oncologists in defining the target volume using CT images (1-3). In the present study, the use of PET data results in greater inter-observer agreement of tumor volume. Although we make the assumption that greater agreement between observers will result in a more accurate target volume, this may not be the case particularly if one considers that individual radiation oncologists may have different expertise and experience in treating rectal tumors. These nuances of treatment planning affect individual decision making and are nearly impossible to quantitate.

An integrated PET/CT makes it possible to image patients with both PET and CT in the same setting and position, thereby allowing highly accurate fusion of these two studies. The importance of being able to target radiation treatments more accurately using PET/CT fusion is noted as we move toward more targeted delivery techniques, particularly with intensity modulated radiotherapy. Ciernik *et al.* demonstrated the feasibility of an integrated PET/CT leading to improved standardization of volume delineation compared with that of CT alone (18). Recently, the benefits of registered versus nonregistered PET and CT in terms of consistency in tumor volume delineation for non-small cell lung cancer was demonstrated (15).

Our study suggests that combined PET/CT-based radiation therapy planning is feasible, accurate, and easily incorporated into routine radiotherapy planning to assist with target volume delineation in rectal cancer. The potential benefits of a combined PET/CT over PET scan alone include shorter total imaging time for patients, improved anatomic localization of target, and reduced motion variability between studies (19). A recent study examining the feasibility of using an integrated PET/CT for all radiation treatment planning resulted in the most significant changes of the GTV for rectal cancer cases (18).

Despite the variations in target delineation, it is unlikely that these differences in contouring would displace the GTV outside of a standard pelvic field. However, unrecognized loco-regional lymph node metastases may be missed when designing a pelvic field. Furthermore, any boost treatment to sites of gross disease would be most impacted by inter-observer variation. As treatment margins using intensity modulated radiation therapy (IMRT) or image-guided radiation therapy (IGRT) techniques decrease, accuracy in tumor delineation becomes even more critical.

FLT is being investigated as a more selective imaging agent of cellular proliferation. A pilot study suggested that FLT was suitable and comparable to FDG in detection of malignant lesions by PET scan in patients with lymphoma (12). Shields and colleagues demonstrated uptake of FLT in patients with colon and other gastrointestinal tumors by PET imaging (14). Theoretically, imaging with FLT may lead to fewer false positives than FDG since FDG can have uptake due to inflammation and FLT is a more selective agent of cellular proliferation. In our study, incorporation of both FDG- and FLT-PET/CT resulted in higher SI for both GTVp and GTVn when compared to CT alone. However, the use of FLT-PET information did not result in improved tumor definition when compared to FDG-PET. We found no significant difference in SI for both GTVp ($p = 0.54$) or GTVn ($p = 0.98$) when comparing FDG- to FLT-PET/CT based volumes.

One caveat in the interpretation of PET scan information is that the PET window best suited for tumor volume delineation has not been well-defined. We decided not to use a PET SUV-based criterion since there is no clearly defined standard. Instead, we started with qualitative standards for image display at our institution, then allowed physicians independently to adjust the window and level when defining the target volume as this most closely simulates what occurs in real practice at present. The extent of the target can clearly change depending on the PET window/level, and therefore the CT data should also be utilized when defining the target volume. Ultimately, robust standards for display settings in PET may require more sophisticated algorithms taking into account local intensity gradients (20). Another factor to consider when defining tumor volumes is that neither CT nor PET acquired in a given session accounts for the effect of variable rectal filling over time.

The impact of PET on target definition variability has been demonstrated for lung cancer (5) and various other solid tumors (18), and our study supports the use of PET/CT in radiation treatment planning for rectal cancer. We observed a higher uniformity between observers' definition of the GTV with the use of FDG or FLT information. More precisely defined treatment volumes should ultimately lead to improved local tumor control and decreased toxicity.

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