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FULL PAPER

Consequences of additional use of contrast-enhanced ^{18}F-FDG PET/CT in target volume delineation and dose distribution for pancreatic cancer

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Objective: To compare the differences between contrast-enhanced (CE) fluorine-18 fludeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT and CECT in target volume delineation and radiotherapy (RT) dose distribution, and to evaluate the sparing of organs at risk (OARs) in the treatment plan of locally advanced pancreatic cancer (LAPC).

Methods: 21 consecutive patients with LAPC with histologically or cytologically confirmed adenocarcinoma underwent both non-CECT and ^{18}F-FDG scans; 11 of whom also underwent CECT scans. Intensity-modulated RT plans (prescribed dose, 54 Gy) were constructed to cover the corresponding gross tumour volume (GTV). The differences among GTV_{CT}, GTV_{PET}, $GTV_{PET\text{-}CT}$ and OARs in these different image sets as well as the uniformity of target dose were analysed.

Results: The mean non-CE GTV_{CT}, GTV_{PET} and $GTV_{PET\text{-}CT}$ were 76.9 ± 47.8, 47.0 ± 40.2 and $44.5 \pm 34.7\ cm^3$ (mean ± standard deviation), respectively. The non-CE $GTV_{PET\text{-}CT}$ was significantly smaller than the non-CE GTV_{CT} ($p < 0.001$). The CE $GTV_{PET\text{-}CT}$ was significantly smaller than the CE GTV_{CT} ($p = 0.033$). For both the non-CE GTV_{CT} and the CE GTV_{CT}, the intestine V_{40} (the percentage of the intestine volume irradiated by 40 Gy), intestine V_{50}, intestine D_{max} (the mean maximum dose), cord D_{max}, left kidney V_{30}, right kidney V_{30}, left kidney D_{mean} (the mean dose), right kidney D_{mean} and liver V_{30} were 5.90%, 2.52%, 5500 cGy, 2194 cGy, 3.40%, 0.68%, 747 cGy, 550 cGy and 5.37%, respectively. There are significant differences between the non-CE CT and the non-CE PET-CT in intestine D_{max} ($p = 0.023$) and right kidney D_{mean} ($p = 0.029$).

Conclusion: Co-registration of ^{18}F-FDG PET with CECT may improve the accuracy of GTV delineation in LAPC and might reduce the adverse effect of irradiation.

Advances in knowledge: Individual adaptation of RT based on functional CE ^{18}F-FDG PET/CT imaging is possible and highly promising in LAPC.

Pancreatic cancer (PC) is the fourth most common cause of cancer death in the USA with 5-year overall survival (OS) rates of <5%.[1] PC is a notoriously insidious disease, and about 70% of patients newly diagnosed with this malignancy are not amenable to curative surgery.[2] Concurrent chemoradiotherapy is the main treatment for locally advanced or recurrent PC, and radiotherapy (RT) plays a key role for local control. There are still many unresolved issues related to the delineation of the gross tumour volume (GTV) in locally advanced PC (LAPC), such as the difficulty in distinguishing the vasculature from tumour parenchyma, defining the tumour boundary on contrast-enhanced CT (CECT) in the absence of functional positron emission tomography (PET) imaging, and the presence of adjoining organs at risk (OARs), such as the small intestine, spinal cord, kidney and liver. The delineation of the GTV based on PET-CT fusion images could improve RT planning by reducing the target volume and the exposure volumes of the respective OARs and safely escalating the target radiation dose. Conventional enhanced CT scanning could not identify the extent of local tumour and lymph node invasion from peripheral structures precisely,[3] which may result in inaccurate target delineation.

Our study aimed to explore the value of the CE fluorine-18 fludeoxyglucose (^{18}F-FDG) PET-CT fusion images for target volume delineation, dose distribution in OARs and the uniformity of target dose compared with the results of CT scan-based plans in LAPC.

METHODS AND MATERIALS

Patients

21 consecutive patients with LAPC with histologically or cytologically confirmed adenocarcinoma received ^{18}F-FDG PET/CT examination, including 11 males and 10 females, mean age of 67 years (range, 47–79 years). All patients provided informed consent. Seven tumours were located in the pancreatic head, four in the tail, eight in the body and two in both the pancreatic body and tail. 18 cases were advanced unresectable PC and the remaining 3 cases were post-surgical recurrences. Tumour standardized uptake values (SUVs) among all patients averaged 7.2, over a range of 4.4–12.1.

Image acquisition

Patients were asked to fast for at least 6 h before 171–305 MBq ^{18}F-FDG (mean, 251 MBq; 3.7 MBq kg^{-1}) was injected intravenously. ^{18}F-FDG PET/CT images were obtained on a hybrid 64-slice PET/CT scanner (Siemens Biograph® 64; Siemens Healthcare, Erlangen, Germany) approximately 60 min after intravenous injection of ^{18}F-FDG. Whole-body PET images were obtained from the base of the skull to mid thigh. A low-dose CT scan (80 mAs; 140 kVp) from the vertex to the pelvis was acquired and subsequently used for attenuation correction of PET images. 11 patients were asked to maintain the original position after PET scanning and received additional high-resolution contrast CT covering the abdomen and pelvis. Images were reviewed after the fusion of both modalities as well as separately.

Target delineation

The treatment planning software (TPS) (Pinnacle TPS v. 8.0 d; Philips Radiation Oncology Systems, Milpitas, CA) was used to obtain several dosimetric parameters from the dose–volume histograms. CT and PET images were acquired by the same scanner and the fused PET/CT images were subsequently analysed automatically with the software program. An experienced radiation oncologist, nuclear medicine physician and imaging physician simultaneously carried out target delineation and the CT/CECT- and PET/CT-fused images were then transferred to the treatment planning software for target volume delineation. For each patient, the oncologist was required to outline the tumours on the CT/CECT data set first, blind to the PET/CT-fused data set. The delineation for OARs was based on the Radiation Therapy Oncology Group consensus panel guidelines.[4] The GTV_{PET} was delineated using the display set with the window width equal to the maximum of the pixel intensity within the target image and the window level equal to half this maximum.[5] After identification of a region of interest (ROI) around the tumour volume, which included the primary tumour and a margin of at least 1 cm but excluding areas of non-malignant uptake, such as major blood vessels, automated segmentation volumes were generated from the PET images using the following thresholds based on published literature recommendations:[6,7] (1) the regions with SUV higher than 2.5; (2) 40% of SUV_{max} within the ROI. The GTV_{CT} was defined per CT result as only the gross tumour and any lymph nodes with a cross-sectional diameter of ≥1 cm. GTV_{PET-CT} was then defined using fully fused PET/CT image sets as the PET visualized enhancement of the gross tumour and any lymph node with an average SUV of ≥2.5 (regardless of any deficiency in adequate nodal size criteria for malignancy as visualized by CT images alone) or any lymph nodes with a cross-sectional diameter of ≥1 cm on CT.[8]

Statistical methods

For comparison of the CT- and PET/CT-based plans, various dosimetric parameters were analysed using SPSS® 17.0 software (SPSS Inc., Chicago, IL). The Wilcoxon signed-rank test and non-parametric tests were used to determine the statistical significance of the differences among these parameters. A p-value <0.05 was considered statistically significant.

RESULTS

Peritoneal metastasis and vascular invasion

Four patients were found to have abdominal metastatic lymph nodes from PET-CT images, and two of them showed invaded celiac artery and vein. Two patients showed abdominal positive lymph nodes from enhanced CT images. There was not any abdominal vascular invasion according to non-CECT or CECT images.

Gross tumour volume from fused non-contrast-enhanced positron emission tomography/CT

17 patients' non-CE GTV_{PET-CT} decreased ≥25% compared with non-CE GTV_{CT}; 1 patient's GTV_{PET-CT} increased 10%. The non-CE GTV_{PET-CT} values were significantly smaller than the CE GTV_{PET-CT} values ($p < 0.001$). The average volumes of the non-CE GTV_{PET} and the non-CE GTV_{PET-CT} were significantly smaller than that of the non-CE GTV_{CT}: 47.0 ± 40.2, 44.5 ± 34.7, 76.9 ± 47.8 cm^3 ($z = -3.77$ and -3.91; $p < 0.001$ and $p < 0.001$), respectively. There was no difference between the non-CE GTV_{PET} and the non-CE GTV_{PET-CT} ($z = -0.19$; $p = 0.848$) (Table 1).

Gross tumour volume from fused contrast-enhanced positron emission tomography/CT

Three patients' enhanced GTV_{PET-CT} decreased ≥25% compared with the CE GTV_{CT}; two patient's GTV increased 3.2% and 18.3%, respectively, because abdominal metastatic lymph nodes were found from PET imaging. Three patients' CE GTV_{PET-CT} increased ≥25% compared with the non-CE GTV_{PET-CT}; the remaining eight patients had no significant differences between CE GTV_{PET-CT} and non-CE GTV_{PET-CT}.

The CE GTV_{PET-CT} was significantly smaller than the CE GTV_{CT} (49.3 ± 47.0 and 64.1 ± 51.5 cm^3, respectively; $z = -2.13$, $p = 0.033$) (Figure 1). The CE GTV_{PET} was smaller than the CE GTV_{CT} (45.1 ± 38.5 and 64.1 ± 51.5 cm^3, respectively; $z = -1.78$, $p = 0.075$). The CE GTV_{CT} was significantly smaller than the non-CE GTV_{CT} (64.1 ± 51.5 and 84.0 ± 61.0 cm^3, respectively; $z = -2.58$, $p = 0.010$). There was no difference between the non-CE GTV_{PET-CT} and the CE GTV_{PET-CT} (49.3 ± 47.0 and 47.8 ± 46.2 cm^3, respectively; $z = -0.80$, $p = 0.424$) (Table 2).

Table 1. Comparison of gross tumour volume (GTV) in 21 patients with pancreatic cancer

Statistical parameters	Unenhanced GTV_{CT}	GTV_{PET}	Unenhanced GTV_{PET-CT}
Mean ± standard deviation (cm^3)	76.9 ± 47.8	47.0 ± 40.2	44.5 ± 34.7
Minimum–maximum (cm^3)	8.2–227.3	8.2–171.9	4.2–167.3
vs unenhanced GTV_{CT}			$p < 0.001$
vs GTV_{PET}	$p < 0.001$		$p = 0.848$

PET, positron emission tomography.

Dose distribution in organs at risk from different image sets

There are significant differences in the right kidney mean dose (D_{mean}) and the intestine mean maximum dose (D_{max}) between the non-CE PET/CT and the non-CE CT ($p = 0.029$ and 0.023, respectively) (Figure 2). No significant difference were found in OARs of intestine V_{40} (the percentage of the intestine volume irradiated by 40 Gy), intestine V_{50}, intestine D_{max}, cord D_{max}, left kidney V_{30}, right kidney V_{30}, left kidney D_{mean}, right kidney D_{mean} and liver V_{30} between the contrast-enhance CT and the CE PET-CT (Figure 3).

DISCUSSION

The use of ^{18}F-FDG PET/CT for tumour delineation in RT has taken on increasing importance, as more and more radiation oncologists believe that target volume selection and delineation cannot be adequately performed without the use of PET. PET-CT fusion images could enhance the sensitivity, specificity and accuracy in the diagnosis of PC and have important clinical significance in the staging of PC and of recurrence diagnosis. Casneuf et al[9] reported that the diagnostic accuracy rates in PC from conventional PET/CT, CT and PET were 91%, 88% and 82%, respectively, and the accuracies of staging assessment were 92%, 90% and 80%, respectively. Molecular imaging has the potential to significantly improve target volume delineation and might also serve as a basis for treatment alteration in the future. Studies[10–12] in non-small-cell lung cancer, glioma and head-and-neck cancers have shown that the use of PET-CT in delineating a tumour target could reduce the differences among clinicians and had higher sensitivity and accuracy in delineating the boundaries of the primary tumour or lymph node metastases.

Concurrent chemotherapy and RT are the main treatment for LAPC, but the 1-year survival rate is only 27% because of local control failure or local recurrence.[13] Effective RT for PC is restricted by the dose limits to surrounding organs such as the small bowels, stomach, kidneys and liver.[14] A number of studies[15–18] have confirmed that increasing local tumour radiation dose can improve the efficacy of RT, but OARs limit the increase of the tumour radiation dose in LAPC, with radiation-induced grade II–IV gastrointestinal toxicity reaching 20–49%. In our study, we used ^{18}F-FDG PET/CT in target volume delineation for LAPC and showed that CE as well as non-CE PET/CT fusion images significantly reduced the average GTV compared with CT alone.

Figure 1. Dose coverage in contrast-enhanced CT-based (a), contrast-enhanced fluorine-18 fludeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT-based (b), non-contrast-enhanced CT-based (c) and non-contrast-enhanced ^{18}F-FDG PET/CT-based (d) treatment plans. Inner lines, PET/CT-based gross tumour volume; outer lines, CT-based gross tumour volume.

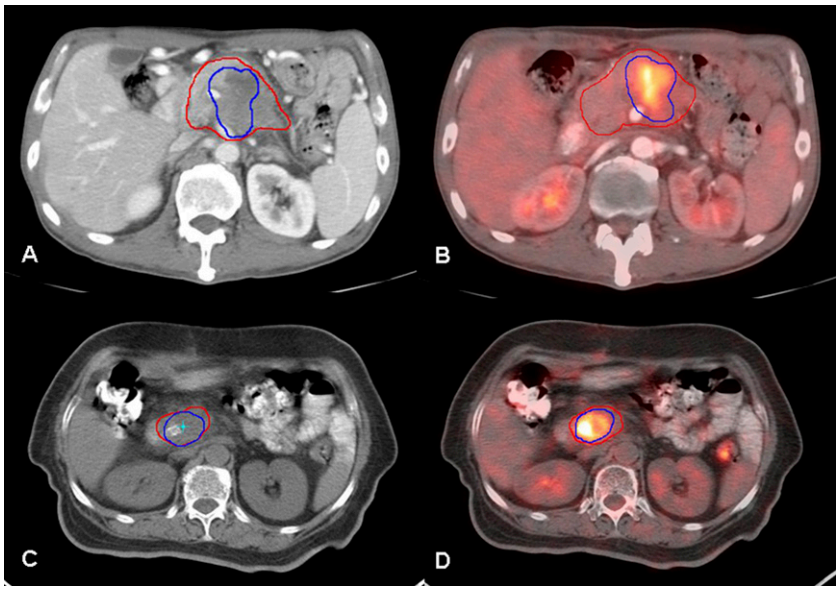


Table 2. Comparison of gross tumour volume (GTV) in enhanced images in 11 patients with pancreatic cancer

	Unenhanced GTV_{CT}	Enhanced GTV_{CT}	GTV_{PET}	Unenhanced GTV_{PET-CT}	Enhanced GTV_{PET-CT}
Mean ± standard deviation (cm^3)	84.0 ± 61.0	64.1 ± 51.5	45.1 ± 38.5	47.8 ± 46.2	49.3 ± 47.0
Minimum–maximum (cm^3)	8.2–227.3	6.5–195.0	8.2–171.9	4.2–167.3	5.7–174.1
vs enhanced GTV_{CT}	$p = 0.010$		$p = 0.075$	$p = 0.091$	
vs enhanced GTV_{PET-CT}	$p = 0.003$	$p = 0.033$	$p = 0.213$	$p = 0.424$	

PET, positron emission tomography.

Continued high local failure rates after current therapies indicate that strategies such as radiation dose escalation and novel radiosensitizers are important avenues for future study of LAPC. One study[19] has shown that compared with non-CE PET/CT, CE PET/CT-fused images were superior for the pre-operative assessment of the resectability of PC, yielding a sensitivity and accuracy between CE *vs* non-CE PET/CT of 96% *vs* 72% and 90% *vs* 64%, respectively. Another study[20] also confirmed that the use of CE PET/CT was accurate and superior to non-CE PET/CT in the assessment of resectability. Moreover, Kauhanen et al[3] reported that CE PET/CT was more sensitive (89%) than conventional imaging (MRI and CT) in the diagnosis of PC. Strobel et al[20] reported that the diagnostic accuracies of resectability for pre-operative PC among CE PET/CT, non-CE PET/CT and PET were 88%, 76% and 70%, respectively; the sensitivity of detection of retroperitoneal metastasis and of peripheral vascular invasion was 80% *vs* 20% *vs* 60% and 100% *vs* 0% *vs* 0%, respectively.

Our study also has certain limitations. First, the sample size of this study was quite small ($n = 21$), and it is effectively a pilot

Figure 2. Comparison between non-contrast-enhanced positron emission tomography (PET)/CT and non-contrast-enhanced CT in organs at risk from the ten patients, including the intestine V_{40}, intestine V_{50}, intestine D_{max}, cord D_{max}, left kidney V_{30}, right kidney V_{30}, left kidney D_{mean}, right kidney D_{mean} and liver V_{30}. D_{max}, mean maximum dose; D_{mean}, mean dose; L, left; R, right; V_{30-40}, percentage of the organ volume irradiated by 30–40 Gy. (* mean $p < 0.05$).

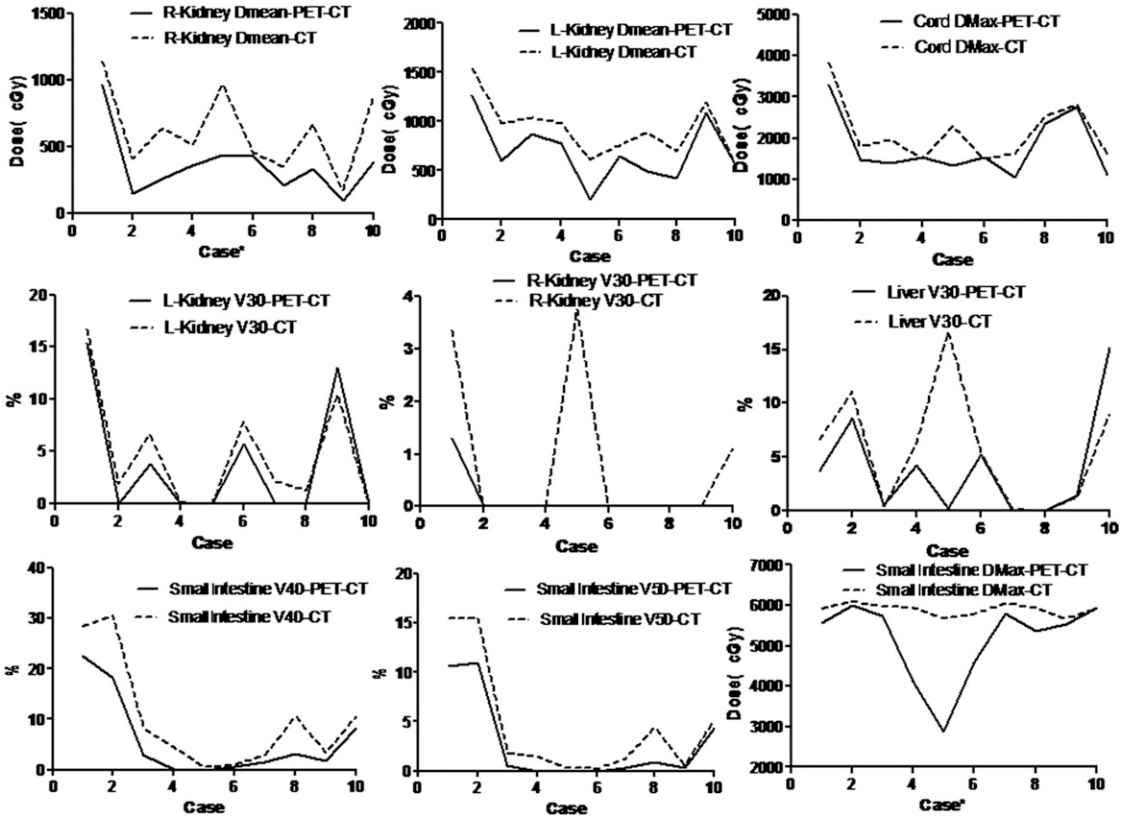
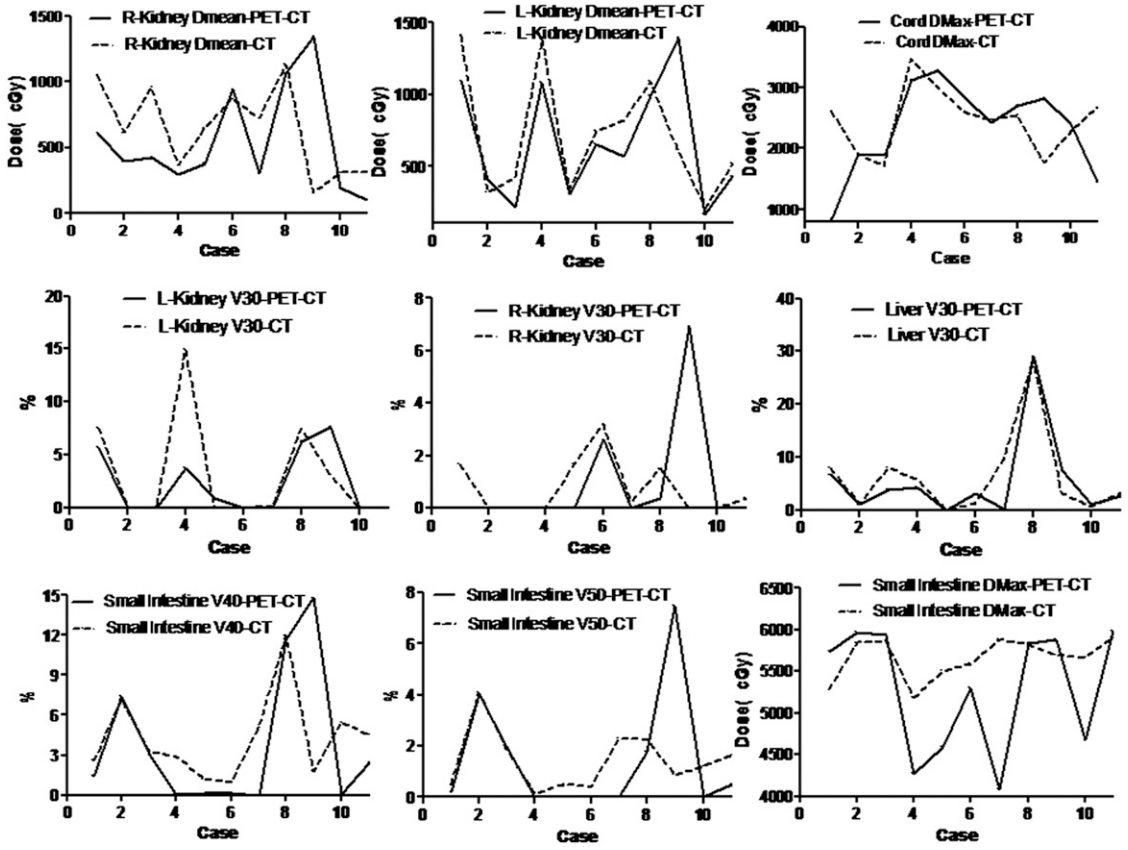


Figure 3. Comparison between contrast-enhanced positron emission tomography (PET)/CT and contrast-enhanced CT in organs at risk from the 11 patients, including the intestine V_{40}, intestine V_{50}, intestine D_{max}, cord D_{max}, left kidney V_{30}, right kidney V_{30}, left kidney D_{mean}, right kidney D_{mean} and liver V_{30}. D_{max}, mean maximum dose; D_{mean}, mean dose; L, left; R, right; V_{30-40}, percentage of the organ volume irradiated by 30–40 Gy.



study. Second, to be clinically relevant, improved assessment of GTV and OARs of LAPC by CE PET/CT requires follow-up demonstrating correspondingly improved OS and progression-free survival. To determine whether the changes based on the addition of CE ^{18}F-FDG PET/CT will result in higher probabilities of local control, prospective studies and a larger study population are still needed to better evaluate the accuracy and specificity of this approach.

In conclusion, CE ^{18}F-FDG PET/CT images may improve the accuracy of GTV delineation, decrease the irradiated GTV and might reduce the adverse effects of irradiation in LAPC, especially in terms of intestinal and renal toxicities. Although challenging to implement, individually adapted treatment planning for radiation therapy of LAPC based on ^{18}F-FDG PET/CT is practical and appears highly promising.

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