Evaluation of Hybrid PET/MRI for Gross Tumor Volume (GTV) Delineation in Liver Cancer Radiotherapy

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Abstract

Background: Hybrid ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/magnetic resonance imaging (PET/MRI) has been increasingly incorporated into the practice of radiation oncologists since it contains both anatomical and biological data and may bring about personalized radiation plans for each patient. The objective of this study was to evaluate the feasibility of gross tumor volume (GTV) delineation from hybrid PET/MRI compared with that from current-practice MRI during radiotherapy planning in patients with liver cancer.

Methods: Twelve patients (eighteen lesions) with liver cancer were enrolled in this study. We chose one of the most popular delineating methods—the visual method—in this study, and three physicians delineated the target volume of each lesion from MRI, PET, and hybrid PET/MRI images. The difference and correlation of GTV values obtained by MRI, PET and hybrid PET/MRI were subjected to statistical analysis. In addition, the Dice similarity coefficient (DSC) was calculated to assess the spatial overlap. GTV-MRI was set as a reference.

Results: Most GTV-PET/MRI (83%) and 50% of GTV-PET were larger than the reference GTV-MRI. Statistical analysis revealed that GTV-PET/MRI (p=0.021) diverged statistically significantly from the reference GTV-MRI. In contrast, GTV-PET (p=0.266) was not significantly different from GTV-MRI. GTV-PET (r=0.991, p<0.001) and GTV-PET/MRI (r=0.997, p<0.001) were significantly related to GTV-MRI. The average DSC value between GTV-MRI and GTV-PET was 0.45 (range 0–0.90) and that between GTV-MRI and GTV-PET/MRI was 0.76 (range 0.43–0.90).

Conclusions: With the database used, PET/MRI-based target volume delineation for liver cancer is feasible. The larger GTV-PET/MRI may allow adequate irradiation of the diseased tissue and improved treatment effect.

Background

Liver cancer is classified into primary and metastatic liver cancer. The incidence rate of liver cancer is increasing rapidly. Although the pace has slowed down in previous years, it increased by 2–3% annually from 2007 to 2016. The 5-year relative survival rate for liver cancer is one of the lowest, 18% [1]. Surgery and liver transplantation are radical treatments for liver cancer patients. However, only a small number of patients initially undergo surgery. For patients with inoperable liver cancer, radiotherapy alone or in combination with other treatments (such as hepatic artery chemoembolization, ablation, chemotherapy) is a very important treatment [2, 3]. Stereotactic body radiation therapy (SBRT), characterized by high-accuracy positioning and dose delivery to the lesions and minimal exposure of normal tissues, has been applied in clinical practice. It is crucial to define the target volumes accurately for liver SBRT.

At present, computed tomography (CT) and magnetic resonance imaging (MRI) are the best imaging modalities for detecting and characterizing liver tumors, and are widely used in target volume delineation [4]. CT or MRI alone can show the anatomical features of the tumor but not the biological behavior, while ^{18}F-FDG PET images can reflect the glycolytic metabolic behavior of the tumor. In addition to its widespread use in the diagnoses, staging, therapeutic evaluation, and posttreatment surveillance of patients with liver cancer [5, 6, 7], ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) has recently increasingly been used in the delineation of target volumes for radiotherapy. The major disadvantages of PET/CT are the relatively high radiation exposure from the two components and the relatively low spatial resolution of PET data. Compared with CT, MRI is more sensitive and accurate in detecting small liver lesions, which makes it an alternative to CT in hybrid imaging [8, 9].

In recent years, integrated PET/MRI technology has been put into clinical practice. The whole-body hybrid PET/MRI system, which combines the metabolic imaging function of PET with the excellent soft-tissue contrast of MRI, can provide more clinically relevant information than PET/CT [9]. It has a great effect on the precise delineation of the target volume in radiotherapy planning. To our knowledge, there is no report on the target volume delineation of PET/MRI in liver cancer radiotherapy planning. As a consequence, we put forward the hypothesis that PET/MRI could improve delineating precision in this situation. The aim of the study was to evaluate the feasibility of contouring GTV by PET/MRI and to assess differences and correlations in GTV delineation from PET/MRI vs. MRI in liver cancer.

Methods

Patients

All of the patients we recruited were over 18 years old. Patients with a creatinine clearance rate < 60 ml/min, anaphylactic reaction upon receiving intravenous contrast medium or ^{18}F-FDG, claustrophobia, metal device implantation or an inability to cooperate were excluded. In the end, 2 patients with liver cancer were enrolled and underwent PET/MRI scans prior to treatment between June 2019 and January 2020. This study was carried out in accordance with the recommendations of the local ethics committee of our hospital. Informed consent Written informed consent was obtained from all participants.

PET/MR image acquisition

The hybrid PET/MR images were acquired from a 3D PET/MRI scanner. All patients received an intravenous injection of ^{18}F-FDG (0.8-1.0 mCi/kg) 50-60 min before PET image acquisition. In addition, a six-hour fast and bladder emptying were required prior to PET scanning. During the process

of reconstruction, the PET component of the system adopts TOF technology to display the image, which can reduce noise and provide higher sensitivity, thus increasing the image quality. The magnetic field strength of the MR magnet is 3 T, which can provide a high resolution of soft tissue.

The PET image was reconstructed by the ordered subsets expectation maximization (OSEM) algorithm (including 2 iterations, 20 subsets, 4 mm full width at half maximum (FWHM) Gaussian filter, and a 150x150 image matrix).

The diagnostic MRI scanning included T1-weighted high-resolution isotropic volume acquisition and T2-weighted (T2W) 3D volume fast spin echo (FSE), both in the axial, sagittal orientation and coronal orientations. Ax T1 sequence parameters: repetition time (TR)/echo time (TE)=5.04/2.24 ms,4 mm slice thickness, 20% interslice gap, 350 mm×350 mm field of view (FOV), and a 256×256 matrix. Ax FSE T2 sequence parameters: TR/TE=3998/88.74 ms, 6 mm slice thickness, 20% interslice gap, 300 mm×300 mm FOV, and a 320×320 matrix.

Tumor volume delineation

All diagnostic MRI and PET images were confirmed by 2 radiation oncologists—a radiologist of radiology and a radiologist of nuclear medicine, both of whom were board-certified and experienced in their disciplines. Three experienced radiation oncologists (A, B and C) performed the tumor delineations independently; lymph nodes were not delineated in our work. Thus, three GTVs (GTV-MRI, GTV-PET and GTV-PET/MRI) were defined by each of the three observers for each patient.

The GTV-MRI was manually contoured by radiation oncologists on axial T2-weighted MRI, with agreement by radiologists of radiology. On the basis of the patients' clinical history and related imaging examination (including MRI, CT and ultrasound), we considered that changes in mass, nodule, and effusion were abnormal and indicative of lesions. The images and reports of the MRI were blinded.

Until now, manual delineation of ^{18}F-FDG PET-positive tissues has been the gold standard, despite poor reproducibility [10]. After the radiation oncologists reviewed the PET images and the hybrid PET/MRI images with the radiologist, PET-GTV and GTV-PET/MRI were contoured. The uptake of ^{18}F-FDG significantly exceeded the normal surrounding tissue background, which we considered metabolic abnormalities and indications of lesions.

Analysis

GTVs obtained by MRI, PET and hybrid PET/MRI were compared. The average and median were calculated for obtained results. In addition, spatial analysis within GTV-MRI, GTV-PET and GTV-PET/MRI was performed. The Dice similarity coefficient (DSC) was calculated using the equation: $2 \times (A \cap B)/(A + B)$, where A and B represent two volumes, $(A \cap B)$ represents the volume of the intersection, and $(A + B)$ represents the absolute sum of their volumes [11].

All statistical analyses were carried out using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). The results of all quantitative data are expressed as the mean (SD). Pearson analysis was used to calculate the correlation between GTV-MRI and GTV-PET, GTV-MRI and GTV-PET/MRI. A nonparametric paired-sample Wilcoxon signed-rank test was used to compare GTVs volumes based on MRI vs. PET and MRI vs. PET/MRI.

A result was considered statistically significant if the determined p value was less than 0.05 ($p<0.05$).

Results

In our study, a total of twelve patients (eighteen lesions) were included; lymph nodes were not evaluated. Of the twelve enrolled patients, three had primary liver cancer, nine had metastatic liver cancer, two were female and ten were male. The median age of the patients was 61 years (range 37–85). The patient characteristics are displayed in Table 1.

Table 1
Patients characteristics and Volume results for each 18 lesion and every patient

Patient number	Age	Sex	Cancer type	Primary cancer	Lesion number	GTV-MRI (cm^3)	GTV-PET (cm^3)	GTV-PET/MRI (cm^3)
1	50	F	Metastatic	Colon cancer	1	167.97	14.00	158.27
2	53	F	Metastatic	Rectal cancer	1	2.93	5	4.5
3	59	M	Metastatic	Rectal cancer	1	7.67	7.67	9.27
					2	32.33	37.47	35.03
4	63	M	Metastatic	Rectal cancer	1	6.47	4.63	7.27
					2	1.93	0.63	2.6
5	73	M	Primary		1	61.43	85.7	73.5
6	65	M	Metastatic	Colon cancer	1	259.17	281.23	283.03
					2	28.2	35.03	34.83
7	53	M	Metastatic	Colon cancer	1	7.45	9.1	7.95
					2	6.5	12.3	9.25
					3	15.45	23.55	21.7
8	76	M	Metastatic	Lung cancer	1	14.35	14.3	12.75
9	43	M	Metastatic	Rectal cancer	1	0.7	0.55	0.75
					2	1.6	2.45	3.3
10	85	M	Primary		1	7.1	1.95	7.45
11	72	M	Primary		1	7.8	7.67	8.67
12	37	M	Metastatic	Rectal cancer	1	3.27	0.47	1.83

The tumor volume measurements for all patients obtained from MRI, PET and hybrid PET/MRI images are shown in Table 1. The MRI-based mean GTV for all patients was 35.13(68.41) cm^3. The PET-based mean (SD) GTV was 37.65 (71.38) cm^3. The hybrid PET/MRI-based mean (SD) GTV was 37.89 (72.05) cm^3. Most GTV-PET/MRI (83%) and 50% of GTV-PET were larger than the reference GTV-MRI. Statistical analysis showed that GTV-PET/MRI ($p = 0.021$) diverged statistically significantly from the referenced GTV-MRI results. On the other hand, there was no statistically significant difference between GTV-PET ($p = 0.266$) and GTV-MRI. GTV-PET ($r = 0.991$, $p < 0.001$) and GTV-PET/MRI ($r = 0.997$, $p < 0.001$) were significantly related to reference GTV-MRI.

The average value of DSC between GTV-MRI and GTV-PET was 0.45 (range 0–0.90) and between GTV-MRI and GTV-PET/MRI was 0.76 (range 0.43–0.90). The results of the volumetric comparison among GTV-MRI, GTV-PET and GTV-PET/MRI are displayed in Table 2.

Table 2
Volumetric comparison among GTV-MRI, GTV-PET and GTV-PET/MRI

Lesion number	GTV-MRI &GTV-PET			GTV-MRI &GTV-PET/MRI			GTV-PET &GTV-PET/MRI		
	Intersection(cm^3)	Sum(cm^3)	DSC	Intersection(cm^3)	Sum(cm^3)	DSC	Intersection(cm^3)	Sum(cm^3)	DSC
1	130.7	315.97	0.83	140.23	326.23	0.86	140.23	326.23	0.91
2	2.07	7.93	0.52	2.53	7.43	0.68	2.53	7.43	0.74
3	3.27	15.33	0.43	5.67	16.93	0.67	5.67	16.93	0.68
4	22.87	69.8	0.66	26.43	67.37	0.78	26.43	67.367	0.77
5	1.83	11.1	0.33	4.7	13.73	0.68	4.7	13.73	0.62
6	0.1	2.57	0.078	1.4	4.53	0.62	1.4	4.53	0.27
7	57.67	147.13	0.78	56.17	134.93	0.83	56.17	134.93	0.84
8	242	540.4	0.9	243.93	542.2	0.90	243.93	542.2	0.96
9	23.37	63.23	0.74	25.6	63.03	0.81	25.6	63.03	0.86
10	2.65	16.55	0.32	6.85	15.4	0.89	6.85	15.4	0.38
11	3.05	18.8	0.32	6.35	15.75	0.81	6.35	15.75	0.39
12	7.9	39	0.41	15.4	37.15	0.83	15.4	37.15	0.50
13	7.25	28.65	0.51	10.25	27.1	0.76	10.25	27.1	0.59
14	0	1.25	0	1.05	1.45	1.45	1.05	1.45	0.08
15	0.05	4.05	0.025	1.05	4.9	0.43	1.05	4.9	0
16	1.7	9.05	0.38	6.25	14.55	0.86	6.25	14.55	0.41
17	5.7	15.47	0.74	6.47	16.47	0.79	6.47	16.47	0.87
18	0.37	3.733	0.2	1.47	5.1	0.58	1.47	5.1	0.41
Mean			0.45			0.79			0.57

Discussion

The traditional method divides malignant tumors into local or locally advanced diseases and metastatic diseases. The former is suitable for local treatment and possibly curable while the latter is appropriate for the combined management of systemic and local treatment [12]. Primary liver cancer has one of the highest incidences of malignancies and is the third leading cause of death worldwide [13]. Since the liver receives a dual blood supply from the hepatic artery and portal vein, its blood flow is abnormally rich, making it a likely site for the growth of metastatic tumors. In addition to regional lymph node metastases, the liver is the second most prone to metastatic disease, often from primary colorectal, breast, lung, kidney, and skin cancers (melanoma) [14]. Malignant tumors in any part of the human body can metastasize to the liver through the portal vein, hepatic artery and lymphatic pathway, or they can directly invade the liver. There were nine patients with metastatic liver cancer, most of whom had metastases from colorectal cancer, only one from lung cancer, and three with primary liver cancer in our study. For patients with inoperable primary liver cancer or metastatic liver cancer, radiotherapy, especially SBRT, has emerged as an effective, noninvasive alternative therapy [12]. The current NCCN guidelines for colon and rectal cancer support aggressive local treatment of metastatic sites.

At present, there is no consensus on the role of PET/MRI in delineating the target area in tumors, though various methods have been proposed and used to determine the contouring of ^{18}F-FDG-positive tissue, which has led clinician to reach different conclusions when using these methods. The visual contour method we chose with lower technical requirements is highly dependent on the observer. Therefore, three doctors with the qualification of attending physician or above were employed to identify the image, define the target area, and delineate the target volume. The average value was used as the final data. We assessed the differences and similarities between target volumes delineated on MRI, PET, and PET/MRI. Our results showed that GTV-PET/MRI was larger than GTV-MRI and GTV-PET, and GTV-PET/MRI ($p = 0.021$) diverged statistically significantly from the referenced GTV-MRI. The reason may be that hybrid PET/MRI integrates the anatomical-, functional-, and molecular-level information of biological tissues, which can provide more clinical correlative information and higher accuracy. A larger GTV may avoid situation in which some lesions are not contoured in the target area and, therefore, are not irradiated, which may affect the efficacy of treatment. The radiotherapy effects of target profiling based on PET/MRI are unknown. However, considering the statistically significant difference in the target volume, we have reason to suspect that this method has an impact on the therapeutic effect, which is of major importance for patients. All these findings inspire us to conduct some prospective research on the implementation of radiotherapy planning in the future studies.

Studies of other tumor locations (e.g., esophagus, lung, pancreas, head and neck) have shown that the additional biological information of PET has an effect on the variation in the GTV during radiation therapy, can reduce the risk of positioning error and influence the normal tissue dose-volume histogram and the calculation of probability values in corresponding normal tissue [15, 16, 17]. Ma, J. T. et al. [18] showed that GTV contouring based on hybrid PET/MRI for head and neck cancers is feasible and may provide improved accuracy. In their study, GTV_{VIS} and GTV_{FUS} were larger than GTV_{MRI} with the use of hybrid PET/MRI images, which was similar to our findings, but tumor site determinations were different. While Wang, K. et al. [11] demonstrated that hybrid PET/MRI- and CT-generated GTVs were similar overall and supplied similar radiation doses to the head and neck. Zhang, Shaomin. et al. [19] reported that there were tumor volume discrepancies between GTV-MRI and GTV-PET for cervical cancer. With the increase in tumor volume, the difference between GTV-MRI and GTV-PET increased. Samolyk-Kogaczewska, N. et al. [20] pointed out that the primary tumor volumes with manual delineation methods from MRI, PET and CT differed slightly from each other, but the differences were statistically irrelevant. Similarly, in our study, GTV-PET ($p = 0.266$) was not statistically significant different from GTV-MRI. We consider that this may be related to the imaging limitations of ^{18}F-FDG PET in liver cancer. Unlike in lung cancer patients, ^{18}F-FDG PET has already been established to play a role in the application of target volume contouring [21]. In addition, the artifacts caused by tumor location, anatomical boundaries, clinical situations, and patient cooperation during examination have a great impact on the quality of the contouring [22, 23].

^{18}F-FDG, a marker of glycolysis in cells, has a short half-life, high imaging spatial resolution, and excellent nuclear and chemical features [24], which make it the most widely used radioactive tracer for PET. After ^{18}F-FDG is transported across the cell membrane by glucose transporters (GLUTs), it is subsequently phosphorylated by hexokinase subsequently, which is the same as what occurs during glucose metabolism. As cancer cells exhibit high glycolysis rates, the uptake of ^{18}F-FDG in cancer tissues is increased [25]. Thus, ^{18}F-FDG reflects the glucose metabolism of tumor tissue, and has demonstrated enhanced value in the diagnosis, staging, appraisal of prognosis and efficacy evaluation of malignant diseases [26].

In moderately and well-differentiated hepatocellular carcinoma (HCC), studies have confirmed that high FDG-6-phosphatase activity, high expression of p-glycoprotein, and low expression of GLUT1 or GLUT2 lead to low uptake of ^{18}F-FDG[6]. High levels of FDG-6-phosphatase hydrolyze intracellular FDG-6-phosphate into FDG, which is then transported outside the cells. P-glycoprotein acts as an efflux, and its high expression of it also transports more FDG out of the cells. GLUT1, GLUT3, and GLUT12 are involved in the transport of ^{18}F-FDG into cancer cells [6], and their low expression reduces the uptake of FDG. All these factors contribute to a lower accumulation of FDG in HCC.

In cholangiocellular carcinoma (CCC) tumor cells, glucose uptake and metabolic mechanisms are different from those in HCC, although both are glucose energy sources. The low glucose-6-phosphatase (close to zero) and significantly higher expression of GLUT1 than that in normal liver tissues were related to ^{18}F-FDG metabolic concentration foci in CCC [27, 28].

In liver metastatic tumor cells, due to the low level of dephosphorylation in cancer cells, the metabolism of ^{18}F-FDG in liver metastases was significantly higher than that in surrounding normal liver cells, and the sensitivity of PET scanning for metastases was higher [29]. The pathological types of liver cancer we included varied, and these may be factors affecting the results.

The range of DSC is 0–1. The value is 0 when there is no spatial overlap between imaging methodologies, while it is 1 when they completely overlap. Higher the DSC values indicate better coincidence degrees. Some scholars have noted that a DSC value ≥ 0.7 indicates a better degree of overlap [30], suggesting that DSC may be highly correlated with the change in volume but less correlated with the change in target shape. Our results show that the DICE index between GTV-MRI and GTV-PET/MRI—0.76—is higher, and the average DSC values were above 0.7. The the DSC value between GTV-PET and GTV-MRI was 0.45, lower than 0.7, which may be related to the low spatial resolution of PET data.

Future studies on tumor volume delineation based on PET/MRI may benefit from more advanced technology such as MR-linac, novel radioactive tracers and 4D-PET. For example, studies are ongoing to investigate the impact of MR-linac on liver SBRT planning [31, 32, 33]. On conventional linacs, based on X-ray-based image guidance, liver lesions are often poor or invisible in this pattern of images; thus, the injection of contrast material, or the implantation of markers is needed address this issue. An advanced treatment device, the Unity MR-linac, with the excellent soft-tissue contrast offered by the integrated MRI, may lead to margin reductions, better organ-at risk (OAR) sparing or dose escalation, and it can enable the use of liver SBRT without invasive fiducial markers.

Moreover, with the deepening of research, recent PET tracers such as 11C-acetate and ^{11}C/^{18}F-choline have attracted much attention from researchers in recent years. As a metabolic precursor of phospholipid synthesis, both of them have been used as a supplement to ^{18}F-FDG PET imaging of well-differentiated HCC with improved values of sensitivity and specificity compared with those of other tracers[34, 35, 36].

Furthermore, during the process of PET/MRI image acquisition, images will be affected by motion artifacts due to breath-hold, which may lead to the underestimation of lesion uptake and to the possibility of missing small lesions [38]. During normal respiratory movement, organs can undergo displacements of up to 2 cm [18, 19], and the liver is particularly vulnerable to respiratory motion. Considering that liver SBRT is a very precise treatment technique in regard to the tissue exposed to radiation toxicity, any procedure designed to make radiotherapy planning more precise is of particular interest. Respiratory-gated PET (4D–PET) has been proposed as one of the approaches to address these issues [38]. Compared with non-gated PET, respiratory-gated PET can improve the image quality and lesion detectability of liver targets and assess the target volumes with

increased accuracy [39]. More appropriate irradiation of the liver volume may improve the safety and effectiveness of SBRT. Therefore, it will become a valuable tool to improve SBRT planning for liver cancer in the future.

This study had a certain limitation. We included a relatively small number of patients. For a more specific and accurate investigation of the advantages of PET/MR, a larger sample size is required.

Taking into consideration our experience in liver cancer and studies of other cancers, we believe that delineation based on hybrid PET/MRI for liver cancer radiation therapy is worth considering. Further prospective studies in this and other settings are needed to assess the optimal use of PET/MRI for target volume contouring.

Conclusions

Target volume delineation based on hybrid PET/MRI requires establishing a clear methodology. In our study, hybrid PET/MRI-based target volume delineation of the liver cancer was practicable. In addition, we found that GTV-PET/MRI was larger than GTV-MRI and GTV-PET, which may allow adequate irradiation to the diseased tissue and better treatment effect. In the future, the role of PET/MRI in radiation therapy cannot be underestimated, and its combination of biological and functional information provides an unprecedented opportunity for the development of radiotherapy towards more precise and personalized treatment planning.

Abbreviations

^{18}F-FDG: ^{18}F-fluorodeoxyglucose

PET/MRI: positron emission tomography/magnetic resonance imaging

GTV: gross tumor volume

DSC: Dice similarity coefficient

SBRT: Stereotactic body radiation therapy

CT: computed tomography

OSEM: ordered subsets expectation maximization

FWHM: full width at half maximum

T2W: T2-weighted

FSE: fast spin echo

TR: repetition time

TE: echo time

FOV: field of view

GLUTs: glucose transporters

HCC: hepatocellular carcinoma

CCC: cholangiocellular carcinoma

OAR: organ-at risk

Declarations

Ethics approval and consent to participate

The study protocol was approved by the institutional review board of Shanghai East Hospital. Informed consent Written informed consent was obtained from all participants.

Consent for publication

Not Applicable.

Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Competing interests

The authors declare that there is no conflict of interest regarding the publication of this article.

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Authors' contributions

YZ: Study design, data collection, data analysis, manuscript preparation and editing. XL: Contouring, Study design, calculated the GTVs, image analysis, manuscript editing. ZY: Contouring, Study design, data analysis, manuscript editing. LF: Contouring, manuscript editing. JZ: Image analysis, data collection. ZX: Study design, image analysis, data analysis, manuscript preparation and editing. All authors read and approved the final manuscript.

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