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Prognostic value of post-Yttrium 90 radioembolization therapy 18F-fluorodeoxyglucose positron emission tomography in patients with liver tumors

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ABSTRACT

Objective: This study assessed the benefit of post-therapy ^{18}F-FDG PET/CT versus CT alone in identifying malignant liver tumor progression following radioembolization with Y-90 microspheres.
Methods: 24 patients with 44 liver tumors underwent CT imaging pre-radioembolization and PET/CT post-radioembolization. Predictive value of Response Evaluation Criteria in Solid Tumors (RECIST 1.1), The World Health Organization (WHO), mRECIST and European Association for the Study of the Liver (EASL) with PET/CT versus CT alone was assessed.
Results: Prediction of liver malignancy progression was improved ($p < 0.05$) for tumors labeled as non-responding based on combined PET/CT with RECIST 1.1, WHO, mRECIST, and EASL criteria compared to assessment without PET.
Conclusions: The addition of post-therapy PET to routine CT in patients with hepatic tumors undergoing radioembolization may improve identification of non-responding tumors.

1. Introduction

Selective internal radiation therapy (SIRT) with Yttrium-90 (Y-90) microspheres is an increasingly employed treatment for patients with hepatocellular carcinoma and metastatic disease to the liver of several primary sources [1–3]. Glass or resin microspheres bound with Y-90 are injected into the hepatic arteries, which preferentially supply the liver malignancies, sparing the normal hepatic parenchyma supplied primarily by the portal venous circulation. As a result, the Y-90 microspheres are administered preferentially to malignant cells in the liver and deliver a lethal dose via beta decay [2,4,5]. More than half of patients who undergo Y-90 radioembolization of metastatic tumors from colorectal cancer subsequently receive additional therapy [6]. Therefore, it is important to promptly recognize non-responders to Y-90 radioembolization and identify candidates for further systemic therapy or additional radioembolization.

While ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) has gained wide clinical acceptance for staging, restaging, and identifying recurrence of many different malignancies, its utility for assessment of therapy response continues to be debated [7–13]. Therapy response protocols which were developed by the pharmaceutical industry as a surrogate outcome measure for overall survival to assess tumor response to cytotoxic chemotherapy drugs during clinical trials have relied primarily upon morphologic assessment of malignancy with CT, initially according to the World Health Organization (WHO) criteria and later the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) or enhancement pattern using modified RECIST (mRECIST) and the European Association for the Study of the Liver (EASL) guidelines [14–17]. Many studies have suggested that the functional assessment provided by ^{18}F-FDG PET may represent an opportunity for improvement in evaluation of therapy response for current cancer therapeutic regimens [10,12,13]. Functional data may be useful for evaluation of cytostatic treatment approaches and locoregional therapies, which may not be adequately evaluated through serial morphologic assessments [17–19].

Recent studies have indicated that consecutive ^{18}F-FDG PET imaging in patients with liver metastases before and after Y-90 radioembolization was more predictive of survival than assessment with CT imaging [20–22]. Since CT measurements of malignant liver masses are typically obtained before and after Y-90 microsphere administration, it may be

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clinically more helpful to evaluate the benefit of additional imaging with ^{18}F-FDG PET, combined with the already commonly available CT findings for prediction of outcomes. Due to the expense of consecutive ^{18}F-FDG PET imaging, obtaining a single post-therapy ^{18}F-FDG PET that can still provide the necessary prognostic information may be a more economically feasible alternative. The aim of this pilot study was to estimate the value of FDG PET/CT as an early biomarker for identifying malignant liver tumor progression following Y-90 radioembolization. Furthermore, the purpose of the study was to collect data required to design a prospective study to test the hypotheses about the benefit of including a single post-therapy 18F-FDG PET/CT to existing morphologic methods.

2. Materials and methods

2.1. Patients

A retrospective computer-based data search yielded names of 98 patients who underwent Y-90 radioembolization with SIR-Spheres® Y-90 resin microspheres (SIRTeX Medical, Lane Cove, Australia). The inclusion criteria for the study were [1] availability of ^{18}F-FDG PET performed within 2 months following Y-90 treatment; [2] abdomen CT images on PACS performed within 2 months prior to and following radioembolization; [3] availability of follow-up CT or MRI imaging and clinical data for evaluation of tumor progression. Patients with multiple malignancies were excluded. Pathologic diagnoses included metastatic disease to the liver from 11 colorectal, 3 non-small cell lung, 3 pancreatic carcinomas, 1 carcinoid, 1 cholangiocarcinoma, 1 neuroendocrine tumor as well as 4 hepatocellular carcinomas. This HIPAA compliant study was approved by the institutional review board. All patients undergoing imaging and radioembolization at our institution signed informed consent documents.

2.2. Pulmonary shunt estimation and Y-90 radioembolization

Calculation of lung shunting was performed according to standard operating procedure. The prescribed Y-90 resin microsphere activity was determined using the body surface area (BSA) equation. $A_{resin} = (BSA - 0.2) + (TV/(TV + LV)$ where A_{resin} is the activity of Y-90 prescribed, TV is the tumor volume, and LV is the volume of liver within the treated territory. Celiac trunk was accessed via femoral artery. Hypervascular target masses were identified in the liver and SIR-sphere dose was delivered with intermittent fluoroscopic observation.

2.3. CT and PET imaging protocols

Pre-therapy and post-therapy abdominal CT imaging was performed on several CT scanners, including GE Medical Discovery HD 64 slice scanner (Milwaukee, Wisconsin) CT (350–700 mAs, 120 kV) with 0.635 mm slices and 3 mm reconstructions using iterative reconstruction algorithm. Exams were performed with intravenous contrast in all patients except those with impaired renal function. Images were transferred to picture archiving and communication system IMPAX (Agfa-Gevaert Group, Mortsel, Belgium).

All patients fasted for at least 6 h before the intravenous administration of a mean dose of 550 ± 165 MBq (14.9 ± 4.46 mCi) of ^{18}F-FDG for PET/CT imaging. Serum glucose levels averaged 101 ± 11 m/dl at the time of radiotracer injection. The standard PET/CT clinical imaging protocol started 60 min after radiopharmaceutical injection. Post-injection syringe activities and patient weights were measured for more accurate calculations of the SUVs. PET/CT imaging was carried out using a Discovery ^{18}F-FDG PET/CT VCT scanner (General Electric Medical Systems, Waukesha, WI). Attenuation correction was performed using a low-dose CT protocol (30–100 mAs, 140 kV) followed by a static 3D ^{18}F-FDG PET/CT imaging covering the upper torso from the skull to mid-thighs (2–3 min emission scan/position), started approximately 60 min after injection. Transaxial, coronal, and sagittal images were corrected for dead-time, decay and photon attenuation, and reconstructed in a 128 × 128 matrix. The images were reconstructed using two iterations and 20 subsets with a 6.0 mm full-width half-maximum post-filter and a fully 3D maximum likelihood ordered subset expectation maximization reconstruction algorithm. PET imaging was performed with an HR+ system (CTI/Siemens; Knoxville, Tennessee). Emission scans were acquired for 6–8 min per bed position (adjusted by patient weight for total emission time encompassing approximately 70% acquisition time) from mid-thigh to above the skull in the two-dimensional mode. Transmission scans were obtained for 2–4 min per bed position (adjusted by patient weight for total transmission time encompassing approximately 30% acquisition time) interweaved with the emission scans. Attenuation-corrected images were obtained by applying the transmission maps and the images were reconstructed using the ordered subsets expectation maximization (OSEM) iterative reconstruction algorithm.

2.4. CT and PET image analysis

Pre-therapy and post-therapy CT images of the abdomen were reviewed by two observers (nine and three years of experience). Up to two target liver tumors (one tumor per liver lobe) were identified per patient. Measurements of liver tumors were performed on CT images according to the RECIST 1.1, WHO, mRECIST and EASL criteria [14–17]. Evaluation using RECIST 1.1 consisted of single largest tumor diameter measurement on axial images. WHO assessment involved measurement of two perpendicular tumor diameters and obtaining the product of these measurements. Application of mRECIST and EASL consisted of evaluation of only contrast enhancing tumor tissue, measured in a single diameter (mRECIST) or two perpendicular diameters (EASL) and obtaining the product of the two diameters. Changes (%) between pre-therapy and post-therapy measurements were calculated and liver tumors were labeled as CR (complete response), PR (partial response), SD (stable disease) and PD (progressive disease) according to RECIST, WHO, mRECIST and EASL [15]. In cases of disagreement between observers, results were discussed until agreement was reached.

Post-therapy PET scans were co-registered with pre-therapy CT scans for exact localization of the liver tumors. Metabolic response to therapy was assessed using a semi-quantitative approach. Regions of interest (ROIs) were drawn over tumors identified on axial PET images of the post-therapy scans and SUVmax (maximal standardized uptake values) normalized for body weight were measured for each liver tumor.

2.5. Tumor response follow-up

Unfavorable outcomes indicating tumor progression were established based on increase in tumor size on follow-up cross-sectional imaging. Patients were monitored at regular intervals with clinical examinations as well as CT or MRI following treatment. Tumor progression was defined as an increase in the longest tumor diameter of at least 20%. The date of progression was defined as the earliest date following a post therapy PET/CT at which tumor progression was detected by cross-sectional imaging. Tumors that did not progress were censored at the date of the last documented encounter.

2.6. Statistical analysis

Agreement between RECIST 1.1 and mRECIST as well as WHO and EASL was calculated using Cohen's Kappa statistic (NCSS and PASS, Number Cruncher Statistical Systems, Kaysville, Utah). Kaplan Meier method was utilized and cumulative hazard functions were generated to evaluate the predictive value of RECIST 1.1, WHO, mRECIST and EASL with and without the inclusion of PET SUVs, as well as PET SUV alone, for assessment of tumor progression. Optimal PET SUV thresholds were established for prediction of outcomes based on minimal