CLINICAL STUDY

Anatomic versus Metabolic Tumor Response Assessment after Radioembolization Treatment

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ABSTRACT

Purpose: To assess applicability of metabolic tumor response assessment on ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/computed tomography (CT) after radioembolization (RE) in patients with colorectal liver metastases (CRLM) by comparison with one-dimensional size-based response assessment on MR imaging.

Materials and Methods: This prospective cohort study comprised 38 patients with CRLM undergoing RE. MR imaging and ^{18}F-FDG PET/CT imaging were performed at baseline, 1 month (n = 38), and 3 months (n = 21). Longest tumor diameter (LTD) reduction on MR imaging at these time points was compared with reduction in total lesion glycolysis (TLG) on ^{18}F-FDG PET/CT. Hepatic response was compared between RECIST and total liver TLG and correlated with overall survival (OS).

Results: TLG and LTD were positively correlated in 106 analyzed metastases (38 patients) at 1 month and 58 metastases (22 patients) at 3 months. Agreement was poor, with LTD underestimating TLG response. A significant association with prolonged OS was found in total liver TLG at 1 month (HR 0.64, $P < .01$) and 3 months (HR 0.43, $P < .01$). For LTD, a significant association with OS was found at 3 months (HR 0.10, $P < .01$). Important differences in liver response classification were found, with total liver TLG identifying more patients and situations where there appeared to be treatment benefit compared with RECIST.

Conclusions: TLG response assessment on ^{18}F-FDG PET/CT appears to be more sensitive and accurate, especially at early follow-up, than size-based response assessment on MR imaging in patients with CRLM treated by RE. Semiautomated liver response assessment with total liver TLG is objective, reproducible, rapid, and prognostic.

ABBREVIATIONS

CI = confidence interval, CRLM = colorectal cancer liver metastases, ^{18}F-FDG = ^{18}F-fluorodeoxyglucose, HR = hazard ratio, LTD = longest tumor diameter, NTL = nontarget lesion, OS = overall survival, PET = positron emission tomography, RE = radioembolization, RECIST = Response Evaluation Criteria in Solid Tumors, SUV = standardized uptake value, TL = target lesion, TLG = total lesion glycolysis, ^{90}Y = yttrium-90

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Figures E1 and E2 and Appendix A are available online at www.jvir.org.

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Adequate tumor response assessment after treatment is essential to enable timely intervention in patients with cancer who show progression of disease. The Response Evaluation Criteria in Solid Tumors (RECIST) system has been widely adopted and currently serves as the standard assessment method. This method is based on changes in one-dimensional tumor diameter on cross-sectional imaging and patient prognosis and has been used in cytotoxic drug studies (1–3). However, it is questionable whether RECIST is applicable for other therapies, as treatment response may not primarily be characterized by tumor shrinkage. Therefore, other response criteria systems have been developed, such as the European Association for the Study of the Liver criteria and modified RECIST for intra-arterial therapy in hepatocellular carcinoma (4,5), the Choi criteria for the treatment of gastrointestinal stromal tumors (6), and the immune-related Response Criteria and immune-related RECIST for immunotherapy (7,8).

As radioembolization (RE) is now increasingly applied in unresectable chemorefractory, colorectal cancer liver metastases (CRLM), it is important to critically reflect on the applicability of the current use of RECIST in this setting as well. Using RECIST might introduce subjectivity by selecting only 2 lesions, disregarding both size and consistency of lesions, and, most importantly, disregarding tumor cell activity (8,9). Using alternative response criteria systems based on tumor vascularization is not a suitable option owing to the relatively hypovascular nature of CRLM. Metabolic tumor response on ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/computed tomography (CT) might offer a solution. Several standardized uptake value (SUV)–based parameters derived from ^{18}F-FDG PET have previously been validated for prediction of survival, but these do not take the lesion volume into account (10). Total lesion glycolysis (TLG)—the product of the mean SUV and metabolic volume of a tumor—reflects the metabolic activity of a tumor and can be automated. This allows for an unbiased, fast, and reproducible comparison between baseline and follow-up scans, while taking all lesions into account. Hence, the purpose of this prospective study was to assess the applicability of metabolic tumor response assessment on ^{18}F-FDG PET/CT after RE in patients with CRLM by comparison with one-dimensional size-based response assessment on magnetic resonance (MR) imaging.

MATERIALS AND METHODS

For detailed information on image acquisition and response assessments, see **Appendix A** (available online at *www.jvir.org*) (11–14).

Patient Selection and Study Design

The medical ethics committee approved this study, and informed consent was obtained from all patients before study inclusion. All study procedures were performed in accordance with the Declaration of Helsinki. Between November 2011 and August 2014, 42 patients with CRLM underwent RE with resin yttrium-90 (^{90}Y) microspheres in a prospective single-arm cohort study. Patients with unresectable, chemorefractory, liver-dominant metastases had to meet eligibility criteria for RE. None of the patients received chemotherapy within 4 weeks before the baseline scan of the study. Chemorefractory is defined as lack of response or toxicity to oxaliplatin-based and/or irinotecan-based therapy with or without cetuximab/panitumumab (based on *KRAS* status). RE workup and treatment were performed in accordance with current standards of practice (15). All patients underwent MR imaging of the liver and ^{18}F-FDG PET/CT at baseline and during follow-up. Imaging after treatment was acquired at 1 month and at 3 months (unless progressive disease [RECIST criteria] was noted at 1 month). Patients were allowed to participate in other clinical studies after the 3-month follow-up point. Only patients with in-house liver MR imaging and ^{18}F-FDG PET/CT, obtained per protocol, at baseline and follow-up, were included because mean SUVs are not interchangeable.

Patient Demographics

Between November 2011 and August 2014, 42 patients were treated with resin ^{90}Y microspheres. Four patients were excluded owing to inability to administer ^{18}F-FDG (n = 1), baseline ^{18}F-FDG PET/CT performed at a different center (n = 1), and no MR imaging (n = 1) or ^{18}F-FDG PET/CT (n = 1) at 1-month follow-up. Complete baseline and treatment characteristics for the remaining 38 patients are summarized in **Tables 1** and **2**, and outcome flow charts are shown in **Figure 1a** and **b**.

Image Acquisition

Dynamic contrast-enhanced images were acquired with MR imaging scans of the liver on a 1.5T scanner (Philips Healthcare, Best, The Netherlands), using a SENSE body coil (Philips Healthcare) (11). A time-of-flight PET/CT scanner with TrueV capacity (Biograph 40 mCT; Siemens Healthcare, Erlangen, Germany) was used for PET imaging. All patients were required to fast for at least 6 hours before image acquisition. Subsequently, 2.0 MBq/kg of ^{18}F-FDG was injected intravenously (12). **Appendix A** (available online at *www.jvir.org*) provides a comprehensive description of the protocols and settings (11–14).

Response Assessments

A comprehensive description of response assessment is provided in **Appendix A** (available online at *www.jvir.org*) (11–14). Briefly, anatomic and metabolic tumor response assessments were performed independently by 2 different raters (M.N.G.J.A.B., A.F.v.d.H.). Anatomic tumor response was assessed per RECIST 1.1 on liver MR imaging (3).