Original Investigations

Tumor Growth Kinetics Versus RECIST to Assess Response to Locoregional Therapy in Breast Cancer Liver Metastases

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Rationale and Objectives: The aim of our study was to evaluate changes in growth kinetics of breast cancer liver metastasis in response to locoregional therapy and compare them to Response Evaluation Criteria in Solid Tumors (RECIST).

Materials and Methods: This Health Insurance Portability and Accountability Act–compliant retrospective study was Institutional Review Board approved. Thirty-four chemorefractory breast cancer liver metastases from 21 patients treated with yttrium-90 (^{90}Y) were evaluated. Pre- and posttreatment computed tomography (CT) scans were used to calculate tumor growth kinetics. The growth parameter analyzed was reciprocal of doubling time (RDT). RDT range for stable disease (SD) was defined by the measurement error rate. A negative RDT below the SD range defined response and was categorized as either partial response (PR) or complete response, whereas a positive RDT value above the SD range indicated progressive disease (PD). Comparison was made to tumor response classification according to percentage change in the lesion's maximal diameter per RECIST. Lin's concordance correlation coefficient, Bland–Altman plot, Wilcoxon signed rank test, and Student *t* test were used for analysis. Significance was set at 0.05.

Results: RDT range for SD ranged from −0.46 to +2.17. Six lesions with PR based on RECIST showed PR based on their volumetric growth rate (mean RDT of -17.3 ± 2.6). Similarly, one lesion with PD according to RECIST was categorized as PD based on its growth kinetics (RDT of 10.2). However, 14 (51.85%) lesions classified as SD by RECIST had PR according to growth kinetics (mean RDT of −7.8), six (22.22%) lesions were categorized as SD (mean RDT of 0.8), whereas seven (25.93%) lesions showed PD (mean RDT of 4.5). Growth kinetic parameters were significantly different for lesions with PR when compared to lesions with PD ($P < .0001$).

Conclusions: In patients with breast cancer liver metastases undergoing locoregional therapy, RECIST categorization may not be an accurate reflection of treatment response.

Key Words: Breast neoplasm; computed tomography; liver metastasis; RECIST; Yttrium-90.

Metastatic breast cancer is not considered a curable disease at present and accounts for most deaths associated with breast cancer (1). About 40%–50% of all patients diagnosed with breast cancer will develop liver metastasis during the course of their illness (1–3), but rarely (5% of cases) liver-only metastatic involvement can be seen (4,5). Management of liver metastases from breast cancer relies heavily on systemic therapies (1,6). Locoregional treatments are also available as adjuncts including surgical resection of liver metastases (7), local ablation (8), chemoembolization, transarterial chemoembolization, transarterial radioembolization (TARE) (3,9), and stereotactic body radiotherapy (1). Surgical resection of liver metastasis is performed in carefully selected patients (9) and because only 10%–20% of patients (10) are surgical candidates, alternatives must be considered. TARE with yttrium-90 (^{90}Y) is an effective alternative and has been successfully used for treatment of liver metastases in patients with chemorefractory breast cancer. Median overall survival in patients with breast cancer liver metastases undergoing treatment with ^{90}Y was recently reported at 11.5 months (9). Because of relatively poorer prognosis and shorter survival in patients with breast cancer liver metastases, there is a need for effective early response assessment to locoregional therapies.

Currently, Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (11) is the commonly used treatment response evaluation tool in clinical cancer trials involving patients with metastatic breast cancer (12) but has several limitations. First,

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RECIST are based on an assumption that tumors are spherical and change proportionally in response to treatment; however, some studies have shown that tumors may have irregular shape and nonspherical morphologies rendering RECIST unreliable (13,14). Second, novel locoregional therapies may induce changes in certain morphologic characteristics (density, necrosis, tumor margins, and so forth) of the tumor with or without any appreciable change in its size (15). RECIST are unable to account for these changes preventing it from assessing response accurately in such scenarios. This has led to the development of certain tumor and therapy specific criteria, which provide better depiction of response (16,17). Third, RECIST guideline categorizes treatment response as stable disease (SD) despite up to 30% decrease or 20% increase in tumor size. Therefore, it will be impossible to accurately assess response to novel locoregional treatments, which may cause clinically significant changes in tumors without crossing the thresholds drawn by RECIST.

Volumetric analysis of lesions allows quantification of tumor growth rate from changes in three-dimensional (3D) volumes on pre- and posttreatment imaging (18,19). Therefore, using the true 3D volume, tumor growth kinetics and hence response to treatment can be determined before any appreciable change in the lesion's size. According to a recent study, tumor growth kinetics provided a more precise evaluation of treatment response in pancreatic adenocarcinoma when compared to RECIST 1.1 (20). Volumetric growth rate is also a measure of tumor aggressiveness, whereas such information cannot be extrapolated from RECIST. Little is known about changes in the growth rate of breast cancer liver metastases after treatment with ^{90}Y radioembolization and its correlation with conventional response assessment criteria (RECIST 1.1). The purpose of our study was to calculate growth kinetics of chemorefractory breast cancer liver metastases treated with ^{90}Y based on changes in tumor volume on multi-detector computed tomography (MDCT) and its correlation with treatment response classification according to RECIST 1.1.

METHODS AND MATERIALS

This study was Institutional Review Board approved and Health Insurance Portability and Accountability Act compliant. The requirement for patient informed consent was waived for this retrospective study.

Patient Cohort

Patient selection. The study population consisted of patients with unresectable chemorefractory breast cancer liver metastases treated with ^{90}Y radioembolization between November 2003 and March 2012. Patients were selected using our departmental electronic radiology report database using the keywords "breast cancer" and/or "liver metastases" and/or "radioembolization." A total of 37 consecutive patients with histologically proven breast cancer liver metastases treated with TARE were initially selected. Patients were excluded if pre- and/or posttreatment contrast-enhanced computed tomography (CT) scans were not available (seven patients), pretreatment or follow-up scan was done with magnetic resonance imaging (four patients), previous radioembolization had been performed at an outside facility (one patient), or if the lesions were confluent and not amenable to volumetric segmentation (four patients). Our final cohort comprised a total of 34 metastatic liver lesions in 21 patients. To avoid any effect from radioembolization of the contralateral lobe in patients with bilobar involvement, lesions in the first treated lobe were included in the study limiting the analysis to one lobe per patient.

TARE with ^{90}Y microspheres. ^{90}Y microspheres are 20–40 μm particles loaded with radioisotope that emit β-radiation and delivered via percutaneous transarterial approach (21). Patients were referred for treatment after evaluation by a multidisciplinary tumor board and deemed candidates for nonsurgical management secondary to multiplicity of liver lesions or comorbidities. The administration of ^{90}Y radioembolization depends on lesion distribution (unilobar or bilobar) and tumor response (chemorefractory and response to previous radioembolization sessions). The administration of ^{90}Y is done on a lobar basis and patients are followed for potential toxicities and response before treating the other lobe for bilobar disease. A selective unilobar infusion of ^{90}Y was performed to deliver a dose of 50 Gy of radiation per kilogram of tissue according to previously published dosimetry techniques (21,22).

MDCT Imaging Protocol

All contrast-enhanced MDCT scans were performed with a 16- or 64-slice MDCT scanner (Somatom Sensation 16 or 64; Siemens Healthcare, Erlangen, Germany) or a 4-slice scanner (Lightspeed QX/I; GE Healthcare, Waukesha WI). Nonionic contrast material (iohexol 350, Omnipaque; GE Healthcare or iopamidol 370, Isovue; Bracco, Plainsboro, NJ, USA) was injected intravenously at a rate of 3–5 mL/second for a total of 125 mL using a mechanical power injector (Stellant, Medrad). Unenhanced, late arterial (40 seconds after initiation of intravenous contrast injection) and portal venous phase (70 seconds after intravenous contrast injection) images were obtained. In all instances, slice thickness for the reconstructed images was $\leq$5 mm as recommended by RECIST guidelines (23). All lesions were evaluated in the portal venous phase images because of improved conspicuity.

Imaging Evaluation

Lesion selection. For patients with multiple hepatic metastatic lesions, a maximum of two well-defined lesions per treated lobe (as ^{90}Y is administered on a lobar basis) with the longest diameter greater than 1 cm on pretreatment MDCT were selected for evaluation according to RECIST 1.1 (11).

Tumor volumetry. MDCT images were transferred to an image processing workstation (Leonardo Workstation, syngo