CLINICAL STUDY

Association of PI3K Pathway Mutations with Early Positron-Emission Tomography/CT Imaging Response after Radioembolization for Breast Cancer Liver Metastases: Results of a Single-Center Retrospective Pilot Study

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ABSTRACT

Purpose: To describe imaging response and survival after radioembolization for metastatic breast cancer and to delineate genetic predictors of imaging responses and outcomes.

Materials and Methods: This retrospective study included 31 women (average age, 52 y) with liver metastasis from invasive ductal carcinoma who underwent resin and glass radioembolization (average cumulative dose, 2.0 GBq ± 1.8) between January 2011 and September 2017 after receiving ≥ 3 lines of chemotherapy. Twenty-four underwent genetic profiling with MSK-IMPACT or Sequenom; 26 had positron-emission tomography (PET)/CT imaging before and after treatment. Survival after the first radioembolization and 2–4-month PET/CT imaging response were assessed. Laboratory and imaging features were assessed to determine variables predictive of outcomes. Unpaired Student *t* tests and Fisher exact tests were used to compare responders and nonresponders categorized by changes in fluorodeoxyglucose avidity. Kaplan–Meier survival analysis was used to determine the impact of predictors on survival after radioembolization.

Results: Median survival after radioembolization was 11 months (range, 1–49 mo). Most patients (18 of 26; 69%) had complete or partial response based on changes in fluorodeoxyglucose avidity. Imaging response was associated with longer survival ($P = .005$). Whereas 100% of patients with PI3K pathway mutations showed an imaging response, only 45% of wild-type patients showed a response ($P = .01$). Median survival did not differ between PI3K pathway wild-type (10.9 mo) and mutant (undefined) patients ($P = .50$).

Conclusions: These preliminary data suggest that genomic profiling may predict which patients with metastatic breast cancer benefit most from radioembolization. PI3K pathway mutations are associated with improved imaging response, which is associated with longer survival.

ABBREVIATIONS

CI = confidence interval, ER = estrogen receptor, HR = hazard ratio, PET = positron-emission tomography, SUV_{max} = maximum standardized uptake value

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EDITORS' RESEARCH HIGHLIGHTS

- The authors continue stepwise work exploring genetic predictors of interventional oncologic interventions with assessments of imaging response and overall survival in breast cancer metastatic to the liver.
- Radioembolization was performed in 31 such women who had been treated with chemotherapy, 24 of whom underwent targeted tumor sequencing. Positron-emission tomography/computed tomography was performed as 2–4-month imaging follow-up, with added performance of laboratory- and imaging feature–based multivariate predictor analysis.
- Imaging response was positively associated with overall survival: patients with PI3K pathway mutations had significantly improved survival compared with those with its wild-type counterpart. Thus, the study provides a promising introduction to the potential utility of genomic profiling into radioembolization outcome prediction in patients with breast cancer metastatic to the liver with PI3K pathway mutation.

Metastatic breast cancer is the second leading cause of cancer death among women (1). Even though only 5% of patients with metastatic breast cancer have metastatic disease confined to the liver, half of patients develop liver metastases, and progression of liver disease is considered the cause of death in nearly one fifth of patients (2). Liver-directed therapy can palliate symptoms such as abdominal pain and has the potential to prolong life.

For multifocal hepatic metastasis, transarterial therapy with chemoembolization and yttrium-90 (^{90}Y) radioembolization have both been used and shown to have acceptable safety profiles, imaging response, and post-procedure survival (3–13). To date, we are aware of no randomized trial comparing these treatments as adjuvant treatments to systemic therapy, emphasizing the importance of identifying biomarkers to aid clinicians in distinguishing patients who might benefit from one treatment versus another. Patients with metastatic breast cancer often show disease progression despite multiple chemotherapies, including those administered during chemoembolization, and will show progression regardless of the type of therapy. In addition, in the context of primary liver malignancy, radioembolization is associated with better quality-of-life scores compared with chemoembolization (14). Retrospective studies have not yielded reproducible preprocedural predictors of response to radioembolization in patients with metastatic breast cancer, with some suggesting preexisting liver dysfunction as an indicator of poor survival (5,9). Large-scale profiling studies after radiation demonstrate that, in breast cancer, several pathways, including HER2, estrogen receptor (ER), PI3K, and JAK/STAT3, and androgen-receptor expression impact radiation resistance and sensitivity (15). MAPK/ERK pathway mutations have been suggested to impact response to radioembolization for colorectal cancer (16), and TP53 mutations are associated with poor response to radiation therapy in breast cancer (17). Hypothetically, mutations in pathways involving radiation sensitivity may impact response to radioembolization.

The purpose of the present study was to describe the imaging response and survival after radioembolization for metastatic breast cancer and to delineate predictors of image response and outcomes, with a focus on potential genetic prognosticators.

MATERIALS AND METHODS

Patient Population

The present retrospective, single-center study included all consecutive patients with metastatic breast cancer who underwent radioembolization before the study (January 2011 to September 2017) at an academic university hospital. Informed consent was waived for this Health Insurance Portability and Accountability Act–compliant, institutional review board–approved study. An institutional database search identified 31 patients with metastatic breast cancer treated with radioembolization. Eligibility criteria for radioembolization included age 18 years or older, measurable liver metastasis involving $>$ 10% of the liver parenchyma, Eastern Cooperative Oncology Group performance status 0/1, serum creatinine level $\leq$ 2.0 mg/dL, total bilirubin level $<$ 1.2 times the upper limit of normal, and albumin level $\geq$ 2.0 g/dL. Patients of any racial or ethnic group were eligible for inclusion. Exclusion criteria included tumor replacement of $>$ 70% of liver; absolute contraindications to angiography and visceral catheterization (eg, uncorrectable coagulopathy or anaphylactic allergy to contrast agent); pulmonary insufficiency or clinically evident chronic obstructive pulmonary disease; cirrhosis, portal hypertension, or history of hepatic encephalopathy; ascites (trace ascites was acceptable); life-threatening or comorbid disease (eg, dialysis dependency, severe infection) that would put the patient at undue risk during radioembolization treatment; progressive extrahepatic metastasis thought to immediately threaten survival; and breastfeeding. Patients were selected for treatment based on a multidisciplinary discussion with breast oncologists. Patients with breast cancer who had multiple liver lesions or oligometastatic liver metastases that were not considered safe for, or amenable to, percutaneous ablation were offered radioembolization. Transarterial chemoembolization was not offered at the study institution.

All 31 patients were female and had metastatic invasive ductal carcinoma, with an average age of 52.2 years ± 11.4 (**Table 1**). One patient had liver-only metastasis; all others had other sites of metastasis. No patient underwent external radiation to the liver or previous transarterial therapy. All but 2 patients had multifocal liver disease. All patients had received at least 3 lines of systemic therapy and were therefore considered heavily pretreated. On average, patients received 11.0 ± 4.5 systemic therapy agents before