Frequency of Hepatic Metastatic Disease in Patients with Stage IV Breast Cancer Is Similar for Steatotic and Non-Steatotic Livers

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ABSTRACT

BACKGROUND: Breast cancer is the most common non-cutaneous malignancy and the second leading cause of cancer mortality in the United States. Breast cancer is a heterogeneous disease; diagnosis at an early stage renders it potentially curable, whereas advanced metastatic disease carries a worse prognosis.

OBJECTIVES: To investigate whether hepatic steatosis (HS) is associated with liver metastases in patients with newly diagnosed stage IV female breast cancer patients (either de novo metastatic breast cancer or recurrent metastatic breast cancer) using non-contrast computed tomography (CT) as a marker of HS.

DESIGN: Retrospective analysis.

METHODS: We retrospectively identified 168 patients with stage IV breast cancer with suitable imaging from a prospectively maintained oncologic database. Three radiologists manually defined hepatic regions of interest on non-contrast CT images, and attenuation data were extracted. HS was defined as a mean attenuation <48 Hounsfield units. The frequency of hepatic metastatic disease was calculated for patient with and without HS. Relationships between HS and various patient (age, body mass index, race) and tumor (hormone receptor status, HER2 status, tumor grade) characteristics were also analyzed.

RESULTS: There were 4 patients with liver metastasis in the HS group (41 patients) versus 20 patients with liver metastases in the non-HS group (127 patients). The difference in frequencies of liver metastases among patients with (9.8%) versus without (15.7%) hepatic steatosis (odds ratio = 1.72 [0.53-7.39]) was not statistically significant ($P = .45$). Body mass index was significantly higher ($P = .01$) among patients with hepatic steatosis (32.2 ± 7.3 vs 28.8 ± 7.1 kg/m^2). Otherwise, there were no significant differences between patients with versus without HS with respect to regarding age, race, hormone receptor status, HER2 status, or tumor grade.

CONCLUSION: The frequency of hepatic metastatic disease in patients with stage IV breast cancer is similar for steatotic and non-steatotic livers.

KEYWORDS: Hepatic steatosis, metastatic breast cancer, liver metastases, hepatic fat content, computed tomography, distant metastatic disease

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Introduction

Breast cancer is the most common non-cutaneous malignancy[1] and the second leading cause of cancer mortality in the United States.[2] Breast cancer is a heterogeneous disease; diagnosis at an early stage renders it potentially curable,[3] whereas advanced disease carries a worse prognosis. Distant metastatic disease unfortunately remains incurable.[4] As such, early detection has the potential to improve long-term survival.[5] As is true for most malignancies, understanding the risk factors that contribute to the metastatic potential of breast cancer may lead to early appropriate interventions. Among patients with stage IV breast cancer, the liver is the first site of metastasis in up to 12% of patients [6] and the fourth most common site of breast cancer metastasis overall, following the bones, lungs, and brain.[7] Hepatic metastases have profound therapeutic and prognostic implications for breast cancer patients.[7-9] The tumor environment may affect the presence and growth characteristics of metastatic disease, as well as the response to treatment.

Hepatic steatosis (also called fatty liver), which is the excess accumulation of lipids within hepatocytes, has been described as a potentially significant factor in the liver microenvironment that may influence metastatic cell implantation and growth.[10]

This may be in part due to lipids providing energy to adjacent tumor.[11] Non-alcoholic fatty liver disease (NAFLD) is prevalent in the United States, reportedly afflicting approximately 34% of some populations[12] and breast cancer treatments such as chemotherapy and endocrine therapy can increase the risk for hepatic steatosis[13] in breast cancer survivors, with as many as 72% of survivors noted to have fatty liver.[14] In addition, there is evidence that adipocytes promote tumor growth.[15] A preclinical study found that mice with NAFLD are at dramatically increased risk of breast cancer metastases.[11] Non-alcoholic fatty liver disease promotes liver metastasis by reciprocal activation initiated by tumor-induced triglyceride lipolysis in juxtaposed hepatocytes. The lipolytic products are transferred to cancer cells via fatty acid transporter protein 1, where they are metabolized by mitochondrial oxidation to promote tumor growth. The histology of human liver metastasis indicated the same occurs in humans. Furthermore, comparison of isolates of normal and fatty liver established that steatotic lipids had enhanced tumor-stimulating capacity.[11] We hypothesized that excessive lipid deposition in the liver would create a favorable "host environment" in patients, promoting the growth and sustenance of breast cancer cells and thereby predisposing individuals with hepatic steatosis to liver metastasis. Despite this biologic rationale for fatty liver to promote liver metastasis, only a few human studies addressing this association have been published in the literature, and these studies have conflicting results. Duran et al[16] found a higher incidence of liver metastasis in patients with metastatic breast cancer and hepatic steatosis. In contrast, Wu et al[17] reported a possible protective effect of hepatic steatosis against liver metastasis; patients with hepatic steatosis had a lower risk of liver metastases. Conflicting results concerning the effects of hepatic steatosis on the incidence of liver metastases are not unique to breast cancer but rather have been reported for multiple other solid tumor types as well.[18]

Although histopathology is the gold standard for diagnosing and quantifying hepatic steatosis,[19,20] the relative amount of lipid within the hepatic parenchyma can be accurately calculated non-invasively with various imaging methods.[21] These non-invasive approaches mitigate risks associated with liver biopsy, including life-threatening hemorrhage.[22] Moreover, steatotic livers often have spatially heterogeneous fat distribution. Percutaneous biopsy only samples a tiny percentage of the total liver volume, which predisposes to sampling errors; as such a single specimen may not be representative of the liver as a whole.[23] Imaging offers an opportunity to mitigate sampling errors and provides a more comprehensive assessment of hepatic steatosis.

Several imaging techniques are available for hepatic steatosis quantification, including ultrasound,[24] computed tomography (CT), and magnetic resonance imaging (MRI).[25] Magnetic resonance imaging is likely the most accurate imaging tool for liver fat quantification, however, CT is the preferred primary imaging modality to evaluate metastatic disease in breast cancer patients. Furthermore, non-contrast CT combined with positron emission tomography (PET/CT) provides anatomic correlation for metabolically active or receptor-targetable breast cancers. Thus, due to its widespread use and validated criteria for liver fat deposition, non-contrast CT is a reasonable non-invasive surrogate for hepatic steatosis in the breast cancer population, whereas contrast-enhanced CT is less reliable.[26] In a cohort of patients with stage IV breast cancer, we used non-contrast CT to investigate whether hepatic steatosis correlates with various tumor and patient characteristics and to assess whether hepatic steatosis alters the frequency of breast cancer liver metastasis.

Materials and Methods

Patient population

We retrospectively reviewed a prospectively maintained oncologic database to identify female breast cancer patients with newly diagnosed stage IV disease (either de novo metastatic breast cancer or recurrent metastatic disease following a prior diagnosis of non-metastatic breast cancer). This database query identified 283 potentially eligible patients from January 1, 2010, to December 31, 2016. Of the 283 patients, 168 (59%) had imaging deemed adequate to serve as a reference standard for hepatic steatosis (see below). These 168 patients constituted the final cohort for this study. Patient age, race, comorbidities, body mass index (BMI), hormone receptor status, HER2 status, tumor grade, prior treatment history (including endocrine and chemotherapeutics associated with hepatic fat deposition, such as methotrexate and 5-fluorouracil),[27] sites of metastatic disease, and survival data were extracted from the database for further analysis. Notably, estrogen receptor or progesterone receptor positivity was defined as hormone receptor positivity.

Reference standard

Non-contrast CT scans performed within 4 months of the stage IV breast cancer diagnosis were considered adequate for assessing hepatic steatosis. Hepatic steatosis reduces the attenuation of X-rays by the liver parenchyma, resulting in lower Hounsfield unit (HU) values. A mean hepatic attenuation of < 48 HU was used for defining significant hepatic steatosis. The specificity, sensitivity, positive predictive value, and negative predictive value of this criterion are 100%, 53%, 100%, and 94%, respectively, for predicting histologic lipid content of 30% or greater.[28] No scans performed within 4 months of systemic therapy were analyzed to avoid treatment-related confounders (eg, chemotherapy-induced hepatic steatosis). When multiple scans met the above criteria for a given patient, the scan temporally closest to the date of the stage IV diagnosis (but before initiation of systemic therapy) was selected. We also prioritized scans that captured the entirety of the liver (eg, CT from PET/CT instead of chest CT).

Image review

Each CT image set was reviewed by 1 of 3 radiologists with at least 3 years of cross-sectional imaging training. These

radiologists were blinded to all clinical information, including breast cancer disease status. Non-contrast CT examinations including the liver were selected to detect hepatic steatosis. Three liver regions of interest (ROIs) were defined as follows: one ROI in the right hemi-liver, one in the central liver (near the hilum), and one in the left hemi-liver. Each ROI was approximately 3 cm in diameter with an area of 7 cm^2 (Figures 1 and 2). The ROIs were carefully drawn to avoid large vessels, dilated bile ducts, significant artifacts (eg, beam hardening), or focal liver lesions (benign or malignant). For cases in which a patient ostensibly had liver metastatic disease at the time of the imaging study used for hepatic steatosis assessment, contrast-enhanced CT/MRI and/or PET/CT examinations were also reviewed (if available) to avoid metastasis inclusion within the ROIs. For each ROI, the mean attenuation was measured in HUs. A final liver attenuation value was calculated as the mean of the 3 separate liver ROIs.

Statistical analysis

A power analysis was conducted to determine the number of years in our database needed to achieve a sufficiently large number of subjects. A prior study addressing a similar research question reported that 26.2% of metastatic breast cancer patients had hepatic steatosis by CT criteria.[16] In that study, 46.4% of patients with hepatic steatosis and 22.8% without hepatic steatosis had liver metastases. To achieve 80% power at the 0.05 significance level for a group proportion difference of 0.2360, we determined that 41 patients with hepatic steatosis and 116 patients without hepatic steatosis were needed for a total sample size of 157 patients. This determination was based on the 2-sided *Z* test with pooled variance.

Data were analyzed using SPSS version 18 (SPSS, Inc., Chicago, Illinois). Categorical and continuous variables were summarized descriptively. The Fisher exact test was used to assess for an association between hepatic steatosis and liver metastases. Relationships between patient and tumor characteristics and hepatic steatosis were assessed via the pooled-variance 2-sample *t* test (BMI, age), Fisher's exact test (HER2 status, tumor grade, race), Chi-square test (hormone receptor status), or Mantel-Haenszel test (location of metastatic disease). In cases of missing data for a given patient or tumor characteristic, subjects were excluded from the analysis of that variable only. Kaplan-Meier curves were generated for overall survival, stratifying patients by the presence versus absence of hepatic steatosis; the log-rank test was used to assess differences in survival. An alpha of 0.05 was used to define statistical significance.

Results

Presence of non-hepatic distant metastases

Out of 168 study patients with stage IV breast cancer, 69 (41.1%) had non-hepatic distant metastatic disease at the time of the imaging study used for analysis. The most common locations were bones ($n = 60$; 87.0%), lung ($n = 16$; 23.2%), and distant lymph nodes ($n = 10$; 14.5%) (Table 1). Note that the sum of distant metastatic disease sites does not equal the total number of patients with distant metastases, as some patients had multiple sites of distant metastatic disease. Patients with non-hepatic distant metastases were not more likely ($P = .25$) to have hepatic steatosis (29.0%; 20/69) than patients without non-hepatic distant metastases (21.2%; 21/99).

Frequency of hepatic steatosis

Among the 168 study patients with stage IV breast cancer (100% women), 41 patients (24.4%) had hepatic steatosis according to our CT-based criteria (Table 2).

Relationship between hepatic steatosis and patient/tumor characteristics

Results from our analysis of the relationships between hepatic steatosis and various patient and tumor characteristics are summarized in Table 2. Body mass index was significantly higher ($P = .01$) among patients with hepatic steatosis (32.2 ± 7.3 kg/m^2) than among patients without hepatic steatosis (28.8 ± 7.1 kg/m^2). Otherwise, there were no significant differences between patients with and without hepatic steatosis regarding age, race, hormone receptor status, HER2 status, or tumor grade. In addition, we assessed for any association between chemotherapy and endocrine therapy and found no statistically significant association with chemotherapy ($P = 1.0$, Fisher exact test) or endocrine therapy $P = .7864$, Fisher exact test and hepatic steatosis. There was no difference in overall survival (Figure 3) between patients with versus without hepatic steatosis ($P = .91$).

Association between hepatic steatosis and liver metastasis

There were 4 patients with liver metastasis in the hepatic steatosis group (41 patients) versus 20 patients with liver metastases in the non-hepatic steatosis group (127 patients) (Table 3). The difference in frequencies of liver metastases among patients with (9.8%) versus without (15.7%) hepatic steatosis (odds ratio [OR] = 1.72 [0.53-7.39] was not statistically significant ($P = .45$).

Discussion

Hepatic metastasis in breast cancer is both common and associated with poor prognosis.[7-9] Given the prognostic implications, identifying risk factors for the development of hepatic metastasis may ultimately lead to reduction in the incidence of this condition, and ultimately improve breast cancer prognosis. Clinical and preclinical studies have suggested that hepatic steatosis, a common finding in patients with breast cancer, promotes liver metastases[11,16,17]; thus we aimed to determine whether there was a correlation between hepatic steatosis (as reflected in a non-contrast CT-based metric) and the presence of hepatic metastatic disease at the time that stage IV breast

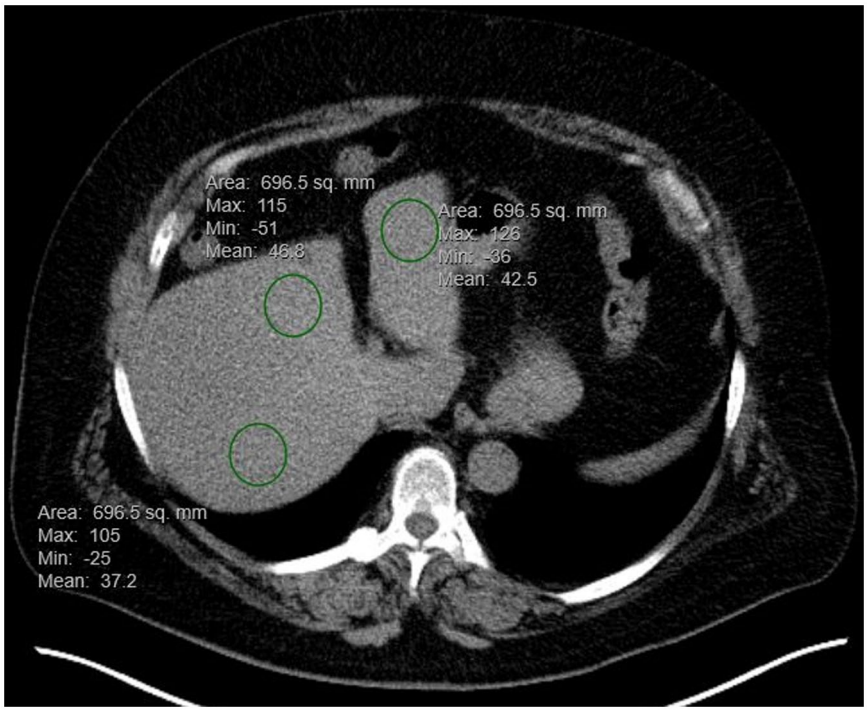

Figure 1. Liver ROIs in a patient with hepatic steatosis.
Axial non-contrast CT image, showing 3 ROIs. These ROIs are placed in the right hemiliver, the central liver, and the left hemiliver. The approximate diameter is 3 cm with an area of 7 cm^2. Across the 3 ROIs, the mean attenuation was 42.2 HU (below the 48 HU threshold).
CT indicates computed tomography; HU, Hounsfield unit; ROI, region of interest.

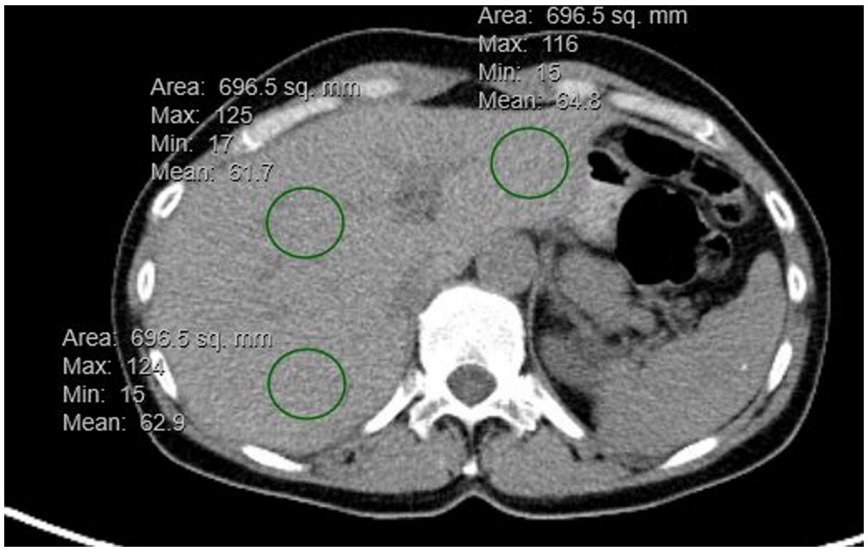

Figure 2. Liver ROIs in a patient without hepatic steatosis.
Axial non-contrast CT image, showing 3 ROIs in right hemiliver, central liver, and left hemiliver with an approximate diameter of 3 cm and area of 7 cm^2. Across the 3 ROIs, the mean attenuation was 63.1 HU (above the 48 HU threshold).
CT indicates computed tomography; HU, Hounsfield unit; ROI, region of interest.

cancer is diagnosed, in a population of female breast cancer patients at our institution. We hypothesized that excessive lipid deposition in the liver would create a favorable "host environment" in patients, promoting the growth and sustenance of breast cancer cells and thereby predisposing individuals with hepatic steatosis to liver metastasis. However, we found no statistically significant association between hepatic steatosis and liver metastases, despite a relatively high prevalence (roughly 25%) of hepatic steatosis in our studied population, although this may be related to small sample size. Furthermore, beyond

Table 1. Non-hepatic distant metastases in hepatic steatosis and non-hepatic steatosis groups.

NON-HEPATIC METASTASES	HEPATIC STEATOSIS	NO HEPATIC STEATOSIS	TOTAL
Bone	19	41	60
Brain	3	3	6
Lung	5	11	16
Distant lymph nodes	3	7	10
Peritoneal	0	1	1
Pleura	0	5	5
Skin	0	2	2
Other	0	5	5
Total	30	75	105

Note that some patients had multiple sites of distant metastases; therefore, the sum of the numbers is not equal to the total number of patients with distant metastases disease in each category. There were 69 patients with non-hepatic metastases, of whom 20 had hepatic steatosis and 49 had no hepatic steatosis.

Table 2. Relationship between selected patient/tumor characteristics and hepatic steatosis.

CHARACTERISTIC	HEPATIC STEATOSIS *N* = 41 (24.4%)	NO HEPATIC STEATOSIS *N* = 127 (75.6%)	*P* VALUE
Age, y	59.1 ± 12.7	57.6 ± 14.8	.58
BMI, kg/m^2	32.2 ± 7.3	28.8 ± 7.1	**.01**
Race			
Black	12 (29.3)	26 (20.5)	.50
White	28 (68.3)	98 (77.2)	
Other	1 (2.4)	3 (2.3)	
HR status			
Positive	30 (79.0)	87 (71.3)	.35
Negative	8 (21.0)	35 (28.7)	
HER2 status			
Positive	3 (13.0)	17 (20.2)	.56
Negative	20 (87.0)	67 (79.8)	
Tumor grade			
Well differentiated	6 (16.2)	7 (6.1)	.10
Moderately differentiated	16 (43.2)	44 (38.6)	
Poorly differentiated	15 (40.6)	63 (55.3)	

Abbreviations: BMI, body mass index; HR, hormone receptor status.
Continuous variables are reported as mean ± SD. Categorical variables are reported as n (%). Statistically significant *P* value is bolded.

a higher frequency of hepatic steatosis in patients with higher BMIs, an expected finding, we found no association between hepatic steatosis and any of the evaluated tumor or patient characteristics.

Despite studies in other solid tumors,[18,29,30] mostly in the colorectal cancer population, there are (to our knowledge) only 2 previously published studies (both retrospective) addressing a similar question in a population of patients with breast cancer. Duran et al[16] evaluated hepatic steatosis with CT in 107 consecutive patients with metastatic breast cancer and found the frequency of hepatic metastases was significantly higher in patients with hepatic steatosis (46.4% vs 22.8%, *P* = .018). The

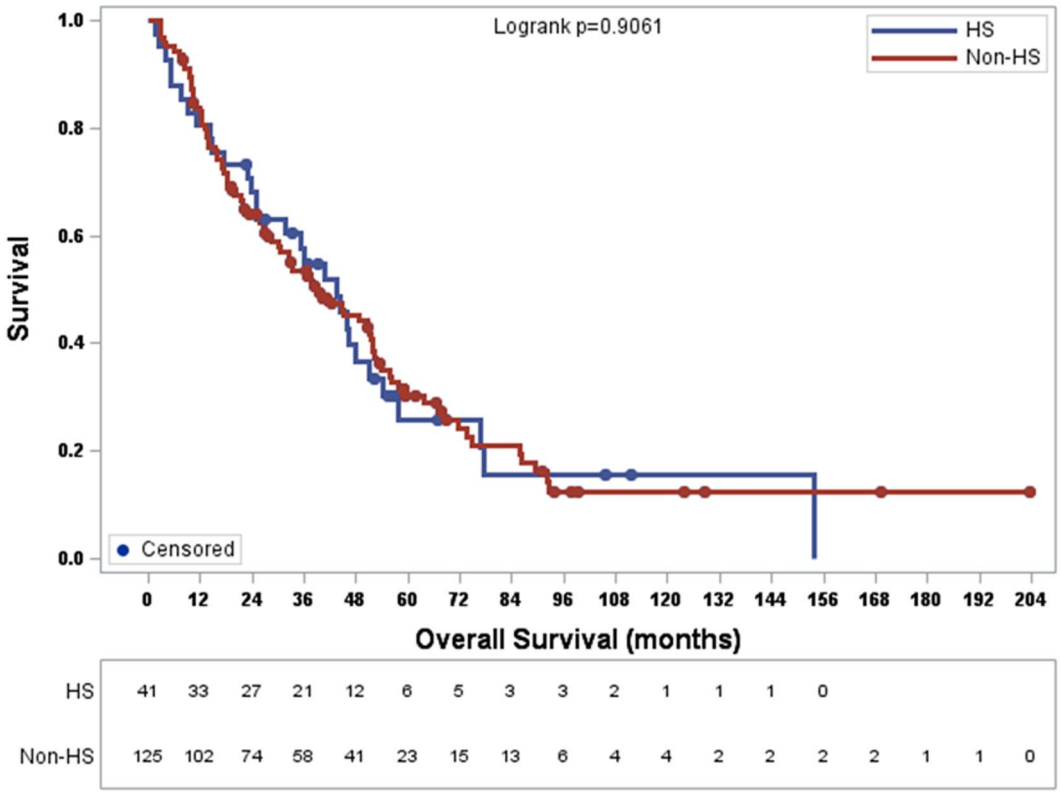

Figure 3. Survival in months for patients with (HS) versus without (non-HS) groups.
HS indicates hepatic steatosis.

Table 3. Relationship between hepatic metastatic disease and hepatic steatosis.

	HEPATIC STEATOSIS	NO HEPATIC STEATOSIS	*P* VALUE
Liver metastasis	4 (9.8)	20 (15.7)	.45
No liver metastasis	37 (90.2)	107 (84.3)	

Data are reported as n (%).

CT criteria utilized in the Duran et al[16] study included evidence of focal fatty sparing at typical locations within the liver on a contrast-enhanced CT or a liver-to-spleen attenuation ratio < 1.1 on a non-contrast CT. In contradistinction, Wu et al[17] conducted a study of 1230 patients with newly diagnosed breast cancer regardless of stage, and found that hepatic steatosis detected by ultrasound was associated with a decreased risk of developing liver metastases on imaging during the study's follow-up period. This "protective effect" of hepatic steatosis was observed in a multivariate analysis (hazard ratio [HR] = 0.55; 0.35-0.86; *P* = .008), as well as in a one-to-one patient matching analysis (HR = 0.42; 0.26-0.69; *P* = .001). Liver ultrasound was performed within 30 days of initial breast cancer diagnosis, although the sonographic criteria used by this study for the diagnosis of hepatic steatosis were not provided.

The lack of an association between hepatic steatosis and liver metastasis in our study may be explained by several differences in study design relative to these 2 prior studies. First, our study utilized only non-contrast CT studies as a means of defining hepatic steatosis, based on a mean attenuation below 48 HU as validated by Pickhardt et al[28] This threshold was chosen in light of its 100% specificity and positive predictive value for moderate-severe hepatic steatosis. Notably, CT is relatively unreliable for diagnosing more mild forms of hepatic steatosis.[31] Among the various approaches for diagnosing hepatic steatosis on CT, hepatic parenchymal mean attenuation on non-contrast CT (the approach used in our study) is more reliable for predicting the degree of steatosis on histology than liver-to-spleen attenuation ratios on non-contrast CT (the approach used by Duran et al[16]) or any approach utilizing post-contrast CT images.[32] Although ultrasound has been reported to have specificity and sensitivity in the 80% to 90% range for moderate-severe hepatic steatosis, based on comparing the echogenicity of the liver to the adjacent right kidney or spleen, Wu et al[17] did not describe their sonographic criteria for diagnosing hepatic steatosis, precluding an assessment of the reliability of their approach.

Overall, these different imaging approaches to identifying patients with hepatic steatosis likely contribute to this lack of concordance between our study and other studies. Future prospective studies utilizing liver MRI or histopathology as the reference standard would likely be more reliable.

Second, the Wu et al[17] study included only women without distant metastases at the time of initial breast cancer diagnosis. In contrast, our study and Duran et al[16] included women with both de novo and recurrent metastatic stage IV disease. Furthermore, the determination of whether a patient had hepatic steatosis was done at the time of initial diagnosis of *non-metastatic* breast cancer in the Wu et al[17] study. In contrast, our study and Duran et al[16] made this determination at the time when stage IV disease was identified. As such, it is conceivable that the effects of hepatic steatosis on the propensity of breast cancer to spread to the liver could vary depending on the duration of hepatic steatosis and/or exposure to prior cancer treatments. One study found that in mouse models and on review of patient imaging, steatosis decreases in the areas of the liver immediately surrounding metastases, suggesting that the tumors may be utilizing hepatic lipids for energy.[11] Therefore, assessing for hepatic steatosis at the time of metastatic disease may be less sensitive than assessing before the diagnosis of liver metastasis, resulting in a potential underestimate of the association between steatosis and metastasis. In addition, the presence of hepatic steatosis can also make the imaging diagnosis of hepatic metastatic disease more challenging, particularly when CT and ultrasound are used rather than MRI. Thus, it is possible that women in the Wu et al[17] study with hepatic steatosis had delayed diagnoses of liver metastatic disease due to suboptimal imaging quality, which could have resulted in longer periods between initial *non-metastatic* breast cancer diagnosis and the recognition of hepatic metastatic disease.

Our study has several limitations, including its single-center retrospective design. As previously mentioned, non-contrast CT is not as accurate as MRI for identifying hepatic steatosis, so some women may have been misclassified. Unfortunately, CT, and not MRI, is routinely used for staging breast cancer. A prospective study of patients who have a routine CT scan, and a time-matched study funded MRI, to compare the ability of the 2 examinations to detect steatosis in this population should be conducted and will provide helpful information as to whether CT is an adequate means to determine steatosis in patients with breast cancer. In addition, we selected a highly specific threshold for hepatic steatosis, meaning that multiple women with hepatic steatosis, particularly at the low end of the steatosis spectrum, were probably misclassified as not having hepatic steatosis, potentially reducing power for detecting a true difference in hepatic metastasis risk between these 2 groups. Furthermore, there is potential for selection bias, as many women (~41%) with stage IV breast cancer during the study period were excluded as they lacked the non-contrast CTs necessary to determine hepatic steatosis. Although our study was designed specifically to analyze patients with stage IV metastatic disease, further studies evaluating the impact of hepatic steatosis in early stage breast cancer on the risk of recurrent liver metastases are warranted.

In conclusion, we found no statistically significant association between hepatic steatosis and breast cancer liver metastasis in a population of women with stage IV breast cancer. As 2 prior studies suggested that hepatic steatosis may either predispose to or protect against breast cancer liver metastasis, the true association (if any) between hepatic steatosis and the incidence of liver metastasis remains unclear. Prospective, multicenter studies utilizing a reliable quantitative imaging marker of hepatic steatosis, such as MRI, are needed to address this question adequately. Data from such a study are needed to inform clinicians as to whether treating hepatic steatosis is likely to impact prognosis and subsequently whether staging scans should include MRI.

Declarations

Ethics Approval and Consent to Participate

This retrospective study was conducted at the Washington University School of Medicine in St. Louis, MO, USA. The study was HIPAA-compliant and approved by the Washington University IRB (number 201704021). The IRB waived the requirement for informed consent.

Consent for Publication

Not applicable.

Author Contributions

Adeel Haq: Formal analysis; Investigation; Methodology; Software; Visualization; Writing—original draft; Writing – review & editing.
Tyler J Fraum: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.
Yu Tao: Data curation; Formal analysis; Validation; Writing – review & editing.
Farrokh Dehdashti: Conceptualization; Methodology; Validation; Visualization; Writing – review & editing.
Maverick LeBlanc: Data curation; Methodology; Visualization; Writing – review & editing.
Mark Hoegger: Data curation; Methodology; Software; Writing – review & editing.
Jingqin Lou: Data curation; Formal analysis; Writing – review & editing.
Katherine Weilbaecher: Conceptualization; Investigation; Methodology; Visualization; Writing – review & editing.
Lindsay Peterson: Conceptualization; Data curation; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing – review & editing.

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Availability of Data and Materials

All requests for raw and analyzed data materials will be promptly reviewed by the Division of Oncology, Washington University in St. Louis to verify whether the request is subject to any intellectual property or confidential obligations. Patient-related data not included in article may be subject to confidentiality. Any data and materials that can be shared will be released via a material transfer agreement.

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