JBUON 2015; 20(4): 963-969
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Hepatic steatosis is associated with higher incidence of liver metastasis in patients with metastatic breast cancer; an observational clinical study

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Summary

Purpose: *To investigate the relationship between hepatic steatosis (HS) (at the time of diagnosis) and hepatic metastasis (at the time of diagnosis and follow-up) in metastatic breast cancer (BC) patients by using computed tomography (CT).*

Methods: *A total of 107 metastatic BC patients who had an abdominal CT were retrospectively enrolled in this study. Patients without HS (N=79) were regarded as the control group and those with HS constituted the HS study group (N=28).*

Results: *Hepatic metastases at diagnosis and during follow-up were more common in patients with HS (p=0.018 and p=0.041, respectively) and in the premenopausal group (p<0.001 and p=0.004, respectively), whereas they were similar in patients with and without HS in the postmenopausal group (p=0.655 and p=0.656, respectively). Overall survival rates were similar in patients with and without HS (p=0.606).*

Conclusion: *Hepatic metastases at diagnosis and during follow-up were more frequent in patients with HS, especially in premenopausal patients. Survival was similar in both groups.*

Key words: *breast cancer, hepatic steatosis*

Introduction

BC is the most common cancer in women worldwide [1]. Current data indicate that 25–40% of BC patients ultimately develop metastasis; approximately 12–20% of BC patients will develop liver metastasis, which is associated with a poor prognosis (median survival about 14 months) [2,3]. Most patients with BC can be treated with surgery and adjuvant therapy (hormone therapy/chemotherapy), which essentially control the evolution or reduce the incidence of recurrence and/or metastasis. Metastasis of cancer cells depends on many factors and the microenvironment of the target tissue (such as fibrosis and steatosis) is one of the important factors that determines the capability for metastasis and the survival of metastatic cells [4].

Non-alcoholic fatty liver disease (NAFLD) is a chronic disorder that ranges from HS to non-alcoholic steatohepatitis (NASH) with no known risk factors of steatosis [5]. NAFLD is a very common liver disease worldwide, occurring in 10–46% of the general population, and is significantly associated with obesity. It is considered a liver manifestation of metabolic syndrome (MS) [6,7]. Obesity is also a risk factor for the development and poor prognosis of BC [1]. HS is commonly encountered in many cancer patients, and especially in BC patients, in clinical oncology practice [8].

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Received: 20/10/2014; Accepted: 08/02/2015

Ultrasound (US) is a non-invasive and useful technique for the assessment of HS [9]; however, its objectivity and reproducibility is quite low due to the important effects of its interpretation by the examiner and the instrument itself. CT scans, by contrast, allow quantitative analysis of HS and have shown good correlation with histological liver biopsy findings [10]. Evaluation of the CT liver attenuation value as well as the ratio between hepatic and splenic attenuation levels [11,12] allows an objective evaluation of HS.

Based on this information, HS can be hypothesised as a risk factor for hepatic metastasis and to be associated with poor prognosis in patients with metastatic BC. Our aim was to use contrast-enhanced and non-enhanced CT to investigate the relationship between HS (at the time of diagnosis) and hepatic metastasis (at the time of diagnosis or follow-up) in metastatic BC patients.

Methods

We retrospectively enrolled 107 consecutive metastatic BC patients who had been diagnosed and treated at the Erciyes University Hospital, from May 2005 to Jun 2010. The HS was evaluated retrospectively by contrast-enhanced and non-enhanced CT. A single radiologist, experienced in abdominal examination, reviewed the abdominal CT images. Based on their abdominal CT data, patients without HS were regarded as the control group and those with HS constituted the HS study group. The patient clinicopathological features (presence of metastasis, presence or development of hepatic metastasis, survival, smoking, alcohol consumption and past medical history) were all recorded using the hospital archive and the correlation with the presence of HS was analysed.

Inclusion/exclusion criteria

Inclusion criteria: 1) the reports included histopathologic findings to confirm the diagnosis of metastatic BC; 2) patients must have undergone abdominal CT examinations at our institution (which has the ability to assess liver steatosis and metastasis) at the time of metastatic BC diagnosis; and 3) patients did not consume alcohol.

Exclusion criteria: 1) patients with non-metastatic BC; 2) patients with second malignancy; 3) patients who received adjuvant chemotherapy in the previous year and patients who received tamoxifen as adjuvant treatment at any time; 4) patients who could not undergo a liver CT at the time of metastatic BC diagnosis; 5) patients with a CT with an artefact that prevented assessment of liver steatosis and metastasis; 6) patients who had viral hepatitis (hepatitis B and C), cirrhosis, liver cancer, or other liver diseases.

HS may develop either due to the diseases or treatment in patients with cancer. For example, 5-Fluorouracil (5-FU), methotrexate (MTX) and tamoxifen (TMX) are the most frequent drugs causing HS [8,14-16]. Therefore, we excluded all patients treated with these particular drugs.

Contrast-enhanced and non-enhanced CT examination

Contrast-enhanced hepatic CT of patients using a GE LightSpeed 16 scanner (General Electric Medical Systems, Milwaukee, Wisconsin, USA) were analysed by an experienced radiologist. The study was performed at baseline and after injection of 2 ml/kg of iodinated contrast medium (Iomeron 300/100 mg/dL, Bracco or Omnipaque 300/100 mg/dL, Opakim or Ultravist 300/100 mg/dL, Bayer-Schering) at a rate of 4 ml/s, followed by 40 ml saline solution at a rate of 4 ml/s in the portal venous phase (50–80 s). Contrast-enhanced CT examinations were evaluated for focal fatty sparing areas suggestive of hepatosteatosis. Focal fatty sparing areas were diagnosed based on typical location (periportal area, segment 4, around the gallbladder fossa) and focal increased density.

Non-enhanced CT was obtained using a Gemini TF PET/CT (Philips Medical Systems, Eindhoven, the Netherlands). All CT images were reviewed using a picture archiving and communication system workstation (General Electric Medical Systems, Milwaukee, WI). The mean CT attenuation values, in Hounsfield units (HU), of the liver and the spleen were obtained using a standard region-of-interest method. The liver attenuation (HU)/spleen attenuation (HU) ratio was calculated and those patients with a liver–spleen ratio lower than 1.1 were diagnosed as HS, as previously reported [13].

Statistics

All analyses were performed with the SPSS v.18 software (SPSS Inc., Chicago, IL, USA). The results were presented as mean±standard deviation for parametric variables, median (minimum/maximum levels) for non-parametric variables or percents for categorical variables. For comparison of clinicopathological parameters with the HS, continuous variables were compared using the Wilcoxon signed rank test or Mann–Whitney U test, as appropriate. Categorical variables were compared using a proportions x^2 test or the Fisher's exact test, as appropriate. Survival analysis was estimated using the Kaplan-Meier method, including number of patients, median survival time and a 95% confidence interval (CI). A difference at $p<0.05$ was considered statistically significant.

Results

Among the 107 patients with metastatic BC, 28 (26.2%) were diagnosed as HS based on CT criteria. The association between the clinical charac-

Table 1. Clinical characteristics, hepatic metastasis and survival of the study cohort grouped as subjects with and without hepatic steatosis

Characteristics	*Hepatic steatosis*		*p value*
	Yes	*No*	
Number of patients (%)	28 (26.2)	79 (73.8)	
Age (years)*	48 ± 9	52 ± 13	0.337
BMI (kg/m^2)*	30.9 ± 5.9	27.6 ± 4.6	0.005
Obesity (BMI>30) N (%)	16 (57.1)	24 (30.4)	0.012
Diabetes N (%)	2 (7.1)	11 (13.9)	0.345
Smoking N (%)	2 (7.1)	4 (5.1)	0.681
Premenopausal N (%)	14 (50.0)	39 (49.4)	0.954
Hepatic metastasis at diagnosis N (%)	13 (46.4)	18 (22.8)	0.018
Hepatic metastasis during follow-up N (%)	6 (21.4)	9 (11.3)	0.041
Death N (%)	15 (53.6)	38 (48.1)	0.659

*mean± standard deviation, BMI: body mass index

Table 2. Hepatic metastasis and survival of the premenopausal and postmenopausal patients as subjects with and without hepatic steatosis

	Hepatic steatosis		*p value*
	Yes N (%)	*No* N (%)	
Premenopausal patients			
Hepatic metastasis at diagnosis	10 (71.4)	7 (17.9)	<0.001
Hepatic metastasis during follow-up	3 (21.4)	3 (7.6)	0.004
Death	7 (50.0)	13 (34.2)	0.299
Obesity (BMI>30)	4 (28.6)	7 (17.9)	0.401
Postmenopausal patients			
Hepatic metastasis at diagnosis	3 (21.4)	11 (27.5)	0.655
Hepatic metastasis during follow-up	3 (21.4)	6 (15.0)	0.656
Death	8 (57.1)	25 (62.5)	0.723
Obesity (BMI>30)	12 (85.7)	17 (42.5)	0.005

BMI: body mass index

teristics of the study patients and the HS is shown in Table 1. No statistically significant differences were noted between the two groups in terms of age, history of diabetes, smoking and the number of premenopausal patients. Body mass index (BMI) was higher in patients with HS (30.9±5.9 vs 27.6±4.6, p=0.005). The number of obese patients (BMI>30 kg/m^2) was higher in the HS group (57.1 vs 30.4%, p=0.012).

The number of patients with hepatic metastasis at diagnosis was higher in the HS group than in the group without HS [13 of 28 patients with HS (46.4%) vs 18 of 79 patients without HS (22.8%), p=0.018] (Table 1). The number of patients with hepatic metastasis during follow-up was also higher in the HS group than in the group without HS [6 of 28 patients with HS (21.4%) vs 9 of 79 patients without HS (11.3%), p=0.041] (Table 1). The number of patients who died was higher in the HS group but this difference was not statistically significant (15;53.6% vs 38;48.1%, p=0.659).

When patients were grouped as premenopausal and postmenopausal, the occurrence of hepatic metastases at diagnosis and during follow-up in the premenopausal group was more common in patients with HS (p<0.001 and p=0.004, respectively; Table 2), whereas the rates of hepatic metastases at diagnosis and during follow-up in the postmenopausal group were similar in patients with and without HS (p=0.655 and p=0.656, respectively; Table 2). The number of patients who died was similar in pre- and postmenopausal patients, regardless of HS status (Table 2).

When patients were evaluated according to obesity, both pre- and postmenopausal groups showed similar rates of hepatic metastases at diagnosis and during follow-up regardless of obesity status (p>0.05; Table 3).

Table 3. Hepatic metastasis and survival of premenopausal and postmenopausal patients as subjects with and without obesity

	Obesity (BMI>30 kg/m²)		*p value*
Premenopausal patients	*Yes (N=11) N (%)*	*No (N=42) N (%)*	
Hepatic metastasis at diagnosis	3 (27.2)	13 (30.9)	0.813
Hepatic metastasis during follow-up	0 (0.0)	6 (14.2)	0.160
Postmenopausal patients	*N=29*	*N=25*	
Hepatic metastasis at diagnosis	9 (31)	5 (20.0)	0.356
Hepatic metastasis during follow-up	6 (20.6)	3 (12.0)	0.256

BMI: body mass index

The overall survival rate was lower but not statistically significant in patients with HS than in patients without HS (median 29 months, 95% CI: 14.9–43.0 for patients with HS vs median 34 months, 95% CI: 27.2–40.7 for patients without HS, p=0.606) (Figure 1). In the pre- and postmenopausal groups, patients with and without HS had similar overall survival rates (for the premenopausal group; median 29 months, 95% CI: 24.5–33.4, in patients with HS vs median 41 months, 95% CI: 21.1–60.8 in patients without HS, p=0.386 and for the postmenopausal group; median 37 months, 95% CI: 12.0–61.9, in patients with HS vs median 32 months, 95% CI: 21.0–42.9 in patients without HS p=0.988).

Discussion

According to our results, in patients with metastatic BC the presence of HS detected by CT was significantly associated with increased risk of subsequently developing hepatic metastasis. Nevertheless, patients with and without HS had similar overall survival rates. To our knowledge, this is the first study to analyse the impact of HS among a group of patients with metastatic BC and its impact on the subsequent development of hepatic metastasis and long-term outcomes.

Obesity is considered a risk factor for the development and poor prognosis BC [1]. Obesity is also an independent prognostic factor for the risk of disease recurrence and shorter overall survival (OS) when compared with patients with normal weight [17]. The liver is a prime target of the direct pathological effects of excessive lipid storage in obesity and 70-80% of obese patients (BMI ≥ 30 kg/m²) have increased liver fat content, according to imaging data and autopsy records [18]. HS is significantly associated with diabetes as well as with insulin resistance and hyperinsulinaemia, even in patients with normal glucose tolerance [19]. In our study, HS was significantly associated with higher BMI and the presence of obesity (p=0.005 and p=0.012, respectively).

Cancer cell metastasis is a multistep phenomenon. The first step is an attack by the cancer cells on the vasculature, migration through the bloodstream and evasion from the primary site. Further sequential steps are invasion of the target organ by attachment to the vasculature, followed by growth in the metastatic organ. We hypothesise

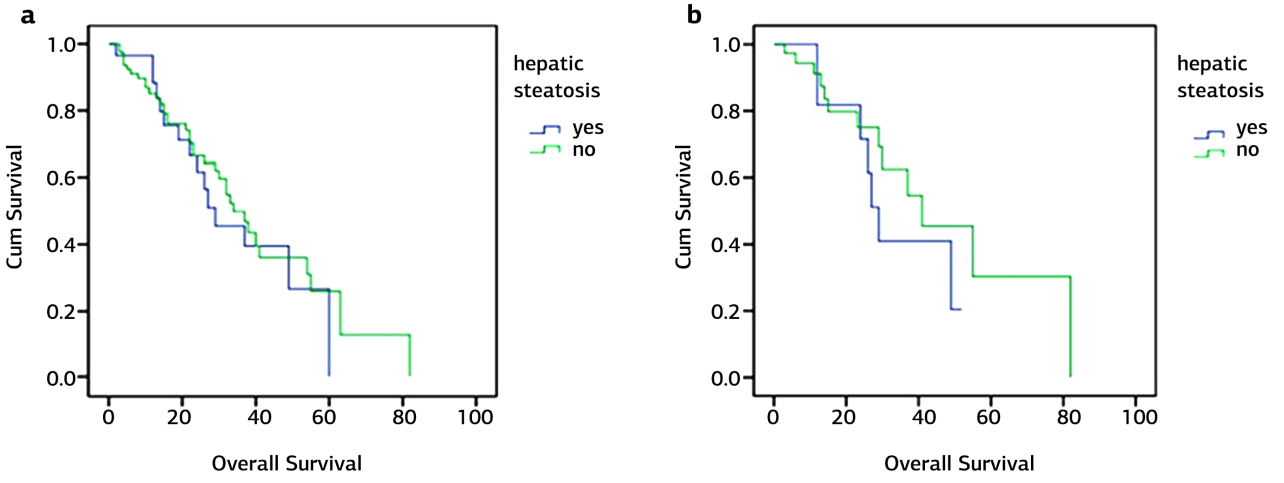

Figure 1. Overall survival rates. **a:** for both groups (median 29 months, 95% CI: 14.9-43.0 for patients with HS vs median 34 months, 95% CI: 27.2-40.7 for patients without HS; p=0.606). **b:** for premenopausal patients (median 29 months, 95% CI: 24.5-33.4 for patients with HS vs median 41 months, 95% CI: 21.1-60.8 for patients without HS; p=0.386).

that the metabolic disorders associated with HS can contribute to metastasis of cancer cells to the liver, especially in the last step, during and after the invasion of the liver.

HS is apparently benign and non-progressive but approximately 20% of all cases feature hepatocellular injury, inflammation and a variable degree of fibrosis [20,21]. HS is commonly encountered in many cancer patients, especially in BC patients, in clinical oncology practice [8]. HS is therefore likely a hepatic manifestation of metabolic syndrome and insulin resistance plays an important role in the pathogenesis of HS [22].

A number of molecular mechanisms have been linked to steatosis that may accelerate the development of hepatic metastasis from BC, such as adipose-derived inflammation, lipid accumulation and lipotoxicity, fibrosis and insulin resistance. HS is associated with adipocytokine metabolism disorders and increased adipose tissue in the liver can contribute to augmented secretion of proinflammatory adipokines [23]. The levels of adiponectin (a major adipokine with potent anti-inflammatory, antiangiogenic and tumor growth-limiting properties) were decreased, while those of leptin (a major adipokine with pro-inflammatory and profibrogenic effects) were increased in patients with HS; leptin has also been linked to HS progression [24,25].

Adiponectin and leptin secreted by adipocytes may therefore play an important role in the relationship between HS and liver metastasis of BC. In addition, chronic inflammation due to adipose tissue remodelling and pro-inflammatory adipokine secretion accompanies obesity and may play a role in the pathophysiology of hepatic metastasis from BC by inducing irregular inflammatory pathways, cell proliferation, apoptosis and metastasis [26,27]. Other mechanisms that may affect the relationship between HS and BC liver metastasis are ectopic lipid accumulation, lipotoxicity and insulin resistance, leading to increased levels of insulin and insulin-like growth factors (IGF).

Ectopic lipid accumulation is directly associated with lipotoxicity, defined as chronic cellular dysfunction [28]. Lipid accumulation and fibrosis in the liver give rise to a favorable microenvironment for the invasion and growth of metastatic tumor cells. Direct toxic effects of fatty acids and inflammation associated with obesity may cause multiple defects in this signalling network and lead to insulin resistance [29]. Lipid accumulation in the liver may directly worsen hepatic insulin resistance, creating an important feed-forward loop in this primary process.

Production of IGF-binding protein, stimulated by prolonged hyperinsulinemia, increases the production and bioavailability of IGF1 and IGF2 [30]. High insulin and IGF levels may promote the development of primary and metastatic liver cancer by activating various oncogenic pathways [31]. These mechanisms, in synergy with those occurring in the liver, may accelerate BC metastasis to the liver.

The association between BMI or obesity and prognosis of metastatic BC is is still controversial. Gennari et al. reported that BMI was not associated with the outcome of patients with metastatic BC treated with first-line chemotherapy [32]. However, several investigators reported that obesity is independently associated with poorer outcomes in premenopausal and postmenopausal women with BC [33-35]. The adverse effect of obesity was apparently independent of menopausal status and appears to be due to the effects of obesity on increased production of oestrogen and insulin activation of tyrosine kinase growth factor pathways [36]. We did not find a relationship between the presence of obesity and hepatic metastases at diagnosis and during follow-up in either premenopausal or postmenopausal women (Table 3). This result may be due to the small number of patients in our study.

Murono et al. investigated the association between HS and the incidence of liver metastasis from colorectal cancer (CRC) using CT scans [37]. They reported that patients with HS tended to have a lower incidence of synchronous metastasis in the liver. They hypothesised that steatosis may possibly create an unfavorable microenvironment for metastatic formation in the liver. They also suggested that fibrotic changes in the liver are associated with the loss of the protective effect of HS on liver metastasis formation. In fact, this mechanism proposed by Murono et al. supports the accuracy of our findings. The effect of hepatic steatosis that begins with liver cell lubrication facilitates hepatic metastases via influences on the liver tissue microenvironment (such as adipose-derived inflammation, lipotoxicity, fibrosis and insulin resistance).

Our results support the idea of HS as a predisposing factor for development of hepatic metastasis in patients with BC, especially in premenopausal women. Our findings also suggest that, during the follow-up period, patients with BC, and especially premenopausal women, should be more closely monitored if they have HS.

Although US is more widely used than CT in routine clinical practice for detecting HS and hepatic metastasis because of its lower economic and biological cost, CT is a more sensitive modality for detecting steatosis. Compared to the conventional US, CT also has a specific standardisation and is not as subjective a measurement as US [38]. Therefore, in our study, we included only patients that were assessed by CT for HS and metastasis

This study has a number of limitations. 1) The cross-sectional and retrospective study design precluded any specific conclusions regarding a causal relationship between HS and BC. 2) The study population came from a single centre and multi-center research is needed. 3) The determination of steatosis and metastasis was made by a single radiologist.

Conclusion

Metabolic syndrome and obesity are considered as risk factors for the development and poor prognosis BC [1]. We concluded that HS, diagnosed by CT, is an effective prognostic indicator for the risk of hepatic metastasis in patients with BC and this may be the underlying mechanism of poor prognosis. Further histological studies using liver biopsy specimens would be helpful to confirm the changes in the liver tissue responsible for the predisposition of liver metastasis.

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