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How Reliable Is Ultrasound for Detection and Follow Up on Breast Cancer Liver Metastases?

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Abstract

BACKGROUND: To find out whether and to what extent the two diagnostic methods are necessary – both the computed tomography and the ultrasound for diagnosis and staging at the same time on breast cancer liver metastases.

AIM: In order to protect patients from unnecessary CT ionizing radiation, we compared the level of agreement of two methods: ultrasound and computed tomography.

METHODS: We analyzed 41 patients with diagnosed breast cancer and synchronous liver metastases.

RESULTS: There is a poor level of agreement between the ultrasound and computed tomography in the arterial and portal phase in terms of showing hepatic metastases in primary breast cancers. The individual kappa values calculated for each category individually, show that the two methods agree best in detecting ring changes (0.573) and do not agree at all in detecting hyper lesions.

CONCLUSION: Only ultrasound is sufficient in the diagnosis and monitoring of annular hepatic metastases, because it best agrees with computed tomography in the arterial and venous phase, while computed tomography is the only method of choice for hyperechoic metastases. When it comes to hypoechoic metastases the computed tomography remains the gold standard for diagnosis in our institution.

Introduction

As the most prevalent cancer diagnosed worldwide (an estimated 2.3 million cases were documented in 2022), the breast cancer is the primary cause of cancer death for women and poses a serious threat to global health. Despite being traditionally thought of as a disease primarily affecting industrialized nations, in 2020 the world's less developed regions accounted for two-thirds of breast cancer-related fatalities and over half of all diagnoses [1].

In industrialized countries, mortality rates are gradually declining due to advances in medication and earlier detection, even with the high incidence rate [1].

However, 10% of women still receive a diagnosis of primary diffuse breast cancer, and only 25% of these patients survive for five years [2].

Approximately 25% of all new malignancies found in the female population in the near future are predicted to be breast cancers [3].

It is the development of metastases in breast cancer, not the primary tumour, that is responsible for more than 90% of cancer deaths.

Recent research indicates that up to 60–75% of patients with metastatic breast cancer will have bone metastases, 32–37% will develop lung metastases, 32–35% will develop liver metastases, and up to 10% will develop brain metastases [4], [5]. Metastases to the adrenal glands are uncommon, while the frequency of metastases to the gastrointestinal system in breast cancer ranges from 4% to 8% [6].

Certain risk variables, like the degree of lymph node involvement and tumor size, may have an impact on the course of metastasis and the prognosis for survival. Furthermore, in the context of clinical practice, the molecular / histopathological subtype of the tumor provides an approximate indication of the likelihood of metastasis to particular target organs.

Nevertheless, none of these variables

adequately enables us to anticipate the precise locations or patterns of metastasis that are distinctive to each tumor. A framework has been put forward that the primary tumor may provide insight about the organ in which metastases may ultimately form. This could significantly affect each patient's treatment and screening plans starting with their initial diagnosis.

While there is a documented "statistical" association between organotropism of breast cancer metastasis and its outcome [4], this process is still completely unknown, and as of right now, there is no diagnostic tool that can reliably forecast the risk and target organ for each individual patient's tumor.

The early detection of liver metastases is crucial for attaining cancer control [7]. This is due to the fact that, although surgical resection is the main treatment for limited synchronous or metachronous liver metastases, other options include preoperative chemotherapy, irradiation, and new ablation techniques [8]. The treatment of liver metastases increases the disease free time and improves the overall survival.

The literature reports that the sensitivity of ultrasonography for metastatic identification is inconsistent and low, ranging from 50% to 76% [7]. It is commonly known that the accuracy of US depends on the patient as well as the operator, and that the patient's habits (body mass index and fat), intestinal gas, and operator experience all affect the technique's accuracy. The primary weakness of US, though, is the poor contrast between liver lesions and the liver parenchyma in imaging exams. Specifically, hyperechoic metastases are challenging to distinguish from hemangiomas, and isoechoic metastases are typically hard to find because they have an acoustic impedance equal to the surrounding parenchyma.

As a separate group of hepatic metastases, those with a peripheral halo – target/bulls eye appearance are also included [9]. It is this wide range of appearance that sometimes makes it difficult to differentiate between benign and malignant lesions, thereby reducing the specificity of ultrasound.

In addition to providing volumetric acquisition with excellent multiplanar reformatted pictures, liver volume calculation, and 3D reconstructions for preoperative tumor resection planning, multidetector CT is a dependable method for identifying liver metastases and preoperative staging [10]. It’s fast and accessible, provides comprehensive coverage of the chest and abdomen, high-quality liver imaging and shows extrahepatic disease.[11] For the detection of liver metastases, CT has a 77.3% specificity and a 73.5% sensitivity [12].

On unenhanced CT, liver metastases typically show up as hypo- or iso-dense nodules. Depending on their size, these nodules might vary from being well-defined to being irregular [13]. There could be cystic change and necrosis, which would show up as a core region of low attenuation. Furthermore, because of their hemorrhagic composition, liver metastases can exhibit considerable attenuation as well [14].

Dynamic imaging is important, and both CT and MRI share a comparable concept, perception, and evaluation of it. The majority of liver metastases have low blood flow, and they are most easily identified in the portal venous phase. During this stage, the portal vein serves as the primary blood supply, enhancing the liver parenchyma. When compared to the background liver parenchyma, hypovascular metastases show up as hypodense or hypoattenuating lesions [15]. In the late arterial phase, they typically exhibit a peripheral rim enhancement that centrally disappears in the venous phase (also known as the "target appearance") [16]. Conversely, hypervascular metastases appear sooner in the LAP as seen by the portal vein's contrast and the hepatic veins' absence. These lesions can display varying degrees of washout in the PVP and delayed acquisitions, or they may diminish and become isodense with the remaining liver parenchyma [17].

Materials and methods

In order to find out whether and to what extent the two diagnostic methods are necessary – both the computed tomography and the ultrasound for diagnosis and staging at the same time, we conducted research in the Shtip Clinical Hospital, at the Department of Radiology, which included a total of 41 patients with diagnosed breast cancer and synchronous liver metastases.

Table 1: General characteristics

Breast cancer	
Variable	n (%)
Age	
40 – 49	7 (17.07)
50 – 59	9 (21.95)
60 – 69	18 (43.90)
70 – 79	7 (17.07)
Pathohistological type	
Ductal	41(100)
Tumor localization	
Left breast	21(51.22)
Right breast	20(48.78)
Degree of differentiation	
Moderately differentiated	20(48.78)
Poorly differentiated	21(51.22)
Ki67	
>15%	11(45.83)
<15%	13(54.17)
Lung metastases	15(36.58)
Bone metastases	17(41.46)
Deceased	5(12.19)

The patients were mostly aged 60-69 years - 18 (43.90%). All of them had pathohistologically proven ductal carcinoma, with localization on the left breast in 21 (51.22%) and on the right breast in 20 (48.78%) patients. Regarding the degree of differentiation, carcinomas were more often poorly differentiated - 21 (51.22%). The Ki67 index was determined in 24 (58.54%) patients, and more often it had a value of up to 15% - 13 (54.17%). Lung metastases were observed in 15 (36.58%) patients and 17 (41.46%) patients had bone metastases. 5 patients died, that is, the mortality rate in this group of 41 patients with metastatic liver disease and primary breast cancer was 12.19% (Table 1).

Results and Discussion

The ultrasound examination of secondary deposits of liver in patients with breast cancer, in terms of echogenicity, it mostly presented hypoechoic lesions - 19 (46.34%), followed by annular (bull eye), isoechoic and hyperechoic lesions – 11 (26.83%), 9 (21.95%) and 2 (4.88%), respectively (Table 2).

Table 2: Ultrasound examination of secondary deposits of liver in patients with breast cancer

Breast cancer	
Ultrasound	n (%)
Isoechoic	9 (21.95)
Hypoechoic	19 (46.34)
Hyperechoic	2 (4.88)
Annular – “bulls eye”	11 (26.83)

Breast cancer liver metastases, the CT findings in the arterial phase in 21 (51.22%) patients showed them as isodense, in 13 (31.71%) as hypodense and in 7 (17.07%) as “bulls eye”; in the portal venous phase in 37 (92.5 %) patients showed them as hypodense and in 3 (7.5%) as “bulls eye”; in the late phase in 6 (14.63%) patients it showed them as isodense and in 35 (85.37%) patients as hypodense lesions (Table 3).

Table 3: CT findings in breast cancer liver metastases

Breast cancer			
	Computed tomography		
	Arterial phase n (%)	Venous-portal phase n (%)	Late phase n (%)
Isodense	21(51.22)		6(14.63)
Hypodense	13(31.71)	37(92.5)	35(85.37)
Hyperdense			
Bull eye	7(17.07)	3(7.5)	

In the group of patients with primary breast cancer, 9 metasases were observed as isoechoic by ultrasound, of which in the arterial phase computed tomography showed 8 as isodense; out of 19 hypoechoic metastases shown by ultrasound, in the arterial phase computed tomography showed 9 as hypodense; the two hyperechoic lesions shown by ultrasound, computed tomography did not show them as hyperdense in the arterial phase; 11 ring lesions were detected by ultrasound, 6 of them by computed tomography in the arterial phase (Table 4).

Table 4: Patients with primary breast cancer in arterial phase

Breast cancer				
	Arterial phase			
Ultrasound	Isodense N	Hypodense N	Bulls eye N	Total N
Isoechoic	8	1	0	9
Hypoechoic	9	9	1	19
Hyperechoic	2	0	0	2
Bulls eye	2	3	6	11
Total	**21**	**13**	**7**	**41**

According to Fleiss' kappa value of 0.340 and 95% confidence interval (CI) of 0.333-0.347, there is a poor level of agreement between the ultrasound and computed tomography in the arterial phase in terms of showing hepatic metastases in primary breast cancers. The individual kappa values calculated for each category individually, show that the two methods agree best in detecting ring changes (0.573) and do not agree at all in detecting hyper lesions (-0.025) (Table 5).

Table 5: The level of agreement between the ultrasound and computed tomography in the arterial phase

Breast cancer						
	Kappa	Asymptotic			Asymptotic 95% Confidence Interval	
		Standard Error	Z	Sig.	Lower Bound	Upper Bound
Overall Agreement	0.340	0.107	3.165	0.002	0.333	0.347
Agreement on Individual Categories[a]						
Isoechoic	0.264	0.156	1.691	0.091	0.254	0.274
Hypoechoic	0.283	0.156	1.809	0.070	0.273	0.292
hyperechoic	-0.025	0.156	-.160	0.873	-0.035	-0.015
Bull eye	0.573	0.156	3.668	0.000	0.563	0.583

From the retrospective study of Bruneton et al., it was proven that in 70.9% of women with hepatic metastases, they were shown as hypoechoic, which proved the ultrasound to be a good method for their diagnosis [18].

The results in Table 6 show that, in the group of patients with primary breast cancer, the isoechoic and hyperechoic metastases shown by ultrasound are not seen as isodense and hyperdense by computed tomography in the venous phase; all 19 hypoechoic metastases shown by ultrasound, the computed tomography in the venous phase showed them as hypodense; out of 10 ring changes shown by ultrasound, in the venous phase computed tomography showed 3 as “bulls eye” (Table 6).

Table 6: The group of patients with primary breast cancer

Breast cancer			
	Portal phase		
Ultrasound	Hypodense N	Bull eye N	Total N
Isoechoic	9	0	9
Hypoechoic	19	0	19
Hyperechoic	2	0	2
Bulls eye	7	3	10
Total	37	3	40

According to the Fleiss' kappa value of 0.043 and 95% confidence interval (CI) of 0.036-0.05, there is a very poor level of agreement between the ultrasound findings and the CT scan in venous phase in terms of showing hepatic metastases in primary breast cancers.

The individual kappa values calculated for each category individually show that the two methods agree only in detecting ring changes (0.357) and do not agree at all in detecting iso, hypo and hyper lesions, with kappa values of -0.127, -0.071 and -0.026, respectively (Table 7).

Table 7: The individual kappa values calculated for each category

Breast cancer						
	Kappa	Asymptotic			Asymptotic 95% Confidence Interval	
		Standard Error	Z	Sig.	Lower Bound	Upper Bound
Overall Agreement	0.043	0.113	0.383	0.702	0.036	0.050
Agreement on Individual Categories[a]						
Isoechoic	-0.127	0.158	-0.802	0.423	-0.137	-0.117
Hypoechoic	-0.071	0.158	-0.452	0.651	-0.081	-0.062
Hyperechoic	-0.026	0.158	-0.162	0.871	-0.036	-0.016
Bull eye	0.357	0.158	2.258	0.024	0.347	0.367

According to a study done at the University of Michigan Hospital by Francis et al., whose purpose was to prove whether the three phases of CT are necessary to make a diagnosis, according to qualitative analyzes that were performed for 11 of 22 hypervascular tumors, the arterial phase was superior to the portal, and for 4 out of 22 the venous. Out of the 30 shown hypodense/hypovascular, 22 were shown best in the venous portal phase, and the rest were shown in the arterial phase. [19]

In the group of patients with primary breast cancer, 9 metastases were seen with ultrasound as isoechoic, of which in the late phase, computed tomography showed 5 as isodense; out of 19 hypoechoic changes shown by ultrasound, in the late phase computed tomography showed 18 as hypodense; hyperechoic and ring changes shown by ultrasound, in late phase, computed tomography showed them as hypodense (Table 8).

Table 8: The group of patients with primary breast cancer

Breast cancer			
	Computed tomography late phase		
Ultrasound	Isodense N	Hypodense N	Total N
Isoechoic	5	4	9
Hypoechoic	1	18	19
Hyperechoic	0	2	2
Bull eye	0	11	11
Total	6	35	41

According to the Fleiss' kappa value of 0.146 and 95% confidence interval (CI) of 0.139-0.153, there is a poor level of agreement between the ultrasound findings and the late-stage CT scans in terms of showing hepatic metastases in primary breast cancers. The individual kappa values calculated for each category individually show that the two methods agree best in detecting iso- lesions (0.592) and do not agree at all in detecting hyper lesions (-0.025) and ring lesions (-0.155) (Table 9).

Table 9: Hepatic metastases in primary breast cancers

Breast cancer						
	Kappa	Asymptotic			Asymptotic 95% Confidence Interval	
		Standard Error	Z	Sig.	Lower Bound	Upper Bound
Overall Agreement	0.146	.111	1.319	.187	.139	.153
Agreement on Individual Categories[a]						
Isoechoic	0.592	0.156	3.791	0.000	0.582	0.602
Hypoechoic	0.024	0.156	0.152	0.879	0.014	0.034
Hyperechoic	-0.025	0.156	-0.160	0.873	-0.035	-0.015
Bull eye	-0.155	0.156	-0.992	0.321	-0.165	-0.145

Conclusions

One of the most frequently affected organs in metastatic disease is the liver. Currently, the methods available in our hospital for evaluating therapy response and follow-up are both US and CT.

We obtained interesting data during the research regarding whether there is a need for both diagnostics to determine the presence and follow-up of liver metastases. In order to protect patients from unnecessary CT ionizing radiation, we compared the level of agreement of these two methods. Considering the obtained results, we concluded that only ultrasound is sufficient in the diagnosis and monitoring of annular hepatic metastases, because it best agrees with computed tomography in the arterial and venous phase, while computed tomography is the only method of choice for hyperechoic metastases. However, when it comes to hypoechoic or hypovascular metastases, which actually represent the largest percentage, and at the same time to avoid error or oversight in diagnosis, the computed tomography remains the gold standard for diagnosis in our institution.

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