Correlation of liver hemodynamics and tumor metabolism in liver metastases

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Purpose

Liver metastasis is a common consequence of many carcinomas and the detection of hepatic metastases is necessary for exact staging and planning of the treatment. The recent technologic improvements enabled quantitative imaging of hepatic parenchymal and tumoral blood flow. The demonstration of the altered hepatic hemodynamics during the tumoral angiogenesis within the liver metastases may subsequently indicate the presence of metastases even in the absence of manifest tumors. To assess the altered hepatic hemodynamics due to tumoral angiogenesis of liver metastasis, hepatic perfusion index (HPI) which is the ratio of the hepatic artery flow to the total liver blood (hepatic artery+portal vein) flow was first investigated by dynamic scintigraphy and found to be abnormal in 94% of colorectal cancer patients with liver metastases. Later doppler parameter index (DPI) measured by doppler US was introduced and it was postulated that even early small hepatic metastases may induce alterations of hepatic blood flow [1-4]. The advantage of DPI is an inexpensive and non invasive method, and it does not require contrast material use or ionizing radiation to investigate hemodynamic alterations of the liver [4]. The aim of this study, is to investigate hepatic perfusion changes of the patients with liver metastasis by means of DPI measurements and find out any correlation between liver hemodynamics and tumor metabolism measured by FDG-PET/CT scan and to research any complementary diagnostic or predictive role in the clinical management.
Methods and Materials

The study was approved by the Local Ethics Committee; informed written consent was obtained from all the patients. Thirty-five patients (21 male and 14 female) with hepatic metastases were included in this prospective study. Patients were selected from the FDG-PET/CT unit of our University Hospital where they were scanned for staging purpose because of their proven malignancies. Primary origin of cancers were lung cancer in 10 patients, colorectal cancer in nine patients, breast cancer in five patients, ovarian malignancy in three patients, thyroid medullary carcinoma in one patient gastric carcinoma in one patient, anal carcinoma in one patient, pancreas carcinoma in one patient and unknown in two patients. The mean patient age was 59.54 ± 11.16 (ranging 31 to 79). The patients had not clinical evidence of liver disease, cardiac dysfunction, dehydration; there was not any history of alcoholism, and intake of antihypertensive or vasoactive medication.

Control group was consisted of 31 patients (15 male and 16 female) with no evidence of any hepatic disease, cardiac dysfunction, dehydration; without history of alcoholism, and intake of antihypertensive or vasoactive medication. The mean age of the control group was 55.77 ± 12.32 (ranging 32 to 63).

FDG-PET/CT was performed using a hybrid system after i.v. injection of 5.4 MBq/Kg of FDG with a minimum 6 h fasting blood glucose level of less than 140 mg/dl. Data acquisitions were performed within 60-120 min after injection. Oral contrast was only given to the patients for the CT portion of the study. Quantification of the tumor metabolic activity was obtained using the maximum standardized uptake value (SUVmax) normalized to body weight. Pathologic 18F-FDG accumulation was identified by focal tracer uptake that exceeded that of the normal hepatic parenchyma. Diffuse hepatic metastases were assessed based on increased glucose metabolism as heterogeneous with an SUV exceeding 3.5.

Patients who were detected metastasis in the liver were examined by CDUS. Interval between FDG-PET/CT and CDUS was 1-2 days. CDUS examination were performed by the same experienced radiologist, in the light of the FDG-PET/CT result. Following 8 h of starving the patients proper hepatic artery (PHA) and portal vein (PV) were identified. Spectral analysis was determined based on the technique described in the previous studies [1-4]. The measurements were recorded electronically. Total liver blood flow was (TLBF) the sum of the volume flow of the PHA (PHAF) and volume flow of the PV (PVF). Accordingly DPI was calculated by the formula: DPI = PHAF / (PHAF + PVF) (Figures 1-6).

The liver was scanned with gray-scale US to reveal the metastatic lesions seen at FDG-PET/CT images. Their detectibility via gray scale US was noted.

FDG-PET/CT scans of the patients were correlated with US findings. The size and the number of the metastases, SUV max of the masses, SUV max of the normal liver
parenchyme, the presence of additional metastases (lymph node, lung, brain, bone) were recorded.

Independent two-sample t-test for comparisons of two groups of more than two for groups comparisons analysis of variance (ANOVA). Linear regression analysis was used to assess the statistical correlations between parameters. For all statistical tests, the level of significance was accepted at p<.05.
**Fig. 1:** 56 years-old male patient with lung cancer. Multiple hepatic metastasis are seen on PET/CT scan

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**Fig. 3:** The metastases are not obvious on gray scale US.

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Fig. 4: The blood flow of the proper hepatic artery is not too high

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Fig. 5: The measurement of the proper hepatic artery in a Hodgkin lymphoma patient.

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Fig. 6: The measurement of the portal vein in the same patient. Flow of the portal vein is increased.

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Results

The overall hepatic blood flow of the liver was higher in hepatic metastases than control group, but predominantly PHAF was increased resulting by the higher levels of DPI (Table 1).

Table 1: Comparison of the patients with and without liver metastasis by means of liver blood flow measurements.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PHAF (mL/min)</th>
<th>PVF (mL/min)</th>
<th>TLBF (mL/min)</th>
<th>DPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>142.06 ± 120.75</td>
<td>± 883.26</td>
<td>± 1025.3 ± 672</td>
<td>0.17 ± .11</td>
</tr>
<tr>
<td>Controls</td>
<td>57.45 ± 29.5</td>
<td>564.0 ± 466.4</td>
<td>622.4 ± 9</td>
<td>0.12 ± .02</td>
</tr>
<tr>
<td>P</td>
<td>0</td>
<td>.02</td>
<td>.008</td>
<td>.025</td>
</tr>
</tbody>
</table>

PHAF was highly correlated with the liver SUV and SUV max of the metastases \((r=.774, p=0\) and \(r=.36; p=.003\) respectively). No correlation was found between DPI and SUV max of the metastatic lesions \((r=.322; p=.059)\) and between PVF and SUV max of the masses \((r=0.5, p=.692)\).

Furthermore, the patients were also grouped as the follows: Patients with single metastasis, patients with 2-5 metastasis; more than 5 metastases and diffuse metastases. The groups were compared in terms of liver SUV and SUV max of the masses, PHAF, PVF and DPI. Only PHAF was significantly higher in diffuse metastases \((p=0)\) (Table 2).

Table 2. Comparison of liver SUV, SUV max, DPI and PHAF measurements according to the number of the metastases.

<table>
<thead>
<tr>
<th>Number of metastase</th>
<th>Liver SUV (Mean ± SD)</th>
<th>Liver SUV max (Mean ± SD)</th>
<th>DPI</th>
<th>PHAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n=10)</td>
<td>2.68 ± .45</td>
<td>6.33 ± 3.2</td>
<td>0.61±0.15</td>
<td>92.50±40.65</td>
</tr>
<tr>
<td>2-5 (n=6)</td>
<td>2.7 ± .73</td>
<td>11.28 ± 3.8</td>
<td>0.70±0.07</td>
<td>123.50±64.308</td>
</tr>
<tr>
<td>#5 (n=16)</td>
<td>2.58 ± .61</td>
<td>9.7 ± 6.4</td>
<td>0.72±0.13</td>
<td>115.37±58.98</td>
</tr>
<tr>
<td>Diffuse (n=3)</td>
<td>6.23 ± .9</td>
<td>9.8 ± 2.3</td>
<td>0.94±0.15</td>
<td>486.67±83.03</td>
</tr>
<tr>
<td>p*</td>
<td>.031</td>
<td>.06</td>
<td>.645</td>
<td>0</td>
</tr>
</tbody>
</table>
Furthermore patients with hepatic metastases, were also grouped by terms of maximum diameter of dominant mass as the follows: Maximum diameter < 1cm (n=7 patients); 1-3 cm (n=15); and >3 cm (n=13), Subsequently, DPI was not statistically different between these groups (p=.132).

In 10 patients, liver metastases were not detectable on US, whereas in 25 patients the metastases were visible. DPI and TLBF were not statistically different between detectable and undetectable lesions (p=.089 and p=.43 respectively) but both were significantly higher than the control group (p=0 and p=0.08 respectively).

Liver SUV, SUV max, DPI and PHAF measurements were compared according to the presence of extrametastases and the visibility by gray-scale US. Liver SUV, SUV max, PHAF and DPI values were not significantly different in patients without extrametastases (n=23) and with extrametastases (n=12) (p#.05).

Liver SUV, SUV max, PHAF and DPI values were not significantly different in the patient group whose metastases were visible on gray-scale US (n=25) and occult metastases (n=10) (p#.05).
Conclusion

As we expected PHAF was strongly correlated with the liver SUV; and mildly correlated with the SUV max of the metastases. But it should be remembered that flow of the hepatic artery could be strongly depended on cardiac output of the patient.

Previous studies [1-7] revealed that liver metastases cause an increase in the hepatic artery blood flow and decrease in the portal vein blood flow and resulting an increase of DPI in patients with colorectal cancer. Accordingly DPI value of the liver with metastases was found >0.3-0.5 [1,7,8]; benign diseases had DPI value <0.15. We revealed an increase in hepatic artery blood flow but contrary to the literature, portal blood flow was also increased. Since increase in hepatic artery blood flow was more prominent than the portal blood flow, DPI is increased but not enough to make a clear cutoff value for the exact differentiatnion of metastases from control group. This discordance would probably result from the heterogenous nature of liver metastases of our study; or the increase of both vascular supply system of the liver, which may be the result of increased metabolic needs of the metastases. The arterial and venous supplies to the liver are not independent systems; there can be several communications between vessels, including transsinusoidal, vasal, tumoral and plexal-peribiliary routes. However in the previous literature, DPI was mainly studied in colorectal cancer metastases, which are known as hypovascular; so that is to say no relationship between vascularity and glucose metabolism [9]. Liver size is certainly an important factor influencing on portal blood flow; unfortunately we did not investigate hepatomegaly and portal venous flow per liver volume in our study group. It is reasonable to hypothesise that the metabolic requirements of tumors reflects by changes in tumor hemodynamics. However the relationship between tumoral blood flow and metabolism is not always parallel. Incongruity of tumor perfusion and metabolism has been noted in previous studies investigating the relationship between perfusion and metabolism of tumors [9]. One should suggest that the heterogeneity of our study cases contribute discongruence of the liver SUV and liver blood flow but previous studies comparing FDG-PET/CT and dynamic perfusion CT have shown the variance in the relationship between tumoral blood flow and metabolism even in a single tumor type. The balance between liver blood flow and metabolism would play an important sign of the biological behavior of the metastases. Poor vascularity and increased glucose metabolism may lead to hypoxia which should make a contribution to resistance to radiotherapy or chemotherapy [9]. PHAF and DPI could be used for the assessment of response to therapy based on the antiangiogenic therapies in clinical practice.

Our study reveals high correlation between the hepatic arterial blood flow and the metabolic needs in molecular level. Beyond debate, dynamic CT or MRI, CT portography and FDG-PET/CT scan are the most accurate imaging tool to determine liver metastases as well as displaying extrametastases to stage or re-stage malignancies during the therapeutic period. FDG-PET/CT scan allows imaging of glucose metabolism; it can lead
to early detection of the tumor by detecting abnormal tumor metabolism prior to the appearance of anatomic changes and localization of tumor. Changing of regional blood flow in various anatomic structures (as a measure of the injected positron emitter) can be visualized and relatively quantified with a PET scan. Meta-analyses of non-invasive imaging methods for detection of hepatic metastases from gastrointestinal tract cancers reported higher sensitivity of FDG-PET/CT scan compared to the other imaging methods [10]. However all these methods are expensive, requiring contrast material and including ionizing radiation; when high possibility of the need of re-scanning of these patients is considered these imaging modalities cannot be used in all patients. DPI or PHAF levels could be a predictor to select the patients underwent to further imaging methods. There was only in 7 patients DPI>0.25 corresponded pathologic SUV values of the liver in the study. Although liver vascular supply increases predominantly by the hepatic artery, the relative arterial and portal blood flow supply may not be so critical in the diagnosis of liver metastases. Higher PHAF can predict the liver SUV and the cutoff PHAF values to predict liver SUV would be determined in further studies. Additionally increased PHAF could predict diffuse liver metastases which are indistinguishable on conventional scanning techniques. Because PET scans are more expensive than CT and MRI; FDG-PET/CT scan in cost-constrained health services will depend on proper health technology assessment. The development of new treatment strategies changed the therapeutic approaches for treating focal liver malignancies.

As a conclusion, multimodality imaging studies of perfusion and metabolism of the tumors has an increasing role in oncologic patients. Measurements of liver blood flow by doppler US is easy, repeatable, cheap, radiation or nephrotoxic contrast agent safe and should be added to standart follow-up protocol of oncology patients. It could be used to select patients for further imaging modalities and follow-up the response after systemic and local therapeutic procedures. To avoid erroneous measurements, proper hepatic artery, the principle artery of the liver should be imaged and less anatomical arterial variations would be the case.
References


