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Hepatopulmonary shunting in patients with primary and secondary liver tumors scheduled for radioembolization

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ABSTRACT

Purpose: In patients undergoing transarterial radioembolization (RE) of malignant liver tumors, hepatopulmonary shunts (HPS) can lead to nontarget irradiation of the lungs. This study aims at analyzing the HPS fraction in relation to liver volume, tumor volume, tumor-to-liver volume ratio, tumor vascularity, type of tumor, and portal vein occlusion.
Materials and methods: In the presented retrospective study the percentage HPS fraction was calculated from SPECT/CT after infusion of Tc-99m macroaggregated albumin (Tc-99m MAA) into the proper hepatic artery of 233 patients evaluated for RE.
Results: HPS fractions correlate very weakly with liver volume ($r = 0.303$), tumor volume ($r = 0.345$), and tumor-to-liver volume ratio ($r = 0.340$). Tumors with strong contrast enhancement ($HPS_{median(range)} = 11.7\%(46.3\%)$; $n = 73$) have significantly larger shunt fractions than tumors with little enhancement (HPS = 8.3%(16.4%); $n = 61$; $p < 0.001$). Colorectal cancer metastases (HPS = 10.6%(28.6%); $n = 68$) and hepatocellular cancers (HPS = 11.7%(39.4%); $n = 63$) have significantly larger HPS fractions than metastases from breast cancer (HPS = 7.4%(16.7%); $n = 40$; $p = 0.012$ and $p = 0.001$). Patients with compression (HPS = 13.9%(43.7%); $n = 33$) or tumor thrombosis (HPS = 15.8% (31.2%); $n = 33$) of a major portal vein branch have significantly higher degrees of shunting than patients with normal portal vein perfusion (HPS = 8.1% (47.0%); $n = 167$; both $p < 0.001$). The shunt fraction is largest in patients with HCC and thrombosis or occlusion of a major portal vein branch (HPS = 16.6% (31.0%); $n = 32$).
Conclusion: The degree of hepatopulmonary shunting depends on the type of liver tumor, tumor vascularity, and portal vein perfusion. There is little to no correlation of HPS with liver volume, tumor volume, or tumor-to-liver volume ratio.

1. Introduction

Radioembolization (RE) of liver tumors is performed using yttrium-90-loaded microspheres semiselectively injected through a catheter placed in a hepatic artery. A few weeks to a few days before the radioactive microspheres are injected, a patient scheduled for this procedure needs to have an angiographic evaluation with coil and/or plug embolization of any hepatoenteral and hepatopancreatic branches and determination of the hepatopulmonary shunt (HPS) fraction [1]. Branches not supplying the liver need to be occluded before RE to prevent microsphere migration and complications such as radiation ulcer [2]. The HPS fraction is estimated from a scintigram obtained after administration of technetium-99m macroaggregated albumin (Tc-99m MAA) into hepatic arteries. It is calculated as the pulmonary proportion of the total Tc-99m MAA signals from the lungs and liver. Both manufacturers currently offering RE microspheres – Sirtex Medical (Lane Cove, Australia) and BTG (London, United Kingdom) – consider the HPS fraction calculated from Tc-99m MAA scintigrams to accurately predict pulmonary shunting of their microspheres [3,4]. A higher HPS fraction results in more excessive nontarget irradiation of the lung after RE and increases the risk of inducing radiation pneumonitis, pulmonary fibrosis, and pulmonary hypertension [5,6]. Sirtex Medical considers RE to be contraindicated when pulmonary

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shunting exceeds 20% and recommends to reduce total activity by administering a smaller amount of microspheres in patients with a HPS of 11–20% [3]. When microspheres from BTG are used, the pulmonary fraction is incorporated in the equation for calculating the activity to be applied in a patient. BTG considers RE to be contraindicated when pulmonary shunting results in a calculated lung activity of 610 MBq (approx. 30 Gy single lung dose) [4]. An elevated pulmonary shunt fraction leads to exclusion of approx. 5–14% of patients evaluated for RE [7,8]. The aim of the present study was to investigate various parameters including liver volume, tumor volume, tumor vascularity, tumor entity, and portal vein occlusion (PVO) by compression or thrombosis determined by computed tomography (CT) in terms of their predictive value for pulmonary shunting in 233 patients scheduled for RE.

2. Materials and methods

2.1. Patients

The study included all patients who were evaluated for RE and underwent whole-liver angiography in our department between 2009 and 2013. Patients with a history of hemihepatectomy of any kind and Patients with hepatic arterial supply other than Michels' type I, IX or X were excluded [9]. A total of 233 patients were analyzed. Approval for this retrospective analysis was obtained from the local ethics committee (ref No. EA1-273-12).

2.2. Computed tomography, volumetry, arterial-phase contrast enhancement, and portal vein occlusion

All patients underwent three-phase computed tomography (CT) of the liver a few days before angiographic evaluation. Liver CT examinations were performed on a GE VCT 64 scanner (General Electric, Fairfield, Connecticut, USA) after IV injection of 120 ml of contrast medium (Xenetix 350, Guerbet, Villepinte, France). The arterial-phase scan was triggered with a 5 s delay after a threshold of 250 HU was observed at the level of the upper abdominal aorta. The portal venous and venous phases were triggered with delays of 35 s and 75 s, respectively. CT was performed with the following parameters: 0.9 pitch factor, 0.5 s rotation time, 0.6 mm slice thickness, 120 pKV tube voltage, and tube current according to Care dose. Liver and tumor volumes were calculated from venous-phase CT scans (5 mm slice thickness) using the BrachyVision™, version 10.0, software tool (Varian Medical Systems, Palo Alto, CA, USA). Volumetry was performed by three interventional radiologists with more than 5 years of experience in RE. Classification of liver tumors according to arterial-phase enhancement was done using arterial-phase CT images. All patients were assigned to one of three categories (no or little enhancement, moderate enhancement, and strong enhancement). Two fully trained radiologists with several years of experience in abdominal CT imaging working in consensus assessed enhancement using Visage 7.1 (Visage Imaging GmbH, Berlin, Germany) as PACS system. Portal vein occlusion (PVO) was identified and classified by underlying cause (external compression of major portal vein branch by tumor or intraluminal presence of tumor or thrombus in major branch) using arterial-, portal-venous-, and venous-phase CT images. Major portal vein branches were the first-order branches of the portal vein. Two fully trained radiologists with several years of experience in abdominal CT imaging working in consensus performed the assessment using Visage 7.1 as PACS system.

2.3. Angiographic evaluation and SPECT/CT

Two to four weeks before radioembolization treatment, candidates were evaluated by angiography, performed on a flat-panel angiography system (Allura XPER FD20, Philips, Best, Netherlands), using a transfemoral access. This angiography included coil and/or plug embolization of gastric (e.g., right hepatic artery) and gastroenteral (e.g., gastroduodenal artery) anastomoses and subsequent catheter-based administration of Tc-99m MAA (Draximage® MAA, Jubilant Draximage Inc., Kirkland, Canada) with an activity of 150–175 MBq into the proper hepatic artery. Thereafter, a whole-body SPECT/CT examination (Symbia T6, Siemens, Munich, Germany) was performed. Regions of interest (ROI) were placed in the lungs and the liver, and the HPS fraction was calculated dividing the total lung counts by the sum of the lung and liver counts.

Table 1
Patient characteristics.

	n [%]	Median [age]	Range [years]
Total	233/100%	64	60
Female	110/47.2%	59	50
Male	123/52.8%	66	60
Volume		Median [ml]	Range [ml]
Liver		1943	5761
Tumor		277	3650
Ratio		Median	Range
V_{tumor}/V_{liver}		0.144	0.733
Tumorentity		*n*	%
mCRC		68	29.2
HCC		63	27.0
mBC		40	17.2
CCC		15	6.4
mPCA		11	4.7
mNET		10	4.3
mSCA		5	2.1
Other		≤2	9.1
Total		233	100

V: volume; mCRC: metastatic colorectal cancer; HCC: hepatic cell carcinoma; mBC: metastatic breast cancer; CCC: cholangio cell carcinoma; mPCA: metastatic pancreatic cancer; mNET: metastatic neuroendocrine tumor; mSCA: metastatic stomach cancer.

2.4. Statistical analysis

Results are presented either descriptively, providing absolute numbers (*n*) and percentages of the total population (%) or, when nonnormal distribution was assumed, providing parameters of nonparametric statistics (median and range) (Table 1). Correlations presented in Fig. 1 and Table 2 were calculated according to Pearson (r = Pearson product–moment correlation coefficient; r^2 = coefficient of determination). The boxplots present medians and first/third quartiles, with the whiskers indicating the minimum and maximum within 1.5-fold interquartile ranges and the circles representing outliers (Tukey boxplot). The null hypotheses (Figs. 3, 4 and 7) were assessed with the Kruskal–Wallis test. When the null hypothesis was rejected ($p \leq 0.05$), this was followed by pairwise testing with the Mann–Whitney *U*-test. The groups in Fig. 3 were additionally analyzed for a trend of increase going from low to high arterial enhancement using the Jonckheere-Terpstra test. In Figs. 5 and 8, the Mann–Whitney *U*-test was applied directly. Statistically significant differences were assumed for $p \leq 0.05$. All data analyses were performed using SPSS 22 (IBM Corporation, NY, USA).

3. Results

The patient characteristics are summarized in Table 1. There was wide scatter of liver sizes, tumor volumes, and tumor-to-liver volume ratios. The three most common liver tumors treated in our patient population were (in decreasing order): colorectal cancer