High Lung Shunt Fraction in Colorectal Liver Tumors Is Associated with Distant Metastasis and Decreased Survival

Amy R. Deipolyi, MD, PhD, A. John Iafrate, MD, PhD, Andrew X. Zhu, MD, PhD, Emel A. Ergul, MA, Suvranu Ganguli, MD, and Rahmi Oklu, MD, PhD

ABSTRACT

Purpose: To assess how intratumoral shunting relates to liver metastasis and to clinical outcome.

Materials and Methods: Lung shunt fraction (LSF) was calculated from macroaggregated albumin scan after transcatheter injection of radioactive particles in 62 patients with colorectal cancer and liver metastases evaluated for selective internal radiation therapy (SIRT) from May 2007 to August 2012. Assessment was performed of how LSF, liver tumor burden, and systemic chemotherapy relate to survival and the presence of lung metastases. LSF and tumor burden were also assessed in a subset of patients who underwent genetic profiling with SNaPshot analysis.

Results: Patients with higher LSF were more likely to have lung metastases and decreased survival, whereas tumor burden was not associated with these outcomes. Patients with genetic mutations had significantly higher LSF than patients with no mutations. Patients who received chemotherapy before SIRT and had low LSF had the longest survival after SIRT.

Conclusions: LSF may be a more robust marker of metastasis than tumor size. Increased LSF secondary to vascular shunting within liver metastasis is an indicator of distant lesions and is associated with decreased survival after SIRT. Intratumoral shunting may provide a conduit for circulating tumor cells to access more remote organs, bypassing filtration by liver parenchyma, and may be an important factor in metastasis from colorectal cancer.

ABBREVIATIONS

LSF = lung shunt fraction, SIRT = selective internal radiation therapy

The mechanisms underlying metastasis of colorectal carcinoma and associated genetic mutations are poorly understood (1–3). Primary tumors shed circulating tumor cells typically 20–30 μm in diameter (4). It is unclear how these large cells traverse capillary beds 8–10 μm in diameter to establish distant lesions. One possibility is that intratumoral vascular shunting provides a conduit for circulating tumor cells to access distant sites (1). Arteriovenous shunt formation within tumors could allow these cells to bypass capillaries. For example, circulating tumor cells emerging from colorectal cancer could form lung metastases by bypassing normal hepatic capillary beds through shunts within hepatic metastases.

Endovascular hepatic arterial procedures have shown that intratumoral vascular shunting is common (5,6). Assessment of the degree of arteriovenous shunting in liver tumors is required before selective internal radiation therapy (SIRT) (7). After transarterial injection of technetium-99m-labeled macroaggregated albumin particles measuring 30–150 μm in the left or right hepatic artery, the fraction of radioactivity detected in the lungs is calculated and expressed as the lung shunt fraction (LSF) (7). Representing the extent of intratumoral shunting within liver lesions, LSF determines the radiation dose that may be safely administered without causing radiation pneumonitis.

To determine whether intratumoral shunting is associated with metastasis, the relationship of tumor shunting

From the Divisions of Interventional Radiology (A.R.D., E.A.E., S.G., R.O.), Molecular Pathology (A.J.I.), and Hematology/Oncology, Center for Liver Cancer (A.X.Z.), Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, 290 Gray/Bigelow, Boston, MA 02114. Received April 21, 2014; final revision received June 22, 2014; accepted June 23, 2014. **Address correspondence to** R.O.; E-mail: roklu@mgh.harvard.edu

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to the presence of disseminated disease and clinical outcome in colorectal cancer was assessed. Specifically, how LSF, compared with liver tumor burden, related to the presence of distant metastases in the lungs and to overall survival was characterized. The association of genetic mutations with shunting and metastasis was analyzed. Additionally, how the use of chemotherapy impacted the degree of intratumoral shunting was studied.

MATERIALS AND METHODS

All patients evaluated for SIRT (May 2007–August 2012) were included in this institutional review board–approved retrospective study (Table). Work-up before SIRT included computed tomography scans of the chest, abdomen, and pelvis followed by evaluation in interventional radiology, as previously described (7). Briefly, this evaluation included hepatic angiography, embolization of the gastroduodenal and other arterial branches to prevent nontarget radioembolization, and transcatheter injection of radioactive particles (technetium-99m-labeled macroaggregated albumin) into the artery planned for treatment, usually the right or left lobar hepatic artery. Planar and single photon emission computed tomography imaging of the head, chest, and abdomen was performed to calculate LSF, reflecting the amount of intratumoral shunting (Fig 1a,b) (8). No patients were excluded.

Table. Summary of Patient Demographics

Age (y)	62.9 (1.5)
Gender	
Male	50%
Female	50%
Performance status*	
0	43%
1	50%
2	7%
Laboratory	
Total bilirubin (mg/dL)	1.7 (1.0)
AST (U/L)	46.9 (4.1)
ALT (U/L)	40.6 (4.4)
CEA level (ng/mL)	411.7 (132.7)
Tumor location	
Bilobar	84%
Right lobe	16%
Liver tumor burden	
Diameter of index lesion (cm)	7.2 (1.0)
Overall tumor volume (mL)	280.3 (46.0)
Prior chemotherapy	60%
Prior invasive intervention	
Radiofrequency ablation	2%
Partial hepatectomy	8%
Hepatic arterial pump	2%

Data are presented as mean (SE) or percentage of study population.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CEA = carcinoembryonic antigen.
*Eastern Cooperative Oncology Group performance status.

Cross-sectional imaging was reviewed for the presence of liver lesions and other metastases before and after SIRT. The greatest diameter of the largest liver lesion on cross-sectional axial images was measured. Total hepatic tumor volume was assessed using three-dimensional software (TeraRecon; Foster City, California) that allowed for multiple regions of interest to be created for all tumors, with summation of the total tumor volume. Regions of interest and measurements were performed by a board-certified vascular radiology fellow (A.R.D.) and reviewed by a board-certified and Certificate of Added Qualification–certified interventional radiologist (R.O.).

The time between SIRT and disease progression and survival after SIRT was recorded. The medical charts were reviewed for cancer staging, baseline laboratory values, and chemotherapy agents administered before, during, and after the evaluation before SIRT. Survival was determined by chart review; when there was no record of death, the last note in the chart was used as an estimate of survival. Additionally, a research database was reviewed for the presence of genetic mutations determined by SNaPshot analysis of pathology specimens obtained by percutaneous biopsy (9).

The relationship of LSF to the presence of lung metastases was assessed with Kaplan-Meier survival analysis by dividing patients into two groups by the median LSF (7.3): patients with lower ($< 7.3\%$; $n = 31$) and higher ($> 7.3\%$; $n = 31$) LSF. Similarly, the relationship of LSF to patient survival after SIRT, progression of liver disease, and time to next new distant metastasis was also characterized. The relationship of tumor burden, assessed by both the greatest diameter of the dominant lesion and the overall hepatic tumor volume, and the presence of lung metastasis and survival were assessed by Cox regression analysis. The impact of receiving chemotherapy before, during, and after the evaluation before SIRT was evaluated using Wilcoxon signed rank sum test. Finally, whether tumor burden or LSF differed among patients with and without genetic mutations was assessed using Mann-Whitney U tests.

RESULTS

The study included 62 patients with liver metastases from colorectal cancer (31 women and 31 men; mean age, 63 y, SD 12) (Table). Documented lung metastases in addition to liver metastases were present in 33 patients. Patients with higher LSF were significantly more likely to have lung metastases at the time of the evaluation before SIRT ($P = .0008$). This relationship was not true for index lesion size or overall liver tumor