Research Article

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Radiation lobectomy: Time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection

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Background & Aims: Portal vein embolization (PVE) is a standard technique for patients not amenable to liver resection due to small future liver remnant ratio (FLR). Radiation lobectomy (RL) with ^{90}Y-loaded microspheres (Y90) is hypothesized to induce comparable volumetric changes in liver lobes, while potentially controlling the liver tumor and limiting tumor progression in the untreated lobe. We aimed at testing this concept by performing a comprehensive time-dependent analysis of liver volumes following radioembolization.

Methods: 83 patients with right unilobar disease with hepatocellular carcinoma (HCC; N = 67), cholangiocarcinoma (CC; N = 8) or colorectal cancer (CRC; N = 8) were treated by Y90 RL. The total liver volume, lobar (parenchymal) and tumor volumes, FLR and percentage of FLR hypertrophy from baseline (%FLR hypertrophy) were assessed on pre- and post-Y90 CT/MRI scans in a dynamic fashion.

Results: Right lobe atrophy ($p = 0.003$), left lobe hypertrophy ($p < 0.001$), and FLR hypertrophy ($p < 0.001$) were observed 1 month after Y90 and this was consistent at all follow-up time points. Median %FLR hypertrophy reached 45% (5–186) after 9 months ($p < 0.001$). The median maximal %FLR hypertrophy was 26% (−14→86). Portal vein thrombosis was correlated to %FLR hypertrophy ($p = 0.02$). Median Child-Pugh score worsening (6→7) was seen at 1 to 3 months ($p = 0.03$) and 3 to 6 months ($p = 0.05$) after treatment. Five patients underwent successful right lobectomy (HCC N = 3, CRC N = 1, CC N = 1) and 6 HCCs were transplanted.

Conclusions: Radiation lobectomy by Y90 is a safe and effective technique to hypertrophy the FLR. Volumetric changes are comparable (albeit slightly slower) to PVE while the right lobe tumor is treated synchronously. This novel technique is of particular interest in the bridge-to-resection setting.

Introduction

Portal vein embolization (PVE) is a standard technique for patients with primary or secondary liver malignancies not amenable to liver resection due to small future liver remnant expressed as a percentage ratio of the whole liver volume (FLR). The aim of the procedure is to induce contralateral hypertrophy by redirecting the portal blood flow, thereby leading to an increased ratio of FLR. The range of cut-off ratios of the remnant liver varies from 20% (normal) to 40% (cirrhotic) [1–3]. However, some authors highlight the limitations of PVE, citing a concern for progression of untreated disease and an increased rate of contralateral metastases while time elapses during the hypertrophy process; this is potentially related to pro-angiogenic factors [4–8].

Promisingly, radiation lobectomy (RL), defined as the transarterial lobar infusion of ^{90}Y-loaded microspheres (Y90), is suspected to induce similar or superior volumetric changes in liver lobes, but potentially offer the concomitant advantage of

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Abbreviations: AFP, alpha-fetoprotein; CC, cholangiocarcinoma; CP, Child-Pugh; CRC, colorectal cancer; CT, computed tomography; FLR, ratio (expressed as percentage) of the future liver remnant (segments 2/3) to the total liver parenchymal volume; %FLR hypertrophy, percentage increase in FLR hypertrophy from baseline; HCC, hepatocellular carcinoma; INR, international normalized ratio; MRI, magnetic resonance imaging; PVE, portal vein embolization; PVT, portal vein thrombosis; RL, radiation lobectomy; Y90, ^{90}Y-loaded glass microspheres radioembolization.

controlling the liver tumor and limiting tumor progression in the tumor-naïve (and untreated) left lobe by limiting the rate of portal blood flow diversion [9]. This "atrophy-hypertrophy complex" suggests lobar Y90 radioembolization as an alternate procedure to PVE as bridge to liver resection.

The goal of this study was to confirm the changes of embolized and unembolized liver volumes and FLR after lobar radioembolization. Additional goals included assessing long-term sequelae of RL (change in Child-Pugh score), assessing clinical factors predictive of %FLR hypertrophy, control of tumor in the treated lobe, and development of new tumor in the untreated radiation-naïve left lobe.

Materials and methods

Between 2003 and 2012, 700 patients were treated with radioembolization for hepatocellular carcinoma (HCC), colorectal cancer (CRC) liver metastases or cholangiocarcinoma (CC) in a lobar manner. In general, HCC, CC, and CRC patients with unilobar right lobe disease and no metastases were evaluated for surgical options during weekly multidisciplinary tumor board. Patients not candidates for immediate resection were considered for RL given the 3 theoretical advantages of this concept over PVE: treatment of the cancer, an embedded biologic test-of-time and contralateral hypertrophy. Hence, we studied patients with: (1) HCC, CRC or CC and (2) right lobe tumor(s) and (3) no extrahepatic metastases and (4) right lobar infusion of Y90 (non-selective). Exclusion criteria consisted of: (1) other malignancies, (2) any left lobe radioembolization, (3) segmental/subsegmental radioembolization, (4) prior liver-directed therapies or (5) any extrahepatic metastases. The conceptual definition of RL included the intentional lobar infusion of Y90 microspheres even in the setting where segmental injections could be performed, thereby optimizing tumor and normal parenchymal coverage. This retrospective study was approved by the Northwestern University Institutional Review Board and was compliant with the Health Insurance Portability and Accountability Act.

Eighty-eight patients fulfilled the study criteria with isolated right lobe disease and could (by imaging) be considered for right surgical hepatectomy. Five patients were further excluded because of missing baseline scans (3 patients), unacceptable motion artifact (1 patient) or non-contrast scans (1 patient). The analysis is therefore based on 83 patients fulfilling all study criteria.

Y90 treatment and imaging

Radioembolization treatment was preceded by a simulation procedure during which ^{99}Tc-macroaggregated albumin was injected into the hepatic arterial vasculature simulating Y90 microspheres distribution in order to estimate the degree of extrahepatic deposition. Coiling of extrahepatic arteries was performed when required to avoid inadvertent deposition. Glass microspheres loaded with ^{90}Yttrium (TheraSphere, Nordion, Canada) were used in this study per standard methodology. Patients were observed for 2 hours (arterial closure device) and subsequently discharged [10,11].

Patients and tumor characteristics

Age, gender, tumor type, diagnosis method, performance status (ECOG), Child-Pugh score (CP), cirrhosis, and underlying liver disease, prior liver-directed therapy/resection and baseline imaging were obtained. Following Y90 treatment, patients were scanned at 1 month, and every 3 months thereafter.

Liver function and clinical outcomes

The Child-Pugh score combining functional (total bilirubin, albumin, International Normalized Ratio (INR)), and clinical/imaging findings (encephalopathy, ascites), was calculated at each follow-up time-point. Adverse events post-Y90, left lobe tumor occurrence, right lobe resection, and orthotopic liver transplant post-Y90 radioembolization were assessed. Alpha-fetoprotein serum level (AFP) was recorded for HCC patients at each time-point.

Liver volumes

A detailed volume analysis was performed at each time point (baseline and all follow-ups). All liver volumes were measured assuming a potential extended trisegmentectomy (segments 6 + 7, 5 + 8, 1 + 4). In total, 292 scans were evaluated (205 magnetic resonance imaging (MRI), 87 computed tomography (CT)).

The volumetric delineation was performed at different time points (baseline, 1, 3, 3–6, and >9 months) by the primary investigators on VITAL IMAGES VITREA® medical imaging software from the Northwestern Memorial Hospital's General Electric CENTRICITY Picture Archiving & Communications System software.

We performed a computer-assisted manual volumetric drawing of hepatic lobes on the portal-venous phase of T1 post-gadolinium MRI sequences (SHARP or VIBE) or on CT by contouring the right (right + medial left) and left (lateral) lobes, separated by the left hepatic vein in the upper left lobe and a virtual line joining the IVC and the insertion of the falciform ligament in the inferior left lobe (Couinaud methodology) [12]. The hepatic hilum (main biliary ducts, vessels [PV, hepatic artery]), gallbladder and IVC were excluded from the segmentation. The volumetric tumor burden (viable and necrotic portions) in each lobe was sculpted by manual volumetric segmentation, using arterial phase series. Steatotic areas were included in the parenchymal volume estimation.

The measured and calculated volumes were defined as follows:

Right lobe volume (RLV): segments 1 + 4 + 5 + 6 + 7 + 8
Left lobe volume (LLV): segments 2 + 3
Total liver volume (TLV): RLV + LLV
Right lobe tumor burden (RLTB): total tumor volume in the right lobe
Left lobe tumor burden (LLTB): total tumor volume in the left lobe
Right lobe parenchymal volume (RLPV): RLV-RLTB
Left lobe parenchymal volume (LLPV): LLV-LLTB
Total liver parenchymal volume (TLPV): RLPV + LLPV

In the literature, there is some confusion behind the use of the term "FLR". In some series, it refers to the volume of the future liver remnant; in others, it refers to the future liver remnant over the total liver volume. We chose to define FLR as the ratio, expressed as a percentage, of the future liver remnant (segments 2/3) over the total liver parenchymal volume, this definition being more appropriate for surgical practice. Furthermore, we defined the %FLR hypertrophy as the percentage of hypertrophy of the FLR from baseline.

$$\text{Future liver remnant percentage ratio (FLR)} = \frac{\text{LLPV}}{\text{TLPV}} \times 100\%$$

$$\%\text{FLR hypertrophy} = \frac{\text{FLR post Y90} - \text{FLR pre Y90}}{\text{FLR pre Y90}} \times 100\% [13]$$

Statistics

Baseline patient/tumor characteristics were compared using the Fisher's exact (categorical variables) and Kruskal-Wallis tests (continuous variables). Volumetric measurements values were expressed as median/range due to non-normal distribution. Volumetric measurements changes (lobes, tumor, FLR) and AFP changes were compared to baseline using the Wilcoxon test for non-normal distributions. Baseline/follow-up FLRs were compared using the Mann-Whitney test. The correlation between maximal %FLR hypertrophy and time post-treatment was tested by Pearson correlation coefficient. Uni/multivariate analysis looking for predictive variables of %FLR hypertrophy was conducted using Cox proportional regression model.

Results

Patient sample

83 patients without extrahepatic disease were treated by right radiation lobectomy (non-selective) using Y90 microspheres for unilobar HCC, CRC or CC. There were 66 males and 17 females with a median age of 68 (range: 36–89). The primary disease was HCC (N = 67, 9 infiltrative), CRC (N = 8, 4 synchronous, 3 metachronous, 1 unknown) and CC (N = 8). The underlying liver