Original Article

The use of neoadjuvant lobar radioembolization prior to major hepatic resection for malignancy results in a low rate of post hepatectomy liver failure

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Background: Neoadjuvant yttrium-90 transarterial radioembolization (TARE) is increasingly being used as a strategy to facilitate resection of otherwise unresectable tumors due to its ability to generate both tumor response and remnant liver hypertrophy. Perioperative outcomes after the use of neoadjuvant lobar TARE remain underinvestigated.

Methods: A single center retrospective review of patients who underwent lobar TARE prior to major hepatectomy for primary or metastatic liver cancer between 2007 and 2018 was conducted. Baseline demographics, radioembolization parameters, pre- and post-radioembolization volumetrics, intra-operative surgical data, adverse events, and post-operative outcomes were analyzed.

Results: Twenty-six patients underwent major hepatectomy after neoadjuvant lobar TARE. The mean age was 58.3 years (17–88 years). 62% of patients (n=16) had primary liver malignancies while the remainder had metastatic disease. Liver resection included right hepatectomy or trisegmentectomy, left or extended left hepatectomy, and sectorectomy/segmentectomy in 77% (n=20), 8% (n=2), and 15% (n=4) of patients, respectively. The mean length of stay was 8.3 days (range, 3–33 days) and there were no grade IV morbidities or 90-day mortalities. The incidence of post hepatectomy liver failure (PHLF) was 3.8% (n=1). The median time to progression after resection was 4.5 months (range, 3.3–10 months). Twenty-three percent (n=6) of patients had no recurrence. The median survival was 28.9 months (range, 16.9–46.8 months) from major hepatectomy and 37.6 months (range, 25.2–53.1 months) from TARE.

Conclusions: Major hepatectomy after neoadjuvant lobar radioembolization is safe with a low incidence of PHLF.

Keywords: Radioembolization; post hepatectomy liver failure (PHLF); major hepatectomy; radiation lobectomy

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Introduction

Complex hepatic resections for primary and metastatic malignancies are now safely performed in high volume centers with a perioperative mortality of less than 5% (1-3). Unfortunately, most patients with primary and metastatic hepatic malignancies are not conventional surgical candidates at the time of diagnosis. Tumor size, multiplicity, location, inadequate residual liver function, patient co-morbidities, and uncertain tumor biology may all preclude the gold standard of resection (4-9).

Insufficient future liver remnant (FLR) is the dominant contributing factor to post hepatectomy liver failure (PHLF), a major source of post-operative morbidity and mortality (10,11). Candidacy for hepatic resection in current practice is largely based upon the volume of the FLR prior to resection with limited insight of the FLR functional capacity (12,13).

Interventions to increase FLR volume and reduce the probability for PHLF include portal vein embolization (PVE), hepatic vein embolization (HVE), associating liver partition and portal vein ligation with staged hepatectomy (ALPPS), and lobar transarterial radioembolization (TARE), also referred to as radiation lobectomy (14). While PVE has traditionally been utilized to increase FLR, it carries a risk of tumor progression during the hypertrophy period (15-17). Systemic chemotherapy may mitigate disease progression during post PVE hypertrophy, but cytotoxic effects can compromise FLR function (18). ALPPS can induce a significant volume of liver hypertrophy in several days, but is associated with a mortality as high as 9.6% and discordance between FLR volume and liver function has been reported (12,13,19-24).

Lobar TARE has been shown to simultaneously generate treated lobe volume reduction, contralateral lobe hypertrophy, and high rates of tumor response. The hepatic parenchymal involution associated with ablative radiation exposure has been speculated to provide additional assurance against PHLF. These properties of TARE have generated interest in its application as a neoadjuvant to hepatectomy (25-29).

Early studies suggest that neoadjuvant TARE often achieves remnant liver hypertrophy volumes that are comparable to PVE while providing tumor control and that surgical resection after radioembolization is safe (27,30). There is limited data regarding perioperative outcomes of liver resection and incidence of PHLF following neoadjuvant lobar TARE (31-34). This study will present the surgical experience with major hepatectomy following neoadjuvant lobar TARE for malignant neoplasms of the liver.

We present the study in accordance with the STROBE reporting checklist. Available at: http://dx.doi.org/10.21037/jgo-20-507.

Methods

This study was performed with Institutional Review Board approval (No. 19-009890) and individual consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Patient evaluation

A retrospective review of all patients undergoing hepatic resections was performed at a single tertiary referral center. A prospectively populated institutional database was used to identify patients who underwent neoadjuvant lobar TARE prior to hepatic resection for primary or metastatic liver malignancy. All care plans were approved by a multidisciplinary tumor board.

From 2007 to 2018, 722 patients who underwent major hepatic resection were reviewed. Patients who received pre-operative lobar TARE with or without an adjunctive segmental tumor radioembolization, and subsequent major hepatic resection were included. Patient demographics, medical history, radiologic data pre- and post-treatment, liver volumetrics, radioembolization dosimetry, preoperative systemic treatment, intra-operative surgical data, and post-operative outcomes were recorded. Adverse events following TARE were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (35) from the time of TARE to resection. Post-operative complications were graded according to the Clavien-Dindo classification for a 90-day time period after surgery (36). The presence and degree of post hepatectomy specific complications such as bile leak, hemorrhage, and liver failure was assessed based on the International Study Group of Liver Surgery (ISGLS) classification system (37-39). Tumor size was calculated by the largest maximum lesion (in the instance of multiple lesions) on baseline imaging. Major hepatic resection was defined as resection of three or more Couinaud segments according to the Brisbane 2000 system of nomenclature (40).

Table 1 Dosimetry for 26 patients undergoing hepatic resection after TARE

Variable	N=26
Y90 activity, mean, Gbq [range]	2.9 [1–9]
Dosage, mean, Gy [range]	147.5 [48–364]
Treated absolute volume of liver, mean, mL [range]	1,062 [354–2,035]
Treated percentage volume of liver, mean, [range]	59.3% [14–83%]

TARE, transarterial radioembolization; Gbq, Gigabecquerel.

Table 2 Demographics for 26 patients undergoing hepatic resection after TARE

Variable	N=26[†]
Age, years, mean (range)	58.3 [17–88]
Body mass index, mean (range)	26 [17–40]
Male	9 (34.6)
Liver disease	5 (19.2)
Steatosis	1 (3.8)
Fibrosis (minimal)	1 (3.8)
Cirrhosis/Mild portal hypertension	4 (15.4)
ASA	
II	3 (11.5)
III	20 (76.9)
IV	3 (11.5)

[†], values reported as n (%) unless otherwise indicated. ASA, American Society of Anesthesiologists score; TARE, transarterial radioembolization.

TARE

TARE was performed using a previously published methodology (41,42). All patients underwent planning angiography to evaluate the hepatic arterial anatomy. Treatment volumes were calculated using pre-TARE cross sectional imaging for patients treated prior to 2016 and using intra-procedural cone beam CT thereafter. Technetium labeled macroaggregated albumin was administered as a surrogate for radioembolization microspheres. Dosimetry was calculated using the Medical Internal Radiation Dose (MIRD) or Body Surface Area (BSA) methodology for glass (TheraSphere™, Boston Scientific, Marlborough, MA) and resin (SIR-Spheres®, Sirtex, Woburn, MA, USA) microspheres, respectively. All patients received TARE to the planned hepatic future resection site (FRS) with or without an additional selective dose to the tumor(s). The target doses are summarized in *Table 1*. TARE was used after PVE to salvage an inadequate volumetric response. In some instances, PVE was utilized after TARE per the surgeon's preference.

Imaging and volumetrics

Multiphase CT or MRI was performed at baseline, at 1 month following TARE, and approximately every 3 months until resection. Preoperative imaging within 30 days of resection was used to calculate the FLR, degree of hypertrophy (DH), and kinetic growth rate (KGR) in relation to baseline imaging. Hepatic volumetrics were measured using iNtuition (TeraRecon, Durham, NC, USA) with hand drawn regions of interest over the FRS, FLR, and total liver. FLR was calculated as a ratio, expressed as a percentage, of the FLR over total liver volume. DH was calculated by dividing the absolute difference between the pre- and post-TARE FLR by the pre-TARE FLR. KGR was calculated by dividing the DH by the time interval (in weeks) from TARE until preoperative imaging. A single patient was excluded from the volumetric analysis as staged segmental resections were performed in the FLR prior to major hepatectomy.

Statistical analysis

Data analysis was performed using R v2020-02-29 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were described as median values with interquartile range (IQR) or mean values with range. Categorical variables were described as frequencies with percentages. Normal distributions were reported as mean while non-normal distributions were reported as medians with IQR, unless specified.

Results

Twenty six patients underwent neoadjuvant lobar TARE prior to major hepatic resection during the study period. Most patients (n=17) underwent liver resection between 2016 and 2018. Patient demographics are summarized in *Table 2*. Five patients underwent percutaneous liver biopsy prior to intervention. Of these, four patients with

Table 3 Operative variables for 26 patients undergoing hepatic resection after TARE

Variable	N=26†
Operative time, min, mean (range)	311 [133–430]
Estimated blood loss, mL, mean (range)	1,173 [100–11,200]
Minimally invasive technique	8 (30.8)
Right hepatectomy/trisegmentectomy	20 (76.9)
Left hepatectomy/extended left	2 (7.7)
Sectorectomy/segmentectomy	4 (15.4)

†, values reported as n (%) unless otherwise indicated. TARE, transarterial radioembolization.

Table 4 Pathology findings for 26 patients undergoing hepatic resection after TARE

Variable	N=26†
Hepatocellular carcinoma (HCC)	9 (34.6)
Metastatic colorectal adenocarcinoma	6 (23.1)
Intrahepatic cholangiocarcinoma (iCCA)	6 (23.1)
Metastatic carcinoid tumor	2 (7.7)
Metastatic melanoma	1 (3.8)
Mixed iCCA/HCC	1 (3.8)
Gallbladder carcinoma	1 (3.8)
Margins	
R0	25 (96.2)
R1	1 (3.8)

†, values reported as n (%) unless otherwise indicated. TARE, transarterial radioembolization.

hepatocellular carcinoma demonstrated signs of cirrhosis and one patient with cholangiocarcinoma demonstrated steatosis and minimal portal fibrosis (*Table 2*). The indications for TARE were: inadequate FLR volume for resection (n=19, 73.1%), prior failed PVE (n=4, 15.4%), downstaging for potential orthotopic liver transplantation (n=1, 3.8%), symptom control from tumor (n=1, 3.8%), and recent myocardial infarction with stent placement (n=1, 3.8%). Approximately 85% (n=22) of patients also had high risk tumor biology, per multidisciplinary consensus, that would benefit from a biologic test of time. The majority (n=20, 76.9%) of patients had pre-operative Albumin-Bilirubin grades of A1 or A2 with a median tumor size of 6.7 cm (3.7–10.2 cm). Tumors were right sided, bilobar, or central in 20 (76.9%), 5 (19.2%), and 1 (3.8%) patients, respectively. Eighteen patients (69.2%) had solitary tumors. Glass and resin microspheres were used in 21 (80.8%) and 5 (19.2%) patients, respectively. Repeat TARE was performed on 2 (7.7%) patients in the setting of large (>10 cm) primary tumors with partial response to initial TARE. PVE was performed in 6 (23.1%) patients after TARE. Four (15.4%) patients underwent prior liver directed intra-arterial therapy with chemoembolization (n=3, 11.5%) or bland embolization (n=1, 3.8%) for lesions in the same hepatic lobe subsequently salvaged with TARE. Nineteen (73.1%) patients received concurrent systemic therapy including 5FU based regiments (n=7, 26.9%), Gemcitabine/Cisplatinum (n=6, 23.1%), Sorafenib (n=3, 11.5%), octreotide analogue (n=2, 7.7%), and immunotherapy (n=1, 3.8%).

Surgical details are noted in *Table 3*. Eleven (42.4%) patients underwent additional resections including bowel resection (n=4, 15.4%), portal vein resection (n=2, 7.7%), diaphragmatic resection (n=2, 7.7%), extrahepatic bile duct resection with Roux-en-Y reconstruction (n=2, 7.7%), and right adrenalectomy (n=1, 3.8%). A staged resection was performed in one (3.8%) patient with bilobar colorectal metastasis who underwent left lateral hepatectomy prior to right hepatectomy as has been previously described (43). The mean time from TARE to surgery was 235 days (107–636 days).

Pathology of the underlying disease is given in *Table 4*. The majority of patients had primary hepatic malignancy (n=16, 62%). Of available (n=17) histologic descriptions of tumor necrosis, 76% (n=13) demonstrated extensive or complete pathologic necrosis.

There were no grade III or higher bilirubin toxicities after TARE prior to hepatic resection. One patient developed grade III diarrhea and another developed grade III abdominal pain after TARE. Post operative outcomes are given in *Table 5*. The majority of patients had no major complications (n=20, 76.9%) and had hospitalizations less than 9 days (n=23, 88.5%). The incidence of PHLF was 3.8% (n=1). There were no reoperations or mortalities within 90 days.

A summary of liver volumetrics is given in *Table 6*. The mean FLR volume/percentage was 671 mL (310–1,608 mL)/38.4% (16–86%) before TARE and 857 mL (372–1,398 mL)/52.7% (31–92%) after TARE. The mean DH and KGR was 45.8 [0–119] and 1.7 [0–6], respectively.

TARE dosimetry and target volumes are given in *Table 1*. The mean treated liver volume was 1,062 mL (354–2,035 mL) and mean treated liver percent was 59.3% (14–83%). The

mean Y90 dose was 147.5 Gy (48–364 Gy).

At the time of manuscript preparation, 15 (58%) patients were still alive and 11 (42%) died of disease progression. Six (23%) patients had no recurrence and the other 20 (77%) patients had recurrence identified at a median interval of 4.5 months (3.3–10 months) from the index operation. Eleven of these patients had distant metastases with no evidence of remnant liver disease. Nine patients had hepatic recurrence, four of them concurrently with distant disease. Median overall survival was 28.9 months (16.9–46.8 months) from the index operation and 37.6 months (25.2–53.1 months) from TARE.

Table 5 Post-operative outcomes (90-day) for 26 patients undergoing hepatic resection after TARE

Variable	N=26[†]
Clavien-Dindo complication	
III	6 (23.1)
IV/V	0
Post hepatectomy hepatic failure	1 (3.8)
Grade B	1 (3.8)
Post hepatectomy bile leak	2 (7.7)
Grade B	1 (3.8)
Grade C	1 (3.8)
Reoperation	0
Length of stay, days, mean (range)	8.3 [3–33]

[†]Values reported as No. (%) unless otherwise indicated. TARE, transarterial radioembolization.

Discussion

Surgical resection remains the gold standard local treatment of primary and metastatic liver malignancy. Many patients are not candidates for resection at presentation due to disease stage, performance status, comorbidities, anatomic factors, or insufficient FLR. PVE and ALPPS have been utilized in patients with inadequate FLR but are associated with a risk of tumor progression and significant morbidity/mortality, respectively (15,16,44-48) (*Figure 1*). Furthermore, post-operative liver failure remains the most common morbidity after both PVE and ALPPS (19,20).

TARE has been shown to ablate both tumoral and adjacent liver parenchyma which enables an extended FLR hypertrophy time compared with PVE (29,49). In appropriately selected patients, this allows further assessment of tumor biology and stage while controlling tumor. Neoadjuvant lobar TARE, also referred to as radiation lobectomy, has seen increased utilization over the past decade. Early experience with lobar TARE

Table 6 Liver volumetric data for 26 patients undergoing hepatic resection after TARE

Variable	Whole cohort	TARE only	PVE prior to TARE	PVE after TARE
Pre-TARE				
FLR absolute volume, mean, mL [range]	671 [310–1,608]	788 [325–1,608]	513 [411–733]	484 [310–582]
FLR percentage volume, mean [range]	38.4 [16–86]	41.1 [25–86]	39 [21–58]	31.5 [16–56]
Post TARE				
FLR absolute volume, mean, mL [range]	857 [372–1,398]	958 [470–1,398]	693 [372–854]	685 [527–1,022]
FLR percentage volume, mean [range]	52.7 [31–92]	56.7 [36–92]	50.5 [32–68]	42.6 [31–60]
Absolute volume increase, mean, mL [range]	203.3 [0–440]	208.5 [0–426]	189.5 [0–339]	198.8 [0–440]
Degree of Hypertrophy [DH], mean [range]	45.8 [0–119]	46.6 [0–104]	34.2 [17–52]	52.4 [7–119]
Kinetic Growth Rate [KGR], mean [range]	1.7 [0–6]	1.5 [0–4]	1.6 [1–2]	2.3 [0–6]
Mean time from TARE to surgical resection				
Days [range]	235 [107–636]	236 [107–614]	158 [115–192]	283 [125–636]
Weeks [range]	33.5 [15–91]	33.6 [15–88]	22.6 [16–27]	40.5 [18–91]
Months [range]	7.8 [3.6–21]	7.9 [3.6–20]	5.3 [3.8–6.4]	9.4 [4.2–21.2]

TARE, transarterial radioembolization; PVE, portal vein embolization.

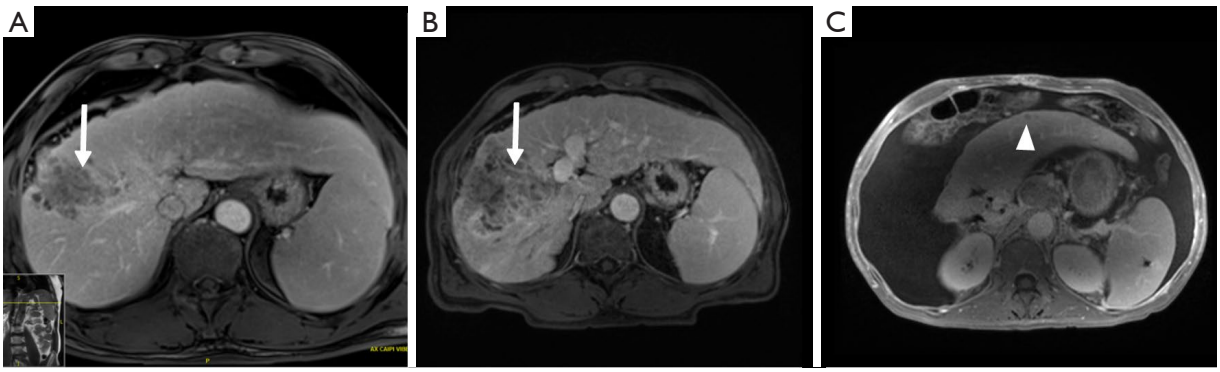

Figure 1 Post contrast MRI demonstrating a cirrhotic liver with hepatocellular carcinoma (arrow) in the right hepatic lobe (A). Post contrast MRI obtained one month after PVE demonstrates progression of tumor (arrow) and an FLR volume of 40% (B). Post contrast MRI obtained 3 months after right hepatectomy demonstrates liver failure with ascites and a subcentimeter tumor recurrence (arrow head) (C). PVE, portal vein embolization; FLR, future liver remnant.

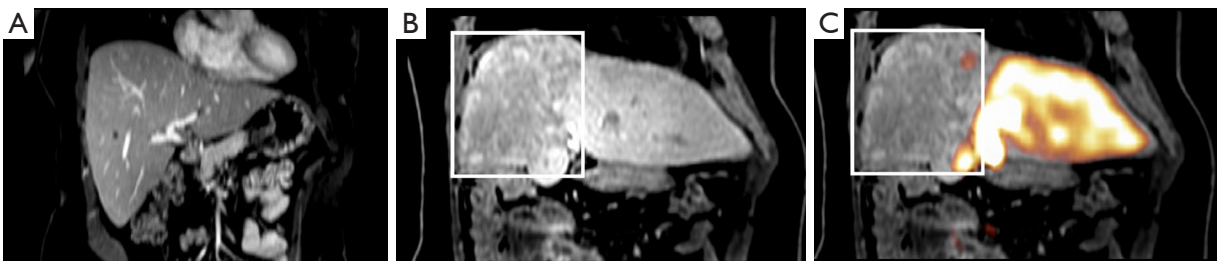

Figure 2 Post contrast MRI prior to neoadjuvant right lobar TARE demonstrates a small FLR (A). Hepatobiliary phase MRI post hepatocyte contrast administration obtained 6 months after initial TARE demonstrates FLR hypertrophy and poor biliary excretory function of the FRS (square) (B). FRS devitalization is supported by reduced radiotracer activity (square) using 99mTc-Mebrofenin MRI fusion (C). TARE, transarterial radioembolization; FLR, future liver remnant; FRS, future resection site.

demonstrated that it was safe, effectively controls tumor, and produces contralateral lobar hypertrophy volume comparable to PVE but at slower rates (26,27,29-31,50,51).

Liver volumetrics and growth kinetics have been used as surrogates of post-operative liver function, but the variability of a patient's hepatic substrate is not completely captured by these indirect measures of physiology. Liver volumetrics may be prone to additional error in patients with underlying liver disease and previous systemic therapy. It is known that PVE and ALLPS reduce FRS hepatic function however, pre-operative devitalization of the FRS is not achieved with either of these techniques and liver failure remains a major associated morbidity and mortality. TARE induced devitalization of the FRS may represent a more accurate surrogate for post resection liver function as the patient is not physiologically relying on the FRS at the time of surgery (*Figures 2,3*). This is supported by the low incidence of PHLF in our cohort (3.8%). Conceptually, growth metrics such as DH and KGR may be less informative of the risk of PHLF in the setting of a devitalized FRS as the liver may not hypertrophy beyond what is adequate for the individual patient.

Although FLR hypertrophy is generally slower after TARE than PVE, the high rates of tumor response observed in this study allowed for extended hypertrophy time without local progression. While our study did not specifically confirm devitalization of the FRS using functional agents such as hepatocyte specific MRI contrast, mebrofenin, or methecetin (52,53), only a single patient who underwent neoadjuvant right lobar TARE experienced PHLF (grade B) in our cohort. The liver failure eventually progressed culminating with the patient's death approximately 19 months after surgery.

Tumor biology plays a critical role in patient outcomes

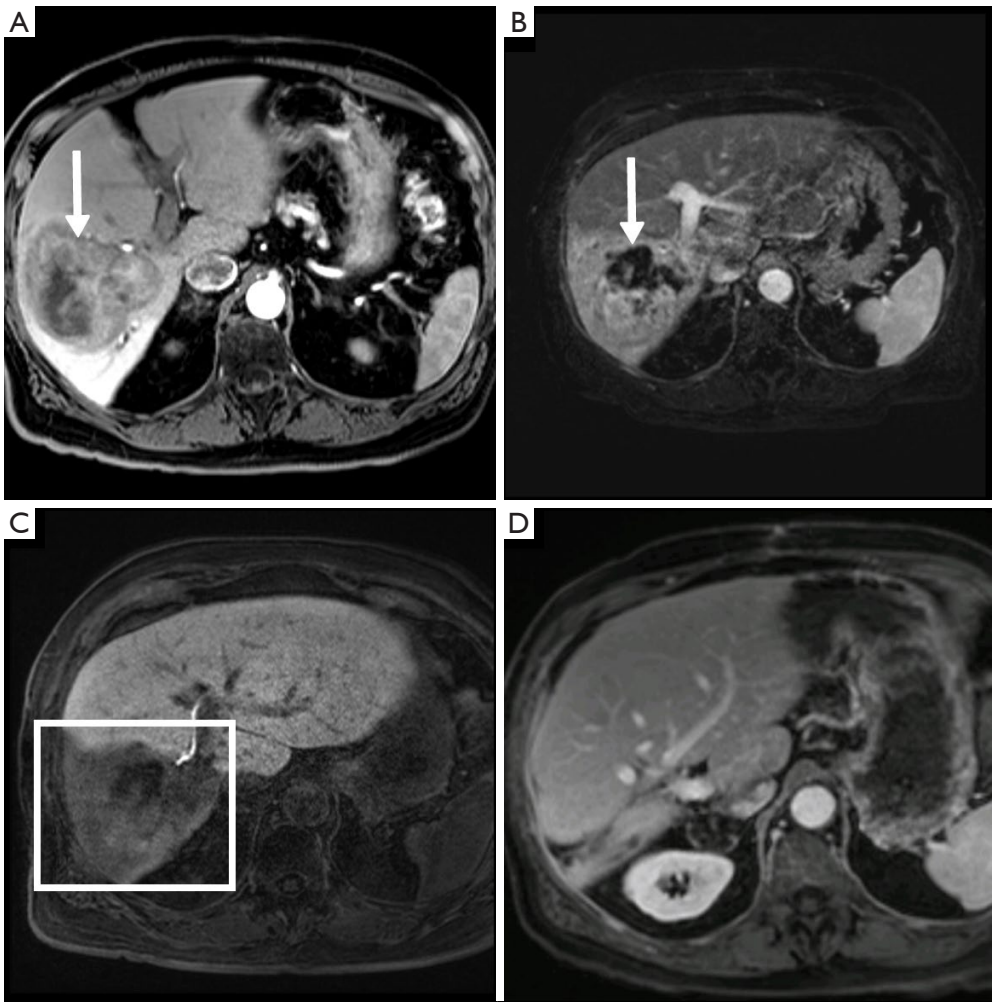

Figure 3 Post contrast MRI demonstrating a right lobe hepatocellular carcinoma (arrow) with a small FLR (A). Post hepatocyte contrast administration MRI obtained 6 months after initial TARE demonstrates tumor necrosis (arrow) (B), interval FLR hypertrophy, and poor excretory function of the FRS (square) (C). Post contrast MRI image obtained 14 months after resection demonstrates no tumor recurrence or evidence of liver failure (D). The patient remains free of recurrence 30 months after resection. FLR, future liver remnant; TARE, transarterial radioembolization; FRS, future resection site.

after resection. In metastatic colorectal cancer to the liver, RAS mutations have been associated higher rates of recurrence and shorter post recurrence survival (54-56). In hepatocellular carcinoma, tumors with micro- and macro-vascular invasion and higher levels of pre-intervention alpha fetoprotein have been shown to be associated with higher rates of recurrence (57-59). Prolonged observation enabled by neoadjuvant TARE may facilitate a more thorough assessment of initially occult intrahepatic and extrahepatic disease.

Pre-operative comorbidity indices and performance status have been shown to be associated with post-operative morbidity and mortality (60-65). In addition to assessment of tumor biology over a longer time period, neoadjuvant TARE also provides an opportunity to consolidate disease and optimize medical comorbidities prior to resection.

There are technical aspects to hepatic resection after neoadjuvant TARE that warrant consideration by the surgeon. As with any neoadjuvant radiation therapy, a longer observation period prior to resection allows for the development of treatment associated adhesions. TARE can create dense fibrotic changes within and adjacent to the liver, particularly with high dose administrations in peripherally located tumors. From our experience, large

lesions located in the dome may require *en bloc* partial diaphragm resection. An exophytic lesion located in the posterior lobe required an ipsilateral adrenalectomy in one case. Additionally, lesions treated with high dose TARE in the undersurface of the liver may induce radiation changes to adjacent viscera. TARE can also complicate margin analysis. While there is often a clear radiographic and superficial capsular demarcation between the treated and non-treated lobe, the contrast is not as well defined within the liver parenchyma. Given this observation, our practice minimizes TARE particle volumes to prevent irradiation of the central portal triad (66). Depending on institutional policy, frozen section analysis cannot be utilized if surgery is performed soon after TARE due to risk of equipment contamination with radioactive microspheres. In these cases, intraoperative margin analysis may be performed by gross inspection and touch preparation. Permanent histologic examination with final margin analysis can proceed in a normal fashion, albeit several days after the hepatectomy.

Despite offering both FLR hypertrophy and tumor control in the FRS, neoadjuvant TARE has some disadvantages. TARE is more costly when compared to outpatient PVE performed with moderate sedation. While single day TARE is increasingly utilized, two treatment sessions over separate days remains the most common approach (67). In addition, the increased time for FLR hypertrophy may not be suitable for certain patients within a more narrow systemic therapy window for resection. TARE is more susceptible than PVE to variances in technique owing to a complex interplay of factors including patient selection, underlying liver disease, microsphere specific activity and number, microsphere preferential flow, and timing with vasoactive systemic therapies. Neoadjuvant TARE dosimetry is currently being investigated and best practice has not yet been established, but there is strong suggestion of both parenchymal and tumor dose thresholds associated with the DH and tumor response, respectively (68-71).

Limitations of our study include its retrospective nature with inclusion of many primary and secondary liver malignancies and small cohort size. The study was not performed as an intention to treat analysis and patients who received TARE who did not ultimately receive resection were not included. TARE dosimetry was estimated using the MIRD or BSA models and post TARE dose distribution was not available for the entire cohort. As in most evolving therapies, practice evolution presents heterogeneities that limit the power of a retrospective analysis. As such, PVE was also utilized for hepatic conditioning post radioembolization in some patients. Lastly, the degree of post TARE tumor necrosis did not receive dedicated pathology reassessment, but this is outside the scope of this study.

Conclusions

The incidence of PHLF and operative complications in patients treated with neoadjuvant lobar radioembolization is low. This treatment provides a high degree of pre-operative tumor control and FLR hypertrophy in otherwise unresectable patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at: http://dx.doi.org/10.21037/jgo-20-507

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Institutional review board approval was obtained (No. 19-009890) and individual consent for this retrospective analysis was waived.

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