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Neoadjuvant Radiation Lobectomy As an Alternative to Portal Vein Embolization in Hepatocellular Carcinoma

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Surgical resection is considered first line and potentially curative for early stage hepatocellular carcinoma. However, many patients presenting with small tumors might not qualify as candidates for surgical resection given their small future liver remnant (FLR); such patients tend to undergo neoadjuvant therapies prior to resection to minimize the risk of hepatic decompensation after major hepatic resection. While there are several techniques for inducing FLR hypertrophy, a recent approach in hepatocellular carcinoma is Y90 radiation lobectomy (RL). RL was discovered serendipitously after noticing contralateral lobar hypertrophy in patients who had ipsilateral lobar Y90 radioembolization. This is now proactively used in bridging patients to surgical resection by inducing FLR hypertrophy. In this article we discuss the evolution of RL as an alternative to portal vein embolization which has been long used to induce FLR hypertrophy, albeit mostly in metastatic liver disease.
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Background

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, and is the second most common cause of cancer related mortality worldwide.[1] Surgical resection has been long regarded as first line curative treatment for early disease.[2] However, many patients presenting with early stage HCC are not typically resection candidates,[3] most commonly due to the presence of portal hypertension and/or a small FLR. Several cut-off values of FLR percentages have been described in literature and 30% has been regarded as the minimum acceptable FLR percentage in a normal (noncirrhotic) liver.[4] Over the past two decades, portal vein embolization (PVE) has been shown to induce contralateral hypertrophy allowing patients to undergo surgery.[5,6] However, this technique has been mainly applied in colorectal liver metastases patients. More recently, lobar application of Yttrium-90 radioembolization (Y90) has been noted to induce ipsilateral atrophy of treated lobe, as well as simultaneous contralateral hypertrophy.[7,8] This phenomenon lead to further investigations on the impact of this approach in inducing hypertrophy of FLR and consequently allowing nonresection candidates to undergo liver resection.[9] HCC patients in particular are the most likely patient population to benefit from radiation lobectomy. In addition to contralateral hypertrophy, tumor necrosis post-Y90 has been shown to provide better tumor control while waiting for resection, as well as fewer tumor recurrences.[10]

Abbreviations: HCC, hepatocellular carcinoma; FLR, future liver remnant; RL, radiation lobectomy; PVE, portal vein embolization; CRLM, colorectal liver metastases; (Y90), yttrium-90 radioembolization; BCLC, Barcelona clinic liver cancer staging system; HCV, hepatitis C virus; HBV, hepatitis B virus; Gy, gray; Gbq, gigabecquerel; CRC, colorectal cancer; IHC, intra-hepatic cholangiocarcinoma; CI, 95% confidence interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; TACE, transarterial chemoembolization; LSF, lung shunt fraction; MAA, technetium 99mTc macro aggregated albumin; OPTN, organ procurement and transplantation network; UNOS, United Network for Organ Sharing; MELD, model for end-stage liver disease

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Radiation Lobectomy Mechanism

The mechanism of RL is hypothesized to be: (1) slow atrophy/scarring of the treated lobe post-Y90, (2) atrophy leads to slow

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diversion of portal flow to the contralateral lobe, and (3) controlled diversion of portal flow increases the contralateral volume. In some sense, it represents a slow and controlled diversion of portal venous flow from the ipsilateral to the contralateral lobe.[7]

Studies have reported that unilateral lobar radioembolization leads to increase in the diameter of contralateral portal vein, confirming to some degree the hypothesis of portal venous diversion toward the contralateral lobe. Despite those changes, portal hypertension sequelae such as splenomegaly were not noted in patients who received unilobar treatments. In contradistinction, bilobar radioembolization was found to result in an increase of splenic volumes.[7]

Patient Selection

In HCC, ideal candidates for RL are patients with Child-Pugh A liver cirrhosis without portal hypertension who would have been deemed surgical resection candidates if it was not for their small FLR. Barcelona Clinic Liver Cancer A HCC patients with solitary tumors are ideal resection candidates. However, some patients presenting with multifocal unilobar tumors can be triaged toward surgery as long as they maintain preserved liver functions and normal portal pressure. Patients exhibiting signs of macrovascular invasion are not suitable candidates for surgical interventions post-Y90 unless they demonstrate prolonged and sustained response. Initial treatment planning includes volumetric assessment of both hepatic lobes in addition to estimating the volume of segment IV alone. Transplant or hepatobiliary surgeons then discuss their plans and the ideal anatomic resection approach they are to perform once sufficient FLR hypertrophy has been reached.

Most patients presenting with right-sided HCC tumors undergo right hepatic trisegmentectomy. However, segment 4 should be preserved when it represents a major portion of the left lobe and/or when all disease can be removed by a simple right or partial hepatectomy.

In patients with nonradiologically apparent cirrhosis, an FLR >30% is postulated to be needed for safe resection with minimal chances of hepatic decompensation. That value increases to 40% in patients with cirrhotic morphology. Nevertheless, there is lack of consensus on this specific cutoff of FLR.

Treatment Planning

All patients must undergo complete cancer staging imaging. Planning angiography should be completed with cone beam CT to ensure tumor vascular coverage within the treated lobe. Lung shunt fraction is estimated after lobar injection of ^{99m}Tc-MAA in the lobar hepatic artery using planar scintigraphy and SPECT/CT. Patients with portal vein invasion or high tumor burden may present with high lung shunt fraction, which will limit the absorbed dose to by the treated lobe. While this may result in lower tumor response, contralateral hypertrophy will still be manifest if hepatic parenchymal absorbed dose is >88 Gy.[11]

Pre-Y90 FLR Estimation

FLR is estimated as the contralateral hepatic lobe volume, which is the left lobe in case of patients presenting with right lobe tumors. However, in many centers, surgeons perform extended right lobectomy (better known as trisegmentectomy) in order to include the entire right lobe plus segment IV, leaving a liver remnant comprised of segments I,II, and III. Prior to Y90, FLR is measured from surgical input from the planned remnant liver. Once FLR is identified (eg, segments I + II + III + IV vs only I + II + III), a 3D-volumetric reconstruction is made using available software such as Vitrea (Vital Imaging, Inc., MN).

FLR percentage is estimated as follows: (volume of FLR ÷ volume of Entire Liver)%

FLR% is then estimated on every follow-up scan.

Rate of FLR hypertrophy is also estimated as follows:

$$\text{FLR hypertrophy} = \frac{\text{FLR\% post-Y90} - \text{FLR\% pre-Y90}}{\text{FLR\% pre-Y90}}$$

In case of large tumors, only functional liver volumes should be included the FLR measurements and tumor volume should be subtracted from both right lobe volume as well as total liver volume.

Technical and Dosimetric Considerations

Generally, radiation lobectomy is defined by performing a unilobar (right lobe) Y90 radioembolization with an average dose to parenchyma (80-150) Gy. Target liver volume should encompass the entire right hepatic lobe, and dosimetry should be calculated *a* prior with dose to be delivered to both tumor and nontumoral hepatic parenchyma. For glass microspheres (TheraSphere microspheres, Biocompatibles UK Ltd, Surrey, UK), which is mainly used in the treatment of HCC, MIRD based dosimetry is applied as follows:

$$\text{Activity} = \frac{\text{dose} \times \text{mass (kg)}}{50}$$

$$\text{Dose} = \frac{\text{acitvity} \times 50 \times (1-\text{LSF})(1-\text{residual activity})}{\text{mass (kg)}}$$

The process of dose estimation requires volumetric assessment the estimation of the treated liver mass which can be calculated by multiplying the volume in cubic centimeters by a factor of 1.03. Hence, 3D-reconstruction of to-be treated liver volume is needed in advance to estimate the treatment dose.

For example, a patient with right lobe volume of 1000 cc will have estimated right hepatic mass of 1030 mg (1.03 kg). Therefore, in order to estimate the activity needed to be administered to deliver a dose of 120 Gy to the right lobe, the following formula will be applied:

$$\text{Activity} = \frac{\text{dose} \times \text{mass (kg)}}{50}\text{. Therefore, activity} = \frac{120 \times 1.03}{50} = 2.472 \text{ Gbq}$$

Thus 2.472 gigabecquerels are needed to deliver a 120 Gray (Gy) radiation dose to right lobe. However, a fraction of this will shunted toward the lung (LSF) and another smaller fraction will be residual in the delivery system. Hence, a slightly higher activity >2.472 Gbq needs to be administered depending on the LSF.

The rate of FLR% increase after Y90 serves as an indicator of hepatic regenerative reserve. As an example, a patient presenting with baseline FLR of 27% that increases to 33% exhibited an FLR% increase of $\frac{33-27}{27} \times 100\% = 22.2\%$. While 33% plays a role in deeming the patient a surgical candidate, it is the 22.2% rate of increase in FLR that reflects the regenerative power of the liver.

The following are the steps required to plan RL in a patient with right-sided HCC and planned right hepatectomy or trisegmentectomy:

1. Child-Pugh A patient, good operative candidate, no comorbidities, small FLR (FLR is segment 23 in case of planned trisegmentectomy, 234 in case of planned right hepatectomy).
2. Mapping angiogram + lung shunt analysis. If present, identification of segmental feeding artery to tumor.
3. If tumor is large and mandates lobar infusion, right hepatic artery injection recommended distal from cystic artery if possible. If catheter placement distal to cystic results in incomplete tumor coverage, recommend splitting activity vials into two; anterior (segments 58) and posterior (segments 67) branches. Since patient is Child-Pugh A, a higher dose is tolerated and 150 Gy second week Monday/Tuesday is recommended.
4. If tumor can be treated with a segmental injection, modified RL technique is recommended. This is defined as radiation segmentectomy dosing (>200 Gy) to the tumor plus lower dose lobar infusion (100 Gy) in the same setting. This ensures maximal chance of complete tumor kill in anticipation of surgery. It also mitigates against the chance of surgery being delayed/postponed/canceled.
5. At months 1, 3, and 6, perform FLR determination as described above. Ensure the tumor itself is excluded from parenchymal volumes. This time-dependent approach treats the tumor, augments the contralateral FLR, and embeds a biologic test-of-time, permitting selection of best patients.
6. Once the FLR hits the desired percentage, surgery may be pursued.

Imaging Follow-Up Post-Y90

RL is generally performed to bridge patients to surgical resection. Hence, imaging follow-up should start at 1-month post-Y90 in order to initiate a time-dependent volume analysis. Studies have shown that volumetric changes take time to occur after radioembolization, with maximal hypertrophy being reached between 6 and 9 months post-Y90. However, most patients achieve sufficient hypertrophy by 3 months which allows those patients to undergo surgical resection. Follow-up imaging scans are therefore recommended at 1, 3, 6, and 9-month post-Y90. In addition to continuous volumetric assessment, tumor response will be assessed. Tumors demonstrating good response within 3 months of Y90 indicate good tumor biology and predict long recurrence-free survival.[10] Tumors failing to respond within 6 months of treatment or even progressing as early as 3 months may be associated with unfavorable biological factors; surgical resection in such cases may be futile.[10,12] In the event of tumor progression, or unsatisfactory FLR hypertrophy, subsequent Y90 treatment is indicated. Toxicity rates in such retreated patients are low.[9,13]

Radiation Lobectomy: Outcomes

RL is mainly used in HCC patients with the intention to achieve tumor necrosis and FLR hypertrophy. Several studies have been published over the past decade showing efficacy of RL in achieving contralateral lobar hypertrophy. Table 1 summarizes the most relevant studies.

The data presented in those studies reveal the safety and efficacy of radiation lobectomy in achieving contralateral hypertrophy while simultaneously providing ipsilateral tumor control, therefore facilitating major hepatic resection in appropriately selected patients.

In 2008, Jakobs et al showed volumetric changes in left untreated hepatic lobes after lobar treatment of right hepatic lobes bearing metastatic colorectal cancer. They also noticed that left lobar hypertrophy occurred simultaneously with right lobar atrophy. This was followed by a study by Gaba et al that showed similar findings but in a cohort of predominantly HCC patients. Subsequent studies of lobar Y90 confirmed this notion of FLR hypertrophy. Rates of FLR hypertrophy were variable depending at the time of volumetric assessment in each study. However, all studies concluded that Y90 leads to time-dependent volumetric changes that occur over the course of 6-9 months from the first lobar Y90 treatment.

Vouche et al showed significant FLR hypertrophy that occurred in a linear time-dependent manner, with early FLR changes observed at 1-month post RL and maximum hypertrophy achieved at ninth month from treatment date.[9] Teo et al showed that hepatitis B virus positive HCC patients can achieve higher rates of FLR hypertrophy than hepatitis C virus patients.[14] Fernandes et al showed that cirrhotic patients might have less regenerative power than noncirrhotic patients translating into reduced rates of FLR hypertrophy.[15]

Although most studies focusing on HCC show robust volumetric assessments as well as low toxicity rates, these studies did not report the data as intention to-treat. This stems from the fact that most patients who received Y90 in earlier cohorts were not resection candidates, and their Y90 was considered to be a palliative treatment for intermediate/advanced disease. Contemporarily newer studies encouraged

Table 1 Studies Reporting Outcomes of Radiation Lobectomy*

Study	Type of Y90 Sphere	Number of RL Patients	Disease	Number of Patients With HCC	Reported FLR% Post-Rx	Hypertrophy Rate of FLR	Time of FLR Hypertrophy	Number of Patients Who Underwent Resection
Vouche et al[9]	Glass	83	HCC, IHC, CRC	67	Median (Range): 26% (9-57)%	24% and 45% at third and ninth months	Time dependent (1-9) months	5
Edeline et al[24]	Glass n = 30, resin n = 4	34	HCC	34	62.1% (median) at third month	Mean 29% (CI: 12-46) at third month and 42% (CI: 49-67) at last follow-up	third month (median)	Not reported
Lewandowski et al[12]	Glass	13	HCC, IHC, CRC	10	43% (median)	Median: 30% (range: 4%-105%)	third month (median)	All patients
Gabr et al[10]	Glass	21	HCC	21	45% (median)	Median (IQR): 23% (20-48)%	third month (median)	All patients
Palard et al[11]	Glass	73	HCC	73	66.7% ± 15.6%	35.4% ± 40.4%	5.9 ± 3.4 months	Not reported
Theysohn et al[25]	Glass	45	HCC	45	50.6%	30.8%	6 months	Not reported
Goebel et al[26]	Glass	75	HCC	75	45% ± 13.6% 50% ± 15.3%	Increase from 36% ± 11.6% to 45% ± 13.6% and 50% ± 15.3% at third & sixth months	3 months & 6 months	Not reported
Ahmadzadehfar et al[27]	Resin	24	CRC, Breast and other metastases	None	Not reported	34% (median)	4-8 weeks	1
Garlipp et al[16]	Resin	26	CRC, Breast and other metastases	None	Not reported	29% ± 22.9%	46 days (median)	Not reported
Teo et al[14]	Resin	17	HCC	17	Not reported	34.2% ± 34.9%	2-12 (months)	1
Fernandez-Ros et al[15]	Resin	83	HCC, CRC, IHC, and other metastases	52	40% ± 12% within 6 months & 50% ± 13% at >26 weeks	45% at >26 weeks	4-26 weeks	Not reported

*All values are expressed as mean ± SD, unless otherwise mentioned.

Table 2 Studies Reporting Outcomes of PVE*

Study	Number of PVE Patients	Disease	Number of PVE Patients With HCC	Reported FLR Post-Rx	Hypertrophy Rate of FLR	Time of FLR Hypertrophy/ Resection	Number of Patients Who Underwent Resection
Farges et al[28]	27	HCC, IHC, other metastases	14	44% (mean) ± 13%	35% ± 28%	49 ± 13 days	All patients
Denys et al[29]	40	HCC	40	36% ± 10%	41% ± 32%	4-5 weeks	Not reported
Okabe et al[30]	19	HCC	19	55% ± 11.5	From Mean FLR 37.8% ± 10.1% at baseline to 55% ± 11.5% before surgery	Median: 28 days (range, 19-63 days)	All patients
Yoo et al[19]	64 PVE vs 71 TACE + PVE	HCC	135	40.3 ± 8.1% (PVE only) 41.4 ± 7.3% (PVE + TACE)	Mean FLR increased from 34.5 to 40.3 (PVE only) Mean FLR increased from 34.1% to 41.4% (PVE + TACE)	1 month	58 (PVE only) and 68 (PVE + TACE)
Siriwardana et al[31]	54	HCC	54	34% (20%-54%)	23% (range: 12%-33.5%) improved to 34% (range: 20%-54%)	Not reported	34
Sakuhara et al[32]	143	Cholangiocarcinoma (84), gallbladder carcinoma (23), HCC (27), other metastases (9)	27	45.7 ± 10.4% (all patients)	FLR increased from 34.9% ± 8.7% to 45.7% ± 10.4% (all patients)	17.3 ± 10.4 days	120 (of all patients)
Garlipp et al[16]	26	CRC, breast and other metastases	None	Not reported	61.5% ± 37.3%	Median (33 days)	Not reported
Shindoh et al[17]	358	Liver metastases (242), HCC (49), BC (31), other (36)	49	Median 29.7% (IQR: 22.5-38.2)	The median FLR increased from 19.5% (IQR: 15.0-25.9) to 29.7% (IQR: 22.5-38.2)	32 days	240
Cazejust et al[33]	63	HCC, CRC, IHC	38	36% ± 12% (all patients)	FLR increased from 25% ± 8% to 36% ± 12%	4-7 weeks	30/38 (HCC patients)
Marti et al[18]	82	HCC	82	Median 40.3 (IQR: 30.6-50.3)	Median hypertrophy 14.6% (IQR: 9.8-21.8%)	4-8 weeks	69

*All values are expressed as mean ± SD, unless otherwise mentioned.

the adoption of Y90 as neoadjuvant treatment prior to surgical resection, and RL would be used to induce contralateral hypertrophy of the untreated hepatic lobe. Most recently, Palard et al the contralateral FLR hypertrophy can be induced as long as nontumoral (normal parenchyma) of treated lobe receive an absorbed dose >88 Gy, while maintaining minimal toxicity rates.

Subsequent hepatic resection has been reported in recent studies.[10,12] In addition to FLR hypertrophy and low toxicity rates after Y90, it was noted that Y90 can help improve the resection margin. None of the current studies reported any hepatic decompensation for RL patient undergoing resection. However, multicenter studies are needed to confirm those findings.

Portal Vein Embolization

Table 2 summarizes the most relevant studies on PVE. PVE in cases of HCC serves as a bridge to potentially curative resection in patients with insufficient FLR. Most studies showed that PVE results in considerable contralateral hypertrophy with a short period of time, 1-2 months.[16] Despite its benefit of allowing surgery in patients previously unsuitable for resection, embolization of the portal vein increases the growth rate of the HCC tumor as compared to the rate of growth before the procedure.[5] This growth and progression could disqualify some patients from undergoing resection, as evidenced by studies in Table 2. Studies reported an incidence of 3%-38% in cases of HCC tumor progression which in many cases prevented resection in patients who underwent PVE.[17−19] A meta-analysis of PVE in cases of major liver resection (HCC, 265; cholangiocarcinoma, 430; other, 393) found that 78 patients (7.2%) did not undergo resection due to severe progression of liver metastases or extrahepatic spread.[20] TACE in combination with PVE has been adopted by some centers as a means of controlling tumor progression and inducing tumor necrosis until sufficient FLR hypertrophy allows resection.[17] However, poor liver functions were reported to be associated with tumor progression even with sequential TACE and PVE approach. The same study also noted that 10 of 54 patients who underwent TACE + PVE treatment had tumor progression that prevented them from undergoing resection (Ronot).[21]

Advantages of RL Over PVE

The majority of the literature on PVE is on colorectal cancer metastases. There are few reports of PVE in the setting of HCC. In one CRC study comparing PVE to RL after propensity score matching of two patient cohorts treated at two different centers, the authors concluded that RL induces significant FLR hypertrophy but at slower rates than PVE.[16] These findings were only applicable to metastatic liver disease patients, with none of the treated patients in either cohorts exhibiting underlying chronic liver disease. Hence, PVE might be the approach of choice in patients with metastatic disease, where expeditious surgical resection should be considered. However, tumor progression after PVE is not uncommon.[20]

In HCC patients where underlying chronic liver disease is common, Y90 RL may be advantageous. RL improves chances of long-term survival by inducing FLR hypertrophy (thereby permitting resection), achieving disease control and/or tumor necrosis. Such response to treatment can be translated into lower chance of recurrence after surgical resection.[10]

Response to Y90 can also serve as a biological test of time of HCC patients prior to surgery. This concept has been adopted in clinical oncology and represents one of the basic rationales of neoadjuvant chemotherapeutic treatment prior to surgical resection of breast as well as gastrointestinal cancers. Similarly, HCC patients who exhibit prolonged response to Y90 might be considered as having favorable tumor biology and lower recurrence rates.[22] This concept is also adopted in the current OPTN/UNOS criteria which require patients to maintain progression free period of at least 6 months from the date of listing in order to gain MELD upgrade points.[23] This is especially relevant in those patients with multifocal disease who are higher risk for early development of new tumors.

Finally, HCC patients who undergo surgical resection might lose their surgical candidacy despite achieving sufficient FLR hypertrophy. This is often observed in cardiac patients or patients who acutely develop major systemic illnesses. In those patients, Y90 induced tumor necrosis will achieve local disease control, and subsequent Y90 (lobar or selective) can be done as necessary. In a similar setting, HCC patients who do not undergo surgical resection after PVE will have limited future therapeutic options.

In conclusion, RL has evolved into an approach where patients with small FLR but otherwise present with resectable disease are optimized prior to surgery. The triad of neoadjuvant treatment, an embedded biologic test-of-time, and controlled hypertrophy of the FLR supports the use of RL in the neoadjuvant preresection setting.

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