WHAT WOULD YOU DO?

Practical IR Approach to Early Stage Hepatocellular Carcinoma

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CASE PRESENTATION

A 58-year-old man with hepatitis C virus cirrhosis presents with a 2.1-cm hepatocellular carcinoma (HCC) in hepatic segment 3. Because of the patient's comorbidities, the patient is not a surgical candidate. Arterial-phase and venous-phase MRI findings are shown in Figure 1.

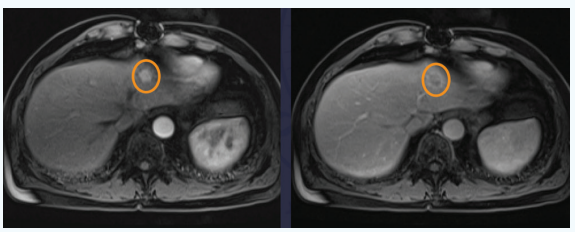

Figure 1

What treatment would you offer?

- **Ablation**
- **Embolization + ablation**
- **Bland embolization**
- **Conventional chemoembolization**
- **Radioembolization**
- **Stereotactic body radiation therapy (SBRT)**

Dr. Brown: A 2.1-cm tumor can be effectively ablated with accurate targeting. Deeper tumors such as this one are more difficult to target with ultrasound or CT. Along these lines, fiducial marker placement for SBRT would also be a challenge as well. Some operators may be able to target this mass for ablation and/or fiducials. However, in my practice, I would treat this via an intra-arterial approach.

Regarding choice of therapy, prolonged survival with Barcelona Clinic Liver Cancer (BCLC) stage 0/A/B tumors is achievable with both chemoembolization or radioembolization.[1,2] Vouche et al described a 53.4-month median survival with radiation segmentectomy,[1] whereas Burrel et al found a median survival of 54.2 months for BCLC stage A HCC treated with chemoembolization.[2]

An important question is whether this patient can ultimately be listed for transplantation. In a randomized prospective study, radioembolization led to a significantly longer time to progression compared to chemoembolization (> 26 months vs 6.8 months; $P = .0012$).[3] However, overall survival was no different between groups when transplant patients were censored (18.6 months for radioembolization vs 17.7 months for chemoembolization; $P = .09$). Similar findings were reported in a retrospective review by Padia et al.[4]

Dr. Salem: This is a case of a patient with a small lesion that would initially prompt the consideration of radiofrequency ablation given the tumor size. However, one of the important factors when considering radiofrequency ablation is location. Lesions traditionally deemed ablatable may not be if they abut the gallbladder, stomach, or colon. Tumors located beneath the heart are also difficult to ablate, requiring significant imaging and tracking software expertise, which may not be available to all physicians. In such cases, arterial options should be considered. At our center, we favor radioembolization using radiation segmentectomy. Several years ago, we published a multicenter study of unablatable small tumors treated with radioembolization. We performed an imaging analysis as well as a radiology-pathology correlation. We learned that by applying > 190 Gy, we can achieve a time to progression of 33 months, response of 90%, and survival of 53 months.[1] This is performed on an outpatient basis often using a same-day technique.[5] Patients exhibit very few (if any) side effects when a very small segment of liver is irradiated. Given the constellation of these findings, radiation segmentectomy, when applicable, has become our standard of care.

Dr. Lee: We will ablate tumors that are BCLC stages 0 and A if they can be targeted for applicator placement and have no contraindications for ablation such as uncorrectable coagulopathies, inability to tolerate anesthesia or deep sedation, or anatomy that makes ablation high risk (discussed in further detail later). Ablation is now considered potentially curative and a first-line therapy for HCC within BCLC stage 0 and A for patients with portal hypertension and those who are not surgical candidates. This protocol is established within treatment guidelines adopted by the largest hepatology societies in America, Europe, and Asia due to decades of experience and robust scientific literature confirming safety and efficacy.[6] For small HCCs treated by experienced operators with modern equipment, local tumor progression is expected to be < 10% after a single treatment, and a high proportion of recurrences can be retreated with ablation.[7,8] For cases successfully treated by ablation, overall survival is governed more by the degree of liver dysfunction and the appearance of metachronous tumors and less by recurrence of the targeted tumor.[7-9]

For this case at our center, we are experienced with ablating tumors in this location, and thus the patient would undergo ablation, as it is the nonsurgical modality that gives HCC patients the best chance at a cure.[6,10] Importantly, ablation is extremely well tolerated in cirrhotic patients, with minimal collateral damage to functioning liver tissue, and postablation liver failure is exceedingly rare.[7-11] However, we understand the hesitation to place needles and apply energy in this location, and there are proponents of all of the previously outlined approaches that have an excellent rationale and results. Ultimately, if you are uncomfortable with ablation and placing applicators in this location, this would be a difficult case, and we would support either referral to an experienced ablation center or an alternative approach such as yttrium-90 (Y-90), transarterial chemoembolization (TACE), or SBRT.

Figure 2

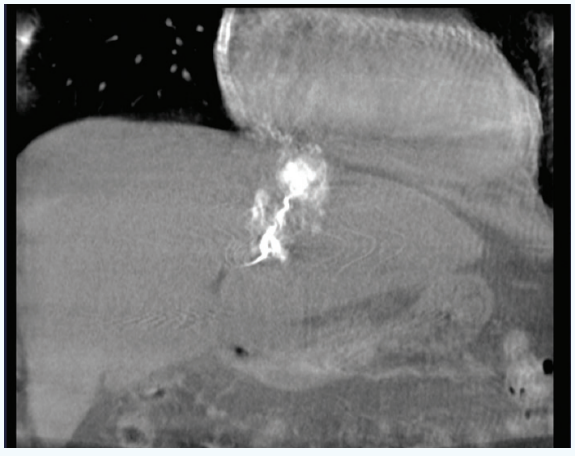

Figure 3

CASE CONTINUED

A celiac angiogram demonstrates an accessory left hepatic artery from the left gastric artery (Figure 2). Cone-beam CT demonstrates proximity of tumor to the heart (Figure 3).

How does anatomy affect technique? Do changes in technique affect expected outcomes?

Dr. Lee: This is an excellent question and one that, in my opinion, is not asked often enough when considering

all the available locoregional therapies at our disposal. Treatment guidelines lump all HCCs of a certain size and number together when considering therapeutic options, but in reality, the anatomy of the tumor will often be the most important factor for determining how a particular case is treated. For example, we are hesitant to ablate tumors of any size in close proximity to the central bile ducts or bowel that cannot be protected with hydrodissection. In this case, the proximity to the heart and diaphragm might raise questions about mechanical or thermal injuries and whether the application of an electrical current or microwave field could provoke serious arrhythmias. In terms of mechanical injuries, a direct injury to the heart during applicator placement is a consideration and could be lessened with the use of meticulous technique and choice of technology. For tumors in this location, I would not advise using deployable ablation devices where it is exceedingly difficult to track each prong during deployment. In general, and in particular for this case, I would advise using ultrasound to guide applicator placement due to the multiplanar real-time capability of ultrasound and the ability for the operator to visualize the tumor target, needle, and heart near-simultaneously. In Europe and Asia, where ablation is routinely used for BCLC stage 0 and A HCC with excellent results, ultrasound is the dominant guidance modality.[8,9,11]

In terms of electrical and thermal damage to the heart, there are increasing data to show that it is safe to ablate in this location as long as a minimum distance is considered. Microwave ablation has a highly localized electromagnetic field, and distances > 5 mm from the heart appear safe.[12,13] When using radiofrequency ablation, there is conduction of electrical current between the electrodes and ground pads, and a minimum safe distance is less clear. In general, static CT images underestimate the amount of cardiac motion, and this motion combined with the large amount of perfusion of the myocardium make the heart fairly resistant to thermal damage. The local tumor progression rates for high-dome tumors may be slightly increased due to the more difficult visualization and more complex probe placement,[10] but this should not preclude an attempt to treat these tumors with ablation if feasible.

Dr. Salem: When it comes to Y-90 and other therapies, technique is very important. For this reason, several studies have been published looking at technique, injection rates, and catheter position.[14,15] The gastrohepatic trunk, as noted in this case, also requires care in catheterizing, and it may be prone to spasm and dissection, particularly in a patient who has undergone chemotherapy. We recommend the use of a base catheter and selective work using microcatheter systems. Care must also be exercised when selective segmental arteries are accessed, as spasm and dissection are also possible. In a case such as this one, we perform the Tc-99m MAA scintigraphy from the gastrohepatic trunk level and only selectively catheterize the segment 2 artery for segmentectomy on the day of treatment, limiting the number of times that vessel is accessed to once. Cone-beam CT is critical here and should be performed in all cases. Finally, the proximity to the heart or other structures is not an issue with Y-90, and we have published evidence noting this point.[15]

Dr. Brown: For tumors at the dome, we generally perform arterial intervention at the time of initial treatment. With use of techniques such as C-arm CT, we can confirm coverage of the entire tumor and perform superselective therapy. Accessing an accessory left hepatic artery is very straightforward, and a tumor of this size is safely and effectively treatable with either chemoembolization or Y-90.

What defines curative intent for HCC?

Dr. Salem: The definition of "cure" can be quite variable depending on the center, tumor type, and long-term expectation. Although many treatments are deemed curative, they often recur (resection, transplantation). We have data (currently under review) in a selected cohort of patients that show that the radiation segmentectomy technique may also be curative, providing a median survival of 6.5 years. Ultimately, from a statistical standpoint, there is only one way to demonstrate that a treatment is curative—a flattening Kaplan-Meier survival curve. Once you show that treatment may yield very long-term survival in a certain percentage of patients, that treatment is "potentially curative," which is what is seen with radiation segmentectomy. In this case, the patient should expect very long-term survival.

Dr. Brown: HCC in a noncirrhotic patient can potentially be resected for cure. Otherwise, transplantation is the only curative option. In cirrhotic patients, there is effectively field carcinogenesis of the entire liver. This likely contributes to the higher rates of recurrence in the hepatitis C population. One review of resection and transplantation patients found that 89% of hepatitis C patients were cirrhotic compared with 68% of those with hepatitis B.[16] This group also found a significantly higher rate of recurrence in hepatitis C compared with hepatitis B patients.

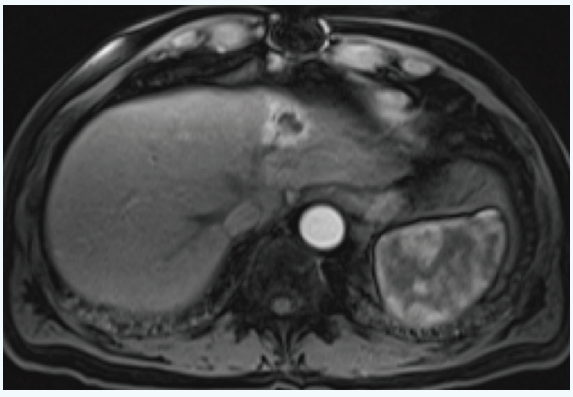

Figure 4

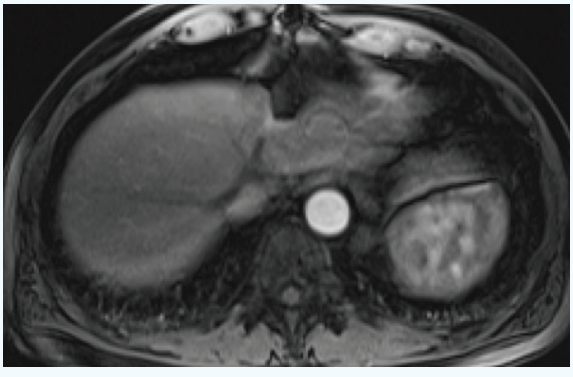

Figure 5

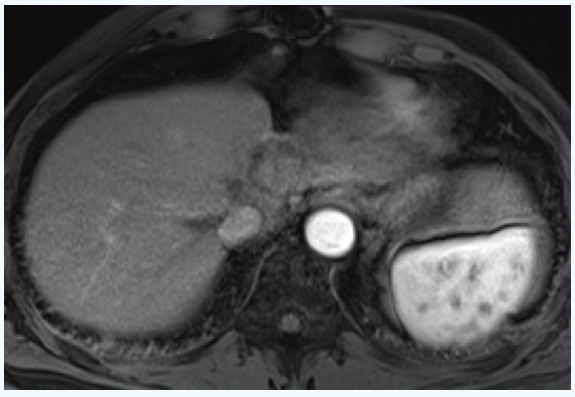

Figure 6

Thermal ablation functions physiologically similarly to resection. Lencioni et al reported excellent tumor control with radiofrequency ablation at 5 years.[17] However, 81% of patients had developed new tumors elsewhere in the liver. Differences in hepatitis B and C patients likely exist with arterial and ablative therapies. Effective treatment of hepatitis B virus with antivirals can lead to a prolonged survival following locoregional therapy (median, 80 months; maximum, 152 months).[18] Similar outcomes have not yet been identified for hepatitis C virus.

Dr. Lee: The goals of ablation are very similar to surgical resection: "removal" of the tumor and maintaining an appropriate margin. Importantly, every malignant cell is targeted for destruction. There is a paucity of data to support the concept of "debulking" HCCs, and so we advise against ablation as monotherapy when the entire tumor and a margin cannot be safely targeted. For tumors larger than 4 cm (and in some smaller tumors with imaging biomarkers of tumor aggressiveness), we will use ablation in combination with intra-arterial therapies. Several studies of radiofrequency ablation/microwave ablation combined with TACE have demonstrated excellent results, which are generally superior to TACE alone.[19,20]

In terms of expectations for cure, most of the largest radiofrequency ablation series demonstrate a local tumor progression rate for a single treatment of approximately 10% to 20%, compared to 10% for microwave ablation.[8,9] Importantly, ablation can be repeated in cases of technical failure, thus yielding even better rates of secondary efficacy. However, it must be kept in mind that ablation is a local treatment, and up to 80% of HCC patients will develop metachronous tumors within 5 years, thus patients will require life-long imaging.[17] Overall survival after ablation of HCC is in the range of surgical series and widely varies across different continents. Representative 1-, 3-, and 5-year overall survivals after radiofrequency ablation and microwave ablation from highly experienced European and Asian centers are 97%, 71%, 48% and 96%, 82%, and 67%, respectively.[17,21] However, I would urge extreme caution when comparing the efficacy of HCC treatments of any type based on overall survival numbers due to potential differences in the cause and degree of underlying cirrhosis. Without very careful control of these factors, an apparent "difference" in survival between modalities may simply be due to a difference in patient comorbidities and cause and degree of cirrhosis.

CASE CONCLUSION

Providing local tumor control for this nonoperative patient can be performed with many treatment modalities, as described by the expert panel discussion. Choice of therapy is based on the available data as well as local expertise. This patient was treated with segmental high-dose glass microsphere radioembolization.

Although an accessory left hepatic artery originating from the left gastric artery may pose a challenge for embolotherapy with an increased risk for nontarget therapeutic delivery, percutaneous thermal ablation would require advanced techniques.

The high tumor dose delivered with radiation segmentectomy maximizes cytotoxic radiation delivery, while the focused delivery minimizes risk of nontarget parenchymal damage. This technique is best applied in those presenting as poor candidates to other curative intent therapies, such as surgical resection or thermal ablation. A threshold segmental dose of 190 Gy to achieve complete pathologic necrosis has been confirmed by explant correlation from transplanted livers.[1]

Follow-up imaging demonstrates the ablative intent of this intra-arterial therapy. At 1 month (Figure 4), there is tumor necrosis with the radiation margin evident as increased enhancement in the perfused volume. By 6 months (Figure 5), as well as at 12 months (Figure 6), the tumor is no longer visible, consistent with a complete response by imaging. As pointed out by the expert panel, continued imaging surveillance is indicated, as 80% of patients will develop new tumors in the liver.[17] ■

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