Ablation versus Radiation Segmentectomy for Small Liver Tumors

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Abstract

Hepatocellular carcinoma (HCC) is a liver malignancy that affects more than a million people worldwide with a complex multifactorial etiology. After the diagnosis of HCC is made, physicians establish management using the Barcelona Clinic Liver Cancer (BCLC) guidelines revolving around tumor stage, liver function, performance status, and patient preferences. According to recent updates to these guidelines, thermal ablation is the second-best curative option apart from surgical resection for small HCC (< 2 cm). While thermal ablation is standard of care, recent studies have suggested that radiation segmentectomy (RS) has similar outcomes, limited hepatotoxicity, and ultimately a cost-efficient approach. Although there is limited literature on RS, this article compares ablation techniques against radiation segmentectomy for small HCC tumors.

Keywords
- hepatocellular carcinoma
- ablation
- Y90
- microwave ablation
- segmentectomy
- interventional radiology
- radioembolization

Hepatocellular carcinoma (HCC), a primary malignancy of the liver, represents a global health concern due to its rising incidence, complex etiology, and challenging management. With an estimated incidence of >1 million cases, HCC accounts for ~90% of liver cancer.[1] The multifactorial etiology of HCC consists of chronic viral hepatitis infections, alcohol abuse, non-alcoholic fatty liver disease (NAFLD), and predisposing genetic mutations. While the disease process may differ based on the underlying cause, the typical progression involves persistent inflammation, fibrosis, the development of cirrhosis, and, ultimately, the emergence of HCC.[2] The Barcelona Clinic Liver Cancer (BCLC) is widely accepted and utilized for the management of HCC. The framework incorporates a holistic approach by accounting for the tumor stage, liver function, performance status, and patient preferences. The first stage (BCLC 0) is classified as a solitary HCC ≤ 2 cm without vascular invasion or extrahepatic dissemination in patients with preserved hepatic function and the absence of cancer-related symptoms.[3] Lesions smaller than 2 cm are also described as "small HCC" in the literature.[4] Management of BCLC 0 preferably consists of liver transplantation (LT) due to the high recurrence rate of HCC.[3] According to BCLC, if LT is not possible, the first approach should be thermal ablation.[5] The second stage (BCLC-A) is characterized by either a single HCC, regardless of its size, or multiple HCCs with a maximum of three nodules, each not exceeding 3 cm in size.[3] Per the 2022 BCLC guideline updates, in addition to chemoembolization, transarterial radioembolization (TARE) could be considered in patients with single nodules $\leq$8 cm. This new BCLC recommendation is based on the results of the Legacy study.[6] With more data demonstrating ablative effects of Y90 radiation segmentectomy (RS), there is an emerging role for RS in treating small HCC. In this article, we aim to compare thermal ablation to RS, and explore when RS may be more beneficial over ablation to treat small unresectable HCC.

Treatment Strategies for Small HCC

The BCLC staging system, recently updated in 2022, stands as one of the most widely accepted classification systems. It is the standard guideline in European countries and the United States, with specific applications such as "bridge to transplant" and "downstaging" for patients awaiting LT and

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advanced HCC cases without distant metastasis. However, it is important to note that alternative staging systems, including the Hong Kong Liver Cancer staging system, the China Liver Cancer staging system, and the Japan Society of Hepatology-HCC guidelines, also exist, and these systems lean toward a more aggressive treatment approach compared with BCLC.[7] Unlike the advanced stages of HCC, surgical resection is recommended for solitary HCC lesions per BCLC guidelines; however, only 5 to 10% of patients are considered surgical candidates.[8] Thermal ablation is considered as next curative option for patients who are not surgical candidates.

Thermal Ablation for Small HCC

The most frequently used two modalities of liver ablation are radiofrequency ablation (RFA) and microwave ablation (MWA). While RFA is a well-described liver ablation technique in the literature, MWA is becoming the standard of care in HCC treatment in the United States due to its many advantages, such as predictable heating thermodynamics, absence of impedance allowing for greater penetration of MW energy through charred tissues, and rapid achievement of the target temperature. Additionally, MWA offers similar outcomes to surgical resection even with a significantly lower baseline in liver function.[9] MWA has emerged as an invaluable and minimally invasive technique that offers precision heat rendering it particularly potent in organs with robust blood perfusion, thereby establishing it as a highly efficient therapeutic approach for HCC.[10]

Historically, certain high-risk locations, such as adjacent to the portal veins, bile ducts, and heart, were considered prohibitive for thermal ablation; however, recent studies showed encouraging results that MWA in such areas is relatively safe and effective when precaution is used.[5,11,12] While the literature provides evidence supporting the safety of utilizing MWA in challenging locations like proximity to the heart, near the diaphragm, and adjacent to the hepatic hilum, additional precautionary measures can be performed based on the skill and experience of the proceduralist to enhance safety.[5,11,12]

Numerous retrospective evaluations have indicated that the combination of transarterial chemoembolization (TACE) and ablation could potentially yield oncological outcomes comparable to surgical resection, particularly for lesions smaller than 3 cm. One meta-analysis found that combination of interventional therapies such as TACE and RFA seem to be more effective than RFA alone.[13] These findings align with more robust evidence suggesting that ablation is on par with resection when applied to carefully selected patients with HCCs measuring less than 3 cm.[14]

Radiation Segmentectomy for Small HCC

When surgical resection or thermal ablation is not feasible, an alternative treatment option available to patients is RS. RS involves the use of yttrium-90 glass microspheres to perform radioembolization ablation on two Couinaud segments or less.[8] RS was developed to selectively treat specific Couinaud segments to not only minimize radiation dosage to the liver parenchyma but also to allow a higher dosage of radiation which would correlate with a higher objective response.[15] While RS can be used to specifically target Couinaud segments, it is prohibited with patients who have compromised liver function causing hyperbilirubinemia, uncorrectable gastrointestinal perfusion, severe coagulation dysfunction, and peripheral vascular disease which prohibit proper arterial catheterization.[16] Considering that radiotherapy induces irreversible cellular injury, elevated doses to hyper-perfused tissue indicates that vascular damage may play a pivotal role in Y90's anticancer efficacy.[17] In the study by Vouche et al,[18] pathological assessment after LT in 33 patients revealed complete tumor necrosis in 52% of patients who underwent RS, and >90% tumor necrosis in 48% of patients treated with Y-90 as a bridge to LT. These findings sparked increased interest in RS as a potential primary treatment for bridging therapy for HCC as an alternative to thermal ablative techniques.

Lewandowski et al[19] conducted a retrospective study spanning 14 years, comparing patient outcomes following RS in 70 patients. Their findings indicated that response rates, tumor control, and survival rates were no different from other curative treatment modalities.[19] Additionally, findings from a study by Gabr et al indicated that a therapeutic ablative effect with complete pathological necrosis (CPN) was consistently achieved when the administered dose exceeded 400 Gy.[20] It has been shown that tumors with CPN have a significantly lower recurrence rate after LT than tumors with incomplete necrosis.[21] One study found no significant hepatoxicity using Y90 even with some patients having mild to moderate liver dysfunction.[22] The evolution of knowledge pertaining to administration techniques, ideal dosages, and the segmental approach has brought about shifts in the practice of radioembolization. In 2022, the RASER trial, conducted as a single-center, single-arm study, examined the effectiveness of RS as a curative therapy for individuals with unresectable solitary HCC measuring less than 3 cm.[23] Over a median follow-up period of 691 days, the median time until target lesion progression was not reached. The risk of target lesion progression stood at 4 and 12% at the 1- and 2-year follow-up intervals, respectively.[23] Conclusively, several research studies have firmly established RS as a safe and effective therapy for solitary HCC.[6,19,23]

Percutaneous Ablation versus Radiation Segmentectomy

RS provides a few advantages over the percutaneous ablation. The first advantage RS has over ablation is that there is no risk of tumor seeding along the tract and can be safety used to treat subdiaphragmatic or subcardiac lesions since it doesn't require percutaneous access.[24] In addition, there is no risk associated with general anesthesia as it is not needed in RS. Another advantage of RS is the ability to target satellite lesions due to the angiosome concept and continued blood flow allowing the particles to reach and access the lesion.[24]

While this is seen as an advantage, it could also end up as a disadvantage as some tumors are hypovascular which would make RS ineffective due to its reliance of the tumor's vasculature.[24] Other disadvantage of using RS is it's side effects such as nausea, anorexia, vomiting, and abdominal pain.[25] Other severe adverse effects, although rare, include radiation induced liver and lung disease.[25]

There is a scarcity of comparative data available concerning imaging response and overall survival (OS) when it comes to RS therapy versus thermal ablation modalities. Only a few studies addressing this subject in patients with HCC have been published. When considering the treatment of HCC, the choice between ablation and RS hinges on factors like clinical presentation, lesion location, outcomes, physician preference, and the cost of the procedure itself. While each technique requires specific patient criteria, both techniques yield similar results in terms of patient outcomes according to the limited literature.

Comparing Outcomes

A frequently employed combination therapy with curative objectives for HCC involves TACE plus RFA or MWA (referred to as TACE ablation), typically performed within 0 to 4 weeks of each other. A retrospective study conducted at a single center, using propensity score matching, focused on HCCs measuring 3 cm or less in 417 and 235 consecutive patients who were treated with either TACE plus ablation or RS, respectively.[26] This study found no statistically significant differences in OS. Mean survival was 30.8 months in the RS group and 42.7 months in the TACE MWA group ($p = 0.80$). Additionally, there was no difference in time to progression (TTP). The overall median TTP was 12.1 months (95% CI: 7.7 months, 19.1 months) in the TACE MWA group and 11.1 months (95% CI: 8.8 months, 25.6 months) in the RS group ($p = 0.99$). According to this study, RS has the potential to achieve efficacy levels comparable to those of thermal ablation.

Another study conducted by Arndt et al[14] compared RS and MWA of solitary surgically unresectable HCC smaller than 4 cm and demonstrated no significant difference in mean OS (the mean OS in the MWA group: 44.3 months vs. RS: 59.0 months; $p = 0.203$) and mean non-target progression-free survival rates (46.7 months for MWA vs. 51.0 months for RS; $p = 0.439$). However, target lesion progression-free survival was significantly greater for RS 59.0 months vs. MWA 44.3 months ($p = 0.021$).[14] These two studies demonstrate that RS achieves comparable outcomes to MWA with or without TACE combination.

Comparing Feasibility and Cost

Considerations related to patient's convenience and expenses should be made when comparing two treatments. As discussed by Biederman et al,[26] patients undergoing TACE-MWA may require overnight admission, in contrast to patients undergoing RS, which is performed as an outpatient procedure. The feasibility of conducting both mapping and Y90 therapy treatment on the same day has also been discussed in the literature. In the future, it may be possible to streamline RS into a single-day outpatient procedure.[27]

While patient outcomes are similar, the cost of the two techniques differs quite profoundly. While the cost of a single TACE procedure is $17,000, radioembolization costs for unilobar and bilobar are approximately $31,000 and $48,000 in the United States, respectively.[28] While TARE costs more per procedure, it does not require hospital admission and it ultimately does not differ in overall cost when compared with traditional approaches like MWA and TACE.[29] In addition, another study yielded similar results in which, when considering variables like hospital admission, pain control, toxicity, and treatment sessions, TARE was the most cost-effective approach when it came to unresectable HCC.[30] When comparing the treatment options for small HCC lesions, TARE emerges as a promising therapeutic choice that delivers similar patient outcomes while being a more cost-effective approach compared with TACE plus MWA.

Conclusion

According to current literature, both MWA and RS offer similar early- and mid-term outcomes in the treatment of early-stage HCC. Although the current standard of care is ablation for non-surgical patients with small HCC, more recent investigations show promising outcomes for RS as a first-line treatment for patients with small HCC. However, more studies are needed to evaluate long-term outcomes. We recommend personalized treatment selection based on BCLC guidelines, as well as patient and tumor variables.

Conflict of Interest
None declared.

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