The stage of hepatocellular carcinoma (HCC) at the time of diagnosis is a critical determinant of patient survival, with a significant portion of the disease burden of HCC imparted by diagnosis during a relatively advanced stage. Treatment recommendations for HCC vary by stage of disease. Surgical resection is the gold standard treatment for patients with early stage HCC, and ablation is considered the next best option in patients who are poor surgical candidates. For intermediate- and advanced-stage disease, the recommended treatment options are transarterial chemoembolization (TACE) and systemic therapy, respectively. The Barcelona Clinic Liver Cancer (BCLC) guidelines recommend transarterial therapy for BCLC stage B patients who have a substantial intrahepatic tumor burden, preserved performance status, and relatively preserved liver function. The randomized controlled trial by Llovet et al provided the foundation for this recommendation.

There have been remarkable technologic advancements in interventional oncology equipment and imaging during the past 2 decades. The widespread use of microwires, microcatheters, and imaging technology such as cone-beam CT have contributed to successive improvements in the ability to selectively treat tumors while minimizing collateral damage to areas of adjacent liver parenchyma. The ability to more directly target tumors led to numerous studies evaluating the use of transarterial therapy in the treatment of later-stage HCC, for which systemic therapy is the recommended treatment. In contrast, there is a relative paucity of literature on the use of transarterial therapy in early stage HCC. This is not surprising given the established differences in efficacy between chemoembolization and ablation, even when the former is performed in a highly selective fashion with the most modern technology.

**RADIATION SEGMENTECTOMY: WHAT DO WE KNOW?**

Radioembolization is a transarterial therapy with a different mechanism of action than chemoembolization: β decay of yttrium-90. When administered via a glass-based vector, it is minimally embolic, and thus, its maximum therapeutic effect is not limited by the quantity of the delivery vector. This is in contrast to cases in which stasis is reached during the delivery of embolic therapies such as chemoembolization or bland embolization. The minimally embolic nature of glass-based yttrium-90 therapy allows for the delivery of lobar doses at a segmental level, a concept described by Vouche et al as radiation segmentectomy.

Studies by Vouche et al and Riaz et al established radiation segmentectomy as a highly efficacious treatment option with a low rate of toxicity. When outcomes were analyzed at a cellular level, impressive rates of pathologic necrosis were reported: radiation segmentectomy resulted in 90% to 100% pathology necrosis in all treated patients, and complete pathologic necrosis was seen in 52% of patients. A threshold of 190 to 200 Gy to the targeted segment was found to be predictive of complete pathologic necrosis when pathologic necrosis rates were correlated with dosing. Subsequent work by Padia et al on patients treated...
with superselective radioembolization reported notable imaging response rates, with a complete response by modified RECIST (Response Evaluation Criteria In Solid Tumors) achieved in 95% of patients.8

Several studies support radiation segmentectomy as the preferred transarterial treatment option in patients who are poor candidates for surgical resection and ablation. Studies by Padia et al and Biederman et al both showed that segmental radioembolization had greater efficacy than segmental TACE.9,10 The highest-quality evidence can be derived from a recent prospective randomized trial comparing radioembolization and TACE administered at both a segmental and lobar level, which demonstrated longer time to progression in patients treated with radioembolization.11 Notably, no studies have detected a significant survival difference between radioembolization and TACE in the treatment of patients with early stage HCC. However, it is important that this finding be interpreted with respect to the established 5-year survival rates of 50% to 75% in HCC patients with BCLC stage A disease.2 Larger sample sizes and longer follow-up times would be required to detect significant differences in survival outcomes.

DISCUSSION

The primary goal of treatment in patients with early stage HCC should be complete cure. Traditional wisdom has held that this can only be accomplished through surgery or ablation, with transarterial therapy considered as temporizing or palliative. Recently, a study by Biederman et al reported similar efficacy outcomes in patients with solitary HCC ≤ 3 cm treated with either radiation segmentectomy or TACE combined with microwave ablation.10 This result, combined with those of studies evaluating the rates of complete pathologic necrosis achieved with radiation segmentectomy, lend credence to the idea that transarterial treatment can be performed with curative intent.

A criticism of the use of radiation segmentectomy in patients with tumors that are difficult to ablate is the absence of concrete guidelines establishing what makes an ablation challenging.12 A variety of factors, such as tumor proximity to vital structures or large vessels, influence the technical feasibility of ablation. Ultimately, operator-specific differences in experience and risk tolerance combine to create a spectrum over which a transarterial or percutaneous approach is preferred.

A contention of the authors that the time spent planning and successfully administering transarterial therapy is inversely proportional to the tumor burden. Thus, the technical challenges encountered when administering endovascular therapy for small solitary peripheral tumors are often greater than the technical challenges of treating large, multifocal tumors through a proximal lobar artery. In contrast, small peripheral tumors, particularly those located in the right lobe, present relatively few technical challenges for surgical oncologists. The advent of technologies that have led to improved transarterial tumor targeting and navigation of small vessels have been instrumental in lowering procedure time and improved the safety profile of transarterial interventions. Furthermore, establishment of a dose threshold of 190 to 200 Gy (above which Vouche et al reported a spike in the rate of complete pathologic necrosis) also represented an important step forward in improving selective internal radiation dosing. Together, these advances have helped pave the way for radiation segmentectomy to develop from a theoretical niche concept into a feasible, highly efficacious, and targetable locoregional therapy.

The study of radiation segmentectomy is still in its early stages, and to date, no study has directly compared radiation segmentectomy to surgery. Although studies exist suggesting similar outcomes in surgery compared to ablation and in ablation relative to radiation segmentectomy, applying the transitive property to retrospective literature to reach the conclusion that radiation segmentectomy is equivalent to surgery is clearly wrought with fallacy. However, the growing number of studies that have reported response rates and recurrence rates on par with therapies for BCLC stage A patients raises the possibility that radiation segmentectomy could one day be included in part of the discussion of therapies with curative intent.

CONCLUSION

Although early studies on radiation segmentectomy are quite promising, the existing literature is insufficient to consider radiation segmentectomy as an equally efficacious alternative to surgery at this time. However, the advent of radiation segmentectomy has clearly challenged the pervasive notion that transarterial therapy is solely palliative and rarely curative. Further studies on radiation segmentectomy are eagerly awaited—particularly those examining dose optimization, longer-term efficacy, and survival outcomes.


