



Radiofrequency ablation and stereotactic body radiotherapy as non-surgical options for hepatocellular carcinoma

Daniel Benjamin Gans, Sidhartha Tavri, Pablo Ros, Indravadan Patel

Department of Radiology, Case Western Reserve University, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

Correspondence to: Daniel Benjamin Gans. Department of Radiology, Case Western Reserve University and University Hospitals Cleveland Medical Center, Cleveland, OH, USA. Email: daniel.gans@uhhospitals.org.

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Introduction

HCC is the most common primary liver malignancy and carries a poor prognosis, with a 5-year survival less than 12%. In the United States, the incidence is increasing at an alarming rate, mostly due to the rise in hepatitis C virus (HCV) infection; there has been more than a 3-fold increase in incidence between 1975 to 2007 (1). Globally, hepatocellular carcinoma (HCC) is the second highest cancer-related cause of death, with approximately 600,000 deaths per annum (2).

Although the treatment algorithms for HCC are complex, the choice of therapy is generally based off of the staging, with very early and early stages [Barcelona Clinic Liver Cancer (BCLC) Stages 0 and A, respectively] potentially amenable to curative treatments (3). Current standard of therapy for these stages include surgical resection, liver transplantation and percutaneous ablation. Now, there is growing evidence for therapeutic efficacy of SBRT. In this editorial, we review a recent, single institution, retrospective study (4) led by Wahl that has compared RFA and SBRT for HCC.

Radiofrequency ablation (RFA)

Since the early 1990s, RFA has been first-line locoregional therapy for very early or early stage small (<3 cm) HCCs. The procedure involves placement of a straight needle electrode into the neoplasm, to which an oscillating electrical current is applied, resulting in resistive heating about the electrode and subsequent tissue

hyperthermia (5).

A review performed by Yamakado *et al.* described complete absence of HCC enhancement following RFA in 90% of tumors <3 cm in size, with local recurrence ranging from 2.4–19.5% at three years (6). Increasing tumor size and tumor location portend worse outcomes. These typically occur with tumors near vessels due to heat sink and those adjacent to the hepatic dome secondary to poor sonographic visualization. These limitations can be overcome with various techniques including creation of artificial pleural effusion or ascites, balloon-occluding vessels which may limit heat sink, and usage of multiple electrodes to target larger tumors.

RFA is a safe procedure with an overall mortality rate of 0.3% and major complication rate of 2.2%. The most common major complications (from highest to lowest incidence) include hemorrhage, tumor seeding, liver abscess, bowel perforation, hemothorax, and liver failure (7).

Stereotactic body radiotherapy (SBRT)

Historically, conventional 2-dimensional radiation therapy has not been highly utilized in the treatment for HCC due to high rates of local progression and short median survival duration (8) SBRT, in comparison, utilizes a coordinate system, with or without fiducial marker placement, for precise extracorporeal delivery of highly conformal radiation (5,9). This significantly limits dose to adjacent normal tissues.

In order to accurately treat the lesion of interest, sharp

target delineation is required. Tight margins are typically used as to avoid collateral damage to surrounding normal tissue and critical structures. Therefore, respiratory motion can complicate these factors. To overcome such obstacles, robust immobilization devices and respiratory gating are used. Fiducial markers are often placed around the lesion as well to improve precision (10).

Like RFA, SBRT is a relatively safe procedure. The dose-limiting complication is radiation induced liver disease (RILD), with incidence of \geq grade 3 RILD ranging from 13–30% (11,12). RILD is a veno-occlusive disease which presents 2 weeks to four months following radiation therapy (13). It is categorized into “classic” and “non-classic” subtypes, based on the presence or absence of underlying chronic liver disease, respectively (8).

The other dreaded complication is gastric and duodenal ulceration or perforation, which limits SBRT for lesions <2 cm from the stomach or duodenum (8).

RFA vs. SBRT

Wahl and group (4) performed a retrospective analysis of 224 patients with inoperable non-metastatic HCCs, 161 of which were treated with RFA, and the remaining 63 treated with SBRT. Patients receiving RFA had higher rates of cirrhosis (96% vs. 78%; $P=0.001$) and lower AFP levels (8.8 vs. 18.6; $P=0.04$) than patients treated with SBRT. Patients treated with RFA also had had fewer prior liver-directed treatments (median, 0 vs. 2; P value <0.001) than patients treated with SBRT, as well as longer follow-up (median, 20 vs. 13 months; $P=0.01$). These differences were corrected by propensity score matching utilizing inverse probability of treatment weighting. No significant difference was observed in freedom from local progression (FFLP) between the two groups for lesions <2 cm. However, for lesions >2 cm, better FFLP rates were observed with SBRT.

Complications were also compared between the two treatment options. No significant difference was observed in the rate of grade 3+ acute adverse events in the RFA group compared to the SBRT group. Acute adverse events for RFA (from highest to lowest incidence) included bleeding, sepsis, GI perforation, and pneumothorax. Grade 3+ adverse events in the SBRT group included RILD, GI bleeding, and worsening ascites. At 12 months following treatment, SBRT was associated with a small but statistically significant worsening of Child-Pugh score when compared to RFA ($P=0.005$). However, on multivariate regression analysis, this was attributed to a higher rate of prior liver-directed

therapies in the SBRT group. Although recent advances has led to decreased risk of RILD with SBRT, it is still a very real risk, as high as 13% in one study (14) with a mortality rate of 10–20% (13).

Discussion

This analysis of RFA and SBRT suggests that for HCCs measuring <2 cm, both RFA and SBRT are equally viable options, and lesions >2 cm in size may benefit from SBRT over RFA. Although this data appears promising, this is a single institution’s retrospective analysis with only a small SBRT cohort (63 patients SBRT vs. 161 patients RFA). Additionally, shorter “living patient” follow-up duration in the SBRT population may have obscured late events (median 27.0 months SBRT vs. 50.9 months RFA, $P<0.001$). This study is a fitting reflection of current SBRT literature, or lack thereof, to include mostly retrospective analyses of small cohorts, ranging from 8 to 108 patients with HCC (11,14-16). These studies are further limited in regards to duration of follow-up, with median follow-up times ranging from 12.9 to 30 months. For RFA, however, there is a much larger volume of high-quality established literature supporting its efficacy and safety, with patient populations ranging from 206 to 1,170 patients and median follow-up times ranging from 24 to 72.5 months (17-20). While this literature also demonstrates a relationship between tumor size and local recurrence, there is ample evidence demonstrating RFA’s efficacy for HCC lesions measuring up to 3 cm in diameter, well beyond the arbitrary 2 cm limit used in this study. Shiina *et al.* performed 2,982 RFA treatments for HCC in solitary tumors ≤ 5 cm in diameter, or three or fewer tumors ≤ 3 cm in diameter, with 5- and 10-year survival rates of 60.2% and 27.3%, respectively (18).

Evidence for HCC lesions in the 3–5 cm range is somewhat limited. Although, a prospective study performed by Poon *et al.* in 2004 compared the efficacy of RFA for HCC <3 cm ($n=51$) with HCC >3.1 cm but <8.0 cm ($n=35$) and found no statistically significant differences in complication rate (12% vs. 17%, $P=0.48$), mortality rate (0% vs. 3%, $P=0.41$), or complete ablation rate (94% vs. 91%, $P=0.68$) (21). Furthermore, a recent randomized controlled trial enrolled 180 patients with a solitary HCC ≤ 5 cm receiving either percutaneous RFA or surgical resection with RFA having similar overall and disease-free survivals as surgical resection for patients with solitary and small HCC at 1 and 4 years (22). Lastly, there is an increasing trend towards utilization of microwave ablation (MWA) in part

due to advantages of lower heat sink effect, more predictable ablation zones, simultaneous treatment of multiple lesions, and larger coagulation volumes in a shorter procedural time when compared with RFA (23,24).

While size plays a large role, other factors must be considered. As alluded to in the article, a potential limitation to this study is the lack of unaccounted differences between the two techniques. For example, RFA is limited for lesions near vessels due to heat sink effects (25), as well as in the hepatic dome due to poor sonographic visualization (26). These factors can confound efficacy results, and therefore, both size and location of HCCs should be considered when choosing your treatment option. Additionally, multiple non-curative therapeutic options exist for the treatment of HCC, such as yttrium-90 radioembolization (Y-90) and transarterial chemoembolization (TACE), potentially with the goal of bridging to transplantation. One study compared RFA, SBRT, Y-90, and TACE as a bridge to transplantation for HCC, all of which demonstrated good pathological response (27). A multidisciplinary approach, including interventional and diagnostic radiology, medical and radiation oncology, hepatology, and hepatobiliary surgery, is highly recommended to determine the best course of action.

The article discusses a non-statistically significant improvement of local failure rates from 10% to 0% if fiducial markers are used. Although the adverse events between RFA and SBRT were analyzed, this did not account for the small but potential risks involved in percutaneous fiducial marker placement. Such potential complications include pneumothorax, hemorrhage, and fiducial marker migration (28-30). Again, cost effective analyses for placement of fiducials should also be included in the overall cost analyses for the SBRT group.

Future perspectives

Currently, RFA per the National Comprehensive Cancer Network (NCCN), the American Association for the Study of Liver Disease (AASLD), and the American College of Gastroenterology (ACG) is considered as definitive treatment for HCC patients with stage 0-A tumors who are not candidates for resection or transplantation. Further, the NCCN and AASLD guidelines also recommend ablation as a possible bridge therapy for patients awaiting transplantation. Due to the lack of long-term, high volume literature for SBRT, continued research into the safety and efficacy of SBRT is needed before it can be considered

first-line therapy or equal to RFA for HCC greater than 2–3 cm or as possible bridging therapy prior to transplantation. Additionally, prospective, randomized trials comparing RFA and SBRT should be considered which would allow for better randomization and potentially less bias. In such a study, inclusion of the risks and benefits of fiducial markers should be assessed. Furthermore, cost-effectiveness of the two therapies can be compared.

For lesions >3 cm, MWA, radiation segmentectomy with intraarterial administration of yttrium-90, and combination locoregional therapies: RFA + TACE, SBRT + TACE, and others should be further developed. Multiple case series describing SBRT in combination with TACE (31,32) have come about recently but the safety and efficacy of such combined locoregional treatments should be further evaluated in prospective, randomized trials.

Lastly, this evaluation was limited to HCC. RFA and SBRT are also used in the treatment for other hepatic malignancies, both primary and metastatic. There is significant potential in comparing the different minimally invasive options for such conditions.

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Footnote

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