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RAPID COMMUNICATION

Radiation Segmentectomy or Ablative External Beam Radiation Therapy as Initial Treatment for Solitary Hepatocellular Carcinoma: A Multicenter Experience

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Purpose: Radiation segmentectomy (RS) and ablative external beam radiation therapy (EBRT) are now accepted, definitive, local therapies for hepatocellular carcinoma (HCC). This report aimed to describe the clinical outcomes of RS and EBRT for treatment-naïve, solitary, HCC.

Methods: A multicenter retrospective review was performed of all patients treated with RS or EBRT from March 2016 through September 2023. Inclusion criteria were initial treatment for solitary HCC ≤8 cm and absence of macrovascular invasion or extrahepatic disease. Outcomes were censored for liver transplantation (LT).

Results: Eighty-six patients (RS: 58; EBRT: 28) met inclusion criteria. The EBRT cohort had older patients (median 76 vs 66 years, $p < 0.001$), larger tumors (median 3.7 vs 2.4 cm, $p < 0.001$), and worse performance status ($p = 0.02$). The RS cohort had more patients with ≥ grade 3 liver fibrosis ($p < 0.001$). Radiologic complete response (rCR) was achieved in 97% of RS and 82% of EBRT patients ($p = 0.02$). Median time to rCR was 1 month (95% CI: 0.9–1.1) after RS and 7 months (95% CI: 6–7) after EBRT ($p < 0.001$). The 1-year local control was 97% vs 93% for RS and EBRT, respectively ($p = 0.80$). Subsequent LT was performed in 48% of RS and 11% of EBRT patients with tumor complete pathologic response rates of 76% (n=22/28) and 33% (n=1/3), respectively. Progression free survival at 1-year was 87% after RS vs 80% after EBRT ($p = 0.26$). 1- and 2-year overall survival was 88% and 85% after RS vs 84% and 59% after EBRT ($p = 0.34$).

Conclusion: RS and EBRT are effective therapies for solitary HCC. Treatment should be determined via multidisciplinary discussion based on individual patient characteristics.

Keywords: hepatocellular carcinoma, radiation segmentectomy, stereotactic body radiation therapy, proton beam therapy, ablation

Introduction

Hepatocellular carcinoma (HCC) has a significant global impact, with the 7th highest cancer incidence and 4th highest cancer-related mortality worldwide.[1] Treatment of HCC remains a challenge given the wide spectrum of disease presentations in both tumor burden and hepatic substrate. Historically, radiotherapies have been considered as palliative modalities for HCC. Recent advancements in ablative transarterial radioembolization, known as radiation segmentectomy (RS), and ablative external beam radiation therapy (EBRT) with stereotactic body radiation therapy (SBRT) using either photon or proton beam therapy (PBT) have led to outcomes comparable with thermal ablation.[2–7]

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RS and EBRT are now guideline-supported therapies for patients with early-stage HCC who are not candidates for conventional first-line treatments.[8–10] Despite the growing multidisciplinary utilization of both RS and EBRT, the comparative performance of these modalities for early-stage HCC is unknown. The aim of this report was to describe clinical outcomes of both RS and EBRT as initial therapy for solitary HCC.

Materials and Methods

Patient Selection and Treatment

This study was approved by the central Institutional Review Board at the authors' institution and written informed consent was waived. A retrospective review was performed of patients treated with RS at a single tertiary medical center or EBRT at three tertiary medical centers within the same healthcare system from March 2016 through September 2023. Inclusion criteria were treatment-naïve, solitary, HCC ≤ 8 cm diagnosed per imaging using United Network for Organ Sharing (UNOS) criteria, Liver Reporting & Data System (LI-RADS) criteria, or biopsy, and the absence of macrovascular invasion or extrahepatic disease. Our institutional policy is to obtain HCC liver imaging with contrast-enhanced magnetic resonance imaging (MRI) unless contraindicated.

Treatment decisions were made via a multidisciplinary hepatobiliary tumor board. Per previously published institutional treatment thresholds and published prospective data, ablative RS was defined as radioembolization to one or two Couinaud hepatic segments with a single-compartment dose ≥500 Gy using the Medical Internal Radiation Dose schema and a specific activity corresponding to the first 8 days after calibration.[11,12] All RS were performed by interventional radiologists using Yttrium-90-containing glass microspheres (TheraSphere™, Boston Scientific, Marlborough, MA). Ablative EBRT was defined as RT with a Biologically Effective Dose (BED) ≥ 80 Gy with an α/β ratio of 10 per expert consensus guidelines.[13] All EBRT was performed by radiation oncologists using either SBRT (photons or protons) or PBT per their discretion. All patients that met inclusion critiera did not receive prior or concurrent therapies for their targeted tumor.

Outcomes

Analyzed outcomes included radiologic tumor response by the modified Response Evaluation Criteria in Solid Tumors (mRECIST), local control, overall progression, time-to-progression (TTP), progression free survival (PFS), complete pathologic necrosis (CPN), and overall survival (OS). All outcomes were censored for liver transplantation (LT). Imaging follow-up consisted of contrast-enhanced, multiphase MRI, or CT when MRI was not feasible. Per institutional practice, the RS cohort underwent imaging at one-month post-treatment followed by every three months. The EBRT cohort underwent imaging at three- and six-months post-treatment followed by every six months thereafter. Radiologic response until last available censored follow-up was assessed by an independent board-certified and abdominal imaging fellowship trained diagnostic radiologist with 8 years of experience. Local control was defined as absence of target tumor progression per mRECIST. Overall progression was evaluated up to last available censored imaging follow-up. TTP and PFS were assessed from time of treatment until documentation of overall progression or last available imaging follow-up. OS was defined as time from treatment to death or last recorded follow-up. CPN was defined as absence of histologically residual target tumor in explanted liver. Hepatic fibrosis was graded according to the Batts-Ludwig system per tissue specimen or elastography, when available. A fibrosis score of 4 was given to patients without tissue who were clinically diagnosed as cirrhotic by a hepatologist.

Statistical Analysis

Continuous data was reported as median (interquartile range [IQR] 25–75) and compared using the Mann–Whitney *U*-test. Categorical data was reported as frequency (percentage) and compared using the chi-square or Fisher's exact tests, as appropriate. The Kaplan–Meier (KM) method was used to assess overall TTP, PFS, and OS. The reverse KM method was used to assess time to radiologic complete response (rCR). The Log rank test was used to compare KM curves between cohorts. Statistical significance was set at a p-value of <0.05. Statistical analyses were performed with IBM SPSS for Windows (Armonk, NY: IBM Corp) v28.

Results

Baseline Characteristics

A total of 58 RS and 28 EBRT patients were included for analysis. The EBRT cohort contained larger tumors (3.7 cm [IQR: 2.4–4.9] vs 2.4 cm [IQR: 2.1–3.1]), older patients (median age: 76 vs 66), and had a greater percentage of patients with an Eastern Cooperative Oncology Group performance status of 2 (11% vs 0) (all $p<0.05$; refer to Table 1). The RS cohort had more patients with ≥ grade 3 liver fibrosis (93% vs 54%; $p<0.001$). Child-Pugh class, ALBI grade, platelet count, and alpha fetoprotein levels were not statistically different between cohorts while etiology of liver disease was.

Table 1 Characteristics of Patients with Treatment-Naïve, Solitary, Hepatocellular Carcinoma ≤ 8 cm

Parameter	RS (n=58)	EBRT (n=28)	*p*-value
Age (years)*	66 (60, 72)	76 (71, 79)	**<0.001**
Sex			0.54
Female	16 (28%)	6 (21%)	
Male	42 (72%)	22 (79%)	
BMI (kg/m^2)*	29.0 (23.7, 33.1)	27.7 (23.3, 33.1)	0.61
Etiology			**<0.001**
MASLD	25 (43%)	2 (7%)	
Chronic hepatitis C	21 (36%)	11 (39%)	
Alcohol	4 (7%)	3 (11%)	
Unknown	1 (2%)	9 (32%)	
Other	7 (12%)	3 (11%)	
BCLC			0.25
0	7 (12%)	3 (11%)	
A	43 (74%)	17 (61%)	
C†	8 (14%)	8 (29%)	
ECOG			**0.02**
0–1	58 (100%)	25 (89%)	
2	0	3 (11%)	
Child-Pugh class			0.46
A5	30 (52)	16 (57)	
A6	10 (17)	7 (25)	
B7	8 (14)	5 (18)	
B8	6 (10)	0	
B9	2 (3)	0	
C10	0	0	
ALBI score*	−2.64 (−2.96, −2.11)	−2.62 (−2.87, −2.39)	0.69
ALBI grade			0.46
1	31 (54%)	15 (54%)	
2	26 (45%)	12 (43%)	
3	0	1 (3%)	
Platelet count (x10^9/L)*	92 (72, 151)	129 (86, 243)	0.06
AFP (ng/mL)*	4.7 (3.2, 12.0)	6.2 (3.1, 29.0)	0.37
Tumor size (cm)*	2.4 (2.1, 3.1)	3.7 (2.4, 4.9)	**<0.001**

(*Continued*)

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Table 1 (Continued).

Parameter	RS (n=58)	EBRT (n=28)	*p*-value
Fibrosis stage			**<0.001**
0–2	4 (7%)	13 (46%)	
3–4	54 (93%)	15 (54%)	

Notes: Unless otherwise specified, data are frequency (percentage). Bold values are statistically significant. *Data are median (IRQ 25, 75). [†]BCLC-C Patients were allocated to this category due to an ECOG performance status of 1 or 2.
Abbreviations: RS, radiation segmentectomy; EBRT, external beam radiation therapy; BMI, body mass index; MASLD, metabolic dysfunction-associated steatotic liver disease; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; ALBI, albumin-bilirubin; INR, International Normalized Ratio; AFP, Alpha-fetoprotein.

The RS cohort was treated with a median dose of 638 Gy (IQR: 544–872), an estimated median specific activity of 703 Bq corresponding to a five day decay assuming a specific activity of 2,500 Bq at calibration (IQR: 692–935), and a median estimated 18,200 spheres per cc of treated liver (IQR: 15,400–24,200) assuming 400,000 particles per GBq reported by the manufacturer at the time of the study (Supplementary Table 1).

In the EBRT cohort, 16 (57%) patients were treated with photon radiation and 12 (43%) with PBT. Median EBRT dose was 50 Gy (range: 39–67.5) and BED 100 Gy (range: 84–100). SBRT was delivered to 71% of patients (most commonly 5 fractions), while 29% received 15 fractions (Supplementary Table 1).

Clinical Outcomes

Median clinical follow-up was 29 months (IQR 17–40) for the RS cohort and 27 months (IQR 13–43) for the EBRT cohort (censored for LT: 12 months (IQR 6–25) and 23 months (IQR 12–41), respectively).

At last available imaging follow-up, rCR was achieved by 97% (n=56/58) of RS patients and 82% (n=23/28) of EBRT patients (p = 0.02). Median time to rCR was 1 month (95% CI: 0.9–1.1) after RS and 7 months (95% CI: 6–7) after EBRT (p < 0.001).

During the first year post-treatment, two RS patients and two EBRT patients had target tumor progression with median target tumor TTP not being reached for both. Local control rates at 12 months were 97% after RS and 93% after EBRT (p = 0.80).

Overall progression was documented in 9 (15%) RS and 9 (32%) EBRT patients, with a median overall TTP of 77 months (95% CI: not reached [NR]) and 42 months (95% CI: NR), respectively (p = 0.26) (Table 2). PFS rates at 1 year were 87% after RS and 80% after EBRT.

Table 2 Survival and Progression Outcomes After Initial Treatment

Outcome	RS (n=58)	EBRT (n=28)	*p*-value
Median follow-up (months)[§]			
Non-censored	29 (17, 40)	27 (13, 43)	
Censored	12 (6, 25)	23 (12, 41)	
Liver transplantation (n)	28 (48%)	3 (11%)	
Death (n)	11 (19%)	11 (39%)	
Overall survival (months)[¶]			
Non-censored	NR	NR	NA
Censored	63 (29, 96)	42 (NR)	0.42

(*Continued*)

Table 2 (Continued).

Outcome	RS (n=58)	EBRT (n=28)	*p*-value
Target tumor progression (n)	2 (3%)	2 (7%)	
Overall progression (n)	9 (15%)	9 (32%)	
Target tumor TTP (months)[¶]	NR	NR	NA
Overall TTP (months)[¶]	Median 77 (NR) Mean 56 (42–70)	Median 42 (NR) Mean 42 (29–55)	0.26

Notes: All outcomes were censored for liver transplantation. For follow-up and overall survival, both censored and non-censored values are reported. Unless otherwise specified, data are frequency (percentage). [§]Data are median (IQR 25, 75). [¶]Data are median (95% CI).

Abbreviations: RS, radiation segmentectomy; EBRT, external beam radiation therapy; NR, Not reached; NA, Not applicable; TTP, time-to-progression.

LT was performed in 28 (48%) RS and 3 (11%) EBRT patients, with a median time to LT after treatment of 187 days (range 86–449). CPN was achieved in 22 (76%) RS target tumors and 1 (33%) EBRT target tumors, respectively.

Median censored OS was 63 months (95% CI: 29–96) after RS and 42 months (95% CI: NR) after EBRT (p = 0.42), with 12-, 24-, and 36-month OS rates of 88%, 85%, and 66% after RS vs 84%, 59%, and 59% after EBRT (p = 0.34). Median uncensored OS was not reached on either cohort, with 12-, 24-, and 36-month OS rates of 95%, 90%, and 78% after RS vs 85%, 62%, and 62% after EBRT (p = 0.019).

Discussion

In this experience, both RS and EBRT were effective therapies for solitary HCC compared to historical curative-intent treatments.[14–18] RS and EBRT were offered to patients with different characteristics, which limited comparison. The former was often performed in patients as a bridge to LT, and the latter in older individuals with worse performance status. The cohort size discrepancy in this study was influenced by EBRT being less frequently utilized than RS as an initial treatment for solitary HCC and prevented propensity score matching.

While many outcomes were similar in both therapies, complete radiologic response rates were demonstrated in more RS patients than EBRT within the limited span of this study (97% vs 82%, p = 0.02). Given that tumors treated with EBRT have been reported to display persistent enhancement for up to 2 years, a more thorough comparison of response would require assessment of histologic viability or longer follow-up.[18] A potential advantage of RS imaging response is its utilization to downstage tumors into Milan criteria, where time to response has listing implications for patients with a concurrent liver hazard pursuing liver transplantation.

Complete pathologic response to pre-transplant locoregional therapy has been described as a surrogate endpoint for lower posttransplant recurrence and superior survival by a US multicenter HCC transplant consortium.[19] Post LT target tumor CPN rates in this study were 77% and 33%, for RS and EBRT respectively, but there were insufficient EBRT patients who received LT for additional comparative analysis. In the prospective RASER trial, 8 of the 29 patients treated with RS underwent LT and 100% exhibited CPN.[12] A recent phase II study on SBRT as a bridge to LT reported a CPN rate of 58%.[20] A previously published, single-center, analysis of RS vs EBRT for HCC which was not limited to treatment-naïve, early-stage tumors, or ablative dosimetry reported larger tumors (4.1 vs 3.0 cm) and rates of prior local therapy (71% vs 13%) in the EBRT cohort, similar PFS (hazard ratio = 0.958, 95% CI: 0.612–1.498; p = 0.85) and OS (hazard ratio = 1.039, 95% CI: 0.645–1.674; p = 0.875), while radiologic and pathologic response were not assessed.[21] Prospective randomized data comparing radioembolization to EBRT have been challenging to obtain with multiple trial closures due to poor accrual and feasibility (NCT04235660 and NCT05157451).

It has been described that both RS and EBRT have therapeutic profiles with advantages and disadvantages that can be tailored to a patient's unique disease phenotype.[22] Furthermore, either therapy may have a role when a patient is not an ideal candidate for the other, or potentially as salvage in the setting of suboptimal response.

The findings of this report are limited by several factors including its retrospective design, cohort characteristics and size, disparate use of LT, local practice patterns, and short follow-up. The heterogeneity of post treatment assessment limits reporting of long-term outcomes and results should be interpreted in this context, including delayed responses to radiotherapy. Furthermore, the differences in frequency of imaging follow-up between cohorts may affect time dependent outcomes. Given mentioned limitations, adverse events were challenging to analyze and compare, but have been previously published, including a larger cohort by the authors, and are outside the scope of this study.[23,24]

Conclusion

In conclusion, RS and EBRT are effective initial therapies for solitary HCC. Treatment decisions should be based on patient presentation as part of a comprehensive and multidisciplinary HCC program.

Ethical Approval and Informed Consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 helsinki declaration and its later amendments or comparable ethical standards. This retrospective, minimal risk study was approved by the Institutional Review Board (IRB) at Mayo Clinic and the requirement to obtain written informed consent was waived. All collected patient data was maintained with confidentiality.

Consent for Publication

For this type of study consent for publication is not required.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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