CLINICAL STUDY

Radiation Segmentectomy versus Selective Chemoembolization in the Treatment of Early-Stage Hepatocellular Carcinoma

Derek M. Biederman, MD, Joseph J. Titano, MD, Ricki A. Korff, BS, Aaron M. Fischman, MD, Rahul S. Patel, MD, Francis S. Nowakowski, MD, Robert A. Lookstein, MD, and Edward Kim, MD

ABSTRACT

Purpose: To compare outcomes of radiation segmentectomy (RS) and segmental transarterial chemoembolization in treatment of unresectable, solitary hepatocellular carcinoma (HCC) $\leq$ 3 cm.

Materials and Methods: From January 2012 to January 2016, 534 and 877 patients were treated with radioembolization and transarterial chemoembolization, respectively. A cohort of 112 (radiation segmentectomy [RS], 55; chemoembolization, 57) locoregional therapy–naïve patients with solitary HCC $\leq$ 3 cm without vascular invasion or metastasis was retrospectively identified and stratified according to baseline patient demographics, tumor characteristics, and laboratory values. Propensity score matching (PSM) was conducted using a nearest neighbor algorithm (1:1). Outcomes analyzed included laboratory toxicities, imaging response, time to secondary therapy (TTST), and overall survival.

Results: Before PSM, complete response (CR) rate was 81.2% for RS and 49.1% for chemoembolization (odds ratio 2.2; 95% confidence interval [CI], 1.4–3.3; $P < .001$). Median (95% CI) TTST after initial therapy was 246 days (135–250 d) in chemoembolization group and 700 days (308–812 d) in RS group (hazard ratio 0.71; 95% CI, 0.55–0.92; $P = .009$). Overall survival before PSM was not significantly different between the 2 groups ($P = .29$). Overall CR rate after PSM was 92.1% in RS group and 52.6% in chemoembolization group ($P = .005$). Median (95% CI) TTST after matching was 161 days (76–350 d) in chemoembolization group and 812 days (363–812 d) in RS group ($P = .001$). Overall survival after matching was not significantly different between the 2 groups ($P = .71$).

Conclusions: RS results in improved imaging response and longer TTST compared with transarterial chemoembolization in treatment of early-stage HCC.

ABBREVIATIONS

CI = confidence interval, CR = complete response, HCC = hepatocellular carcinoma, HR = hazard ratio, IQR = interquartile range, mRECIST = modified Response Evaluation Criteria In Solid Tumors, PR = partial response, PSM = propensity score matching, RS = radiation segmentectomy, TTP = time to progression, TTST = time to secondary therapy

Current guidelines describe the use of percutaneous ablation therapy as the standard of care for solitary hepatocellular carcinoma (HCC) $\leq$ 3 cm in patients with early-stage disease who are poor surgical candidates (1). These guidelines do not account for variability in the technical factors related to performing a percutaneous ablation. Tumors are frequently located adjacent to vital structures, such as the diaphragm or large intrahepatic vessels, significantly

From the Department of Interventional Radiology (D.M.B., J.J.T., A.M.F., R.S.P., F.S.N., R.A.L., E.K.), Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1234, New York, NY 10029; and Albert Einstein College of Medicine (R.A.K.), New York, New York. Received May 30, 2017; final revision received August 24, 2017; accepted August 30, 2017. **Address correspondence to** E.K.; E-mail: edward.kim@mountsinai.org

A.M.F. is a paid consultant for Surefire Medical, Inc (Westminster, Colorado) and Terumo Interventional Systems, Inc (Somerset, New Jersey) and is on the scientific advisory board for Terumo Interventional Systems. R.S.P. is a paid consultant for Medtronic, Inc (Minneapolis, Minnesota) and Sirtex Medical Ltd (Woburn, Massachusetts). R.A.L. is a paid consultant for Boston Scientific (Marlborough, Massachusetts), Cordis Corporation (Milpitas, California), and MEDRAD Interventional (Warrendale, Pennsylvania) and is on the scientific advisory board for Boston Scientific Corporation. E.K. is on the scientific advisory board for BTG International Ltd (London, United Kingdom) and Boston Scientific Corporation. None of the other authors have identified a conflict of interest.

Figure E1 and Appendices A and B are available online at *www.jvir.org*.

J Vasc Interv Radiol 2017; ■:1–8

https://doi.org/10.1016/j.jvir.2017.08.026

altering the risk profile of the procedure. In accordance with stage migration, transarterial locoregional therapy is considered the next most appropriate treatment option (2,3).

Transarterial chemoembolization and radioembolization are the mainstays of transarterial therapy for HCC (4). The use of radioembolization in patients with early-stage HCC has garnered interest, fueled by studies reporting high response rates when lobar doses are administered in a more selective, segmental fashion, termed radiation segmentectomy (RS) (5–7). Existing literature comparing radioembolization and chemoembolization has been limited by broad inclusion criteria (8–11). To address these discrepancies, comparison between these treatments based on tumor stage has been suggested as an area in which further study is needed (12). A study design in which both treatments are administered in a segmental fashion has been singled out as a particularly reasonable comparison (12). Padia et al (13) recently conducted such a clinical inquiry and found that RS was associated with superior tumor response, lower local tumor recurrence, and improved progression-free survival compared with transarterial chemoembolization administered segmentally. The present study compares the efficacy of RS and segmental transarterial chemoembolization in the treatment of patients with unresectable, solitary HCC $\leq$ 3 cm.

MATERIALS AND METHODS

Study Design

This single-center, retrospective, Health Insurance Portability and Accountability Act–compliant study was approved by the local institutional review board. The study period spanned January 2012 through January 2016. Data were obtained searching the EPIC electronic medical record system (EPIC Systems Corp, Verona, Wisconsin). The study inclusion criteria were as follows: (*a*) solitary HCC $\leq$ 3 cm not amenable to surgical resection or percutaneous ablation, (*b*) locoregional therapy naïve, (*c*) absence of macroscopic vascular invasion, and (*d*) absence of extrahepatic disease. HCC was diagnosed according to the American Association for Liver Disease guidelines (2,3). Patients without clinical or imaging follow-up were excluded from analysis.

Over the study period, 535 and 877 patients were treated with radioembolization and chemoembolization, respectively. From these groups, a cohort of 112 patients (chemoembolization, 57; RS, 55) was formed after implementing the inclusion criteria. Baseline demographics for the cohort are presented in **Table 1** ("Before PSM"). Significant univariate asymmetries between the 2 cohorts were seen in both Eastern Cooperative Oncology Group performance status ($P = .02$) and albumin-bilirubin grade ($P = .02$) with metrics being more favorable in the RS group. Implementation of the propensity score matching (PSM) methods outlined subsequently yielded a well-matched cohort of 76 patients (RS, 38; chemoembolization, 38). The demographics of the patients in the matched cohorts are presented in **Table 1** ("After PSM"). Histograms and scatterplots of matching output are displayed in **Figure E1a**, **b** (available online at *www.jvir.org*). After matching, there were no significant univariate or multivariate covariate imbalances between groups (**Table 1**).

All treatment decisions regarding patient selection and locoregional therapy modality were reached by consensus through the collaboration of hepatologists, oncologists, transplant surgeons, and interventional radiologists. Patients were considered candidates for either transarterial chemoembolization or RS in cases in which treatment involved tumors deemed not amenable to ablation by the treating interventional radiologist. Procedures were performed by 5 interventional radiologists with experience ranging from 6 to 15 years (mean 10.6 y). Transarterial chemoembolization and RS treatment protocols are detailed in **Appendix A** (available online at *www.jvir.org*) (14–16).

Study Outcomes

The study outcomes examined included 180-day laboratory toxicities, imaging response, time to secondary therapy (TTST), and overall survival. Retrospective review of laboratory toxicities, which were graded according to Common Terminology Criteria for Adverse Events version 4.03, was performed (17). Two independent reviewers graded imaging response according to modified Response Evaluation Criteria In Solid Tumors (mRECIST). Discrepancies between the 2 independent reviewers were resolved by consensus. The best imaging response within 90 days of treatment is reported.

A TTST metric was introduced to analyze efficacy outcomes of longer duration. In the calculation of TTST, all potential forms of treatment, including locoregional, surgical, and systemic therapies, were included. TTST was censored at the date of transplantation for cases in which there had been an initial complete response (CR) and no radiographic disease progression (determined by independent review) before transplantation (chemoembolization, 2; RS, 1). Date of death was determined through a combination of electronic medical record review, search of an institutional transplant database, and confirmation in comparison with the National Death Index (18). Overall survival was calculated in reference to the date of initial therapy and was censored for curative therapy.

Statistical Analysis

Categorical data are reported as number (percentage), and continuous data are reported as mean (SD) or as median (interquartile range [IQR]) when appropriate. Details of PSM and additional statistical methodology are provided in **Appendix B** (available online at *www.jvir.org*) (19).

RESULTS

Treatment and Laboratory Toxicity

The median (IQR) activity administered in the RS group was 1.38 Gbq (1.06–2.08 Gbq). Grade 3/4 bilirubin toxicity was observed after treatment in 5.5% of the RS group and in 10.5% of the transarterial chemoembolization group ($P = .49$). Grade 3/4 aspartate aminotransferase toxicity was also