International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Role of Stereotactic Body Radiation Therapy Before Orthotopic Liver Transplantation: Retrospective Evaluation of Pathologic Response and Outcomes

Edward Michael Mannina, MD, MPH, MS,[*] Higinia Rosa Cardenes, MD, PhD,[†] Foster D. Lasley, MD,[‡] Benjamin Goodman, DO,[§] Jennifer Zook, MD,[‖] Sandra Althouse, MS,[¶] John Alvin Cox, MD,[#] Romil Saxena, MBBS,[**] Joseph Tector, MD, PhD,[††] and Mary Maluccio, MD, MPH[‡‡]

Department of Radiation Oncology, Slidell Memorial Hospital Regional Cancer Center, Slidell, Louisiana; Departments of [¶]Biostatistics, **Pathology, and [‡‡]Surgery, Indiana University School of Medicine, Indianapolis, Indiana; [†]Department of Radiation Oncology, Schneck Medical Center, Seymour, Indiana; [‡]Department of Radiation Oncology, Mercy Hospital, Oklahoma City, Oklahoma; [§]Department of Radiation Oncology, St. Francis Healthcare, Cape Girardeau, Missouri; [‖]Department of Radiation Oncology, Community Hospital Anderson, Anderson, Indiana; [#]Department of Radiation Oncology, Columbus Regional, Columbus, Indiana; and [††]Department of Surgery, University of Alabama-Birmingham, Birmingham, Alabama

Received Aug 15, 2016, and in revised form Nov 17, 2016. Accepted for publication Dec 28, 2016.

Summary

To analyze stereotactic body radiation therapy before orthotopic liver transplantation for hepatocellular carcinoma, we first compared explant pathology with various radiographic response criteria revealing poor concordance. With extended follow-up, factors affecting the high response and local control rates as

Purpose: To analyze the results of stereotactic body radiation therapy (SBRT) in patients with early-stage, localized hepatocellular carcinoma who underwent definitive orthotopic liver transplantation (OLT).

Methods and Materials: The subjects of this retrospective report are 38 patients diagnosed with hepatocellular carcinoma who underwent SBRT per institutional phase 1 to 2 eligibility criteria, before definitive OLT. Pre-OLT radiographs were compared with pathologic gold standard. Analysis of treatment failures and deaths was undertaken.

Results: With median follow-up of 4.8 years from OLT, 9 of 38 patients (24%) recurred, whereas 10 of 38 patients (26%) died. Kaplan-Meier estimates of 3-year overall survival and disease-free survival are 77% and 74%, respectively. Sum longest dimension of tumors was significantly associated with disease-free survival (hazard ratio 1.93, $P = .026$). Pathologic response rate (complete plus partial response) was 68%. Radiographic scoring criteria performed poorly; modified Response Evaluation Criteria in

Reprint requests to: Dr. Edward Michael Mannina, MD, MPH, MS, Slidell Memorial Hospital Regional Cancer Center, Department of Radiation Oncology, 1120 Robert Blvd., Suite 100, Slidell, LA 70458, United States. Tel: 1-985-280-8688; E-mail: emmannina@gmail.com

Presented at the 56th Annual Meeting of the American Society for Radiation Oncology, September 14-17, 2014, San Francisco, CA.

Conflict of interest: none.

Acknowledgment—Statistical support was provided by the Indiana University School of Medicine.

Int J Radiation Oncol Biol Phys, Vol. 97, No. 5, pp. 931–938, 2017
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2016.12.036

well as treatment failure and death were studied. The analyses ultimately revealed SBRT to be safe and effective, with a need for further stratification of patients according to tumor burden and treatment response parameters.

Solid Tumors produced highest concordance (κ = 0.224). Explants revealed viable tumor in 74% of evaluable patients. Treatment failures had statistically larger sum longest dimension of tumors (4.0 cm vs 2.8 cm, $P = .014$) and non−statistically significant higher rates of lymphovascular space invasion (44% vs 17%), cT2 disease (44% vs 21%), ≥pT2 disease (67% vs 34%), multifocal tumors at time of SBRT (44% vs 21%), and less robust mean α-fetoprotein response (−25 IU/mL vs −162 IU/mL).

Conclusions: Stereotactic body radiation therapy before to OLT is a well-tolerated treatment providing 68% pathologic response, though 74% of explants ultimately contained viable tumor. Radiographic response criteria poorly approximate pathology. Our data suggest further stratification of patients according to initial disease burden and treatment response.

Introduction

Collectively denoted "liver cancer," invasive neoplasms of the liver parenchyma (hepatocellular carcinoma, HCC) and intrahepatic bile ducts (intrahepatic cholangiocarcinoma) have an estimated incidence of 35,660 new cases in 2015, 75% arising from hepatocytes (1). The estimated number of people succumbing to these malignancies in 2015 is 24,550, for a crude mortality rate of 68.8%. Statistics from the American Cancer Society illustrate a 3.4% increased yearly incidence from 2007 to 2011, with the mortality rate climbing 2.5% per year during that time, now with 5-year survival rates of 18% (1).

At our institution, once localized HCC is confirmed, cases are reviewed by a multidisciplinary team. Surgical candidates are evaluated for partial resection versus transplantation. Select operable or inoperable patients are candidates for local therapies, such as radiofrequency ablation, arterial catheter-directed therapies, or external beam radiation therapy. Operable patients with advancing cirrhosis by the model for end-stage liver disease (MELD) score and a diagnosis of HCC within expanded Milan criteria are directed toward orthotopic transplantation. Stratification for these therapies is largely based on Child Pugh classification (CPC) degree of cirrhosis.

Stereotactic body radiation therapy (SBRT; also stereotactic ablative radiation therapy) as a viable treatment strategy has emerged, with our own phase 1 to 2 trials demonstrating excellent local control, >90% at 6 months, with estimated sustained local control at 3 years of 82% (CPC-B) up to 91% (CPC-A) with acceptable 11% grade 3/4 liver toxicity in CPC-A patients (2-4). Grade 3/4 liver toxicity of 38% was seen in class B patients, with toxicity best predicted by low dose volumes (5). Only patients who received SBRT then subsequent orthotopic transplantation were analyzed as the subject of this publication.

Methods and Materials

Eligibility criteria, simulation, immobilization techniques, and treatment methods have been previously described (2-4). Briefly, for the institutional review board−approved phase 1-2 SBRT trial patients were eligible with: (*1*) a diagnosis of primary HCC with CPC-A or -B liver dysfunction of any etiology; (*2*) an Eastern Cooperative Oncology Group performance status of 0 to 2 (Karnofsky performance status ≥70%); (*3*) greater than 18 years of age; and (*4*) a minimum life expectancy of 3 months. All patients were considered ineligible for resection by a dedicated liver surgeon then discussed in a Liver Oncology Multidisciplinary Group, where nonsurgical options were considered, including radiofrequency ablation, transarterial chemoembolization, bland embolization, and ^{90}Y radioembolization. For the phase 1 component, CPC-A or -B patients with scores <10 were initially allowed. After interim analysis only patients with scores ≤7 were allowed, owing to excessive toxicities (2). Subsequent non-protocol patients met the above criteria and had CPC score ≤7. For this report, SBRT took place from October 2006 to July 2014, and follow-up was through September 2015.

Hepatocellular carcinoma was diagnosed per international guidelines on the basis of imaging characteristics, pathology, and/or α-fetoprotein (AFP) value (6). Patients were required to have either a solitary tumor with a maximum diameter ≤6 cm or up to 3 lesions with sum diameter ≤6 cm, located at least 0.5 cm from hollow viscera, with no evidence of progressive or untreated gross extrahepatic disease and no evidence of acute hepatitis. Liver-directed treatment within 14 days of SBRT was not allowed. Additional requirements included adequate liver, renal, and hematologic function. Protocol patients signed a study-specific informed consent form. Lesions that could not meet dosimetric constraints owing to proximity to the porta hepatis or hollow viscera did not receive SBRT and thus are not included in this report (2-4).

At simulation, patients underwent triple phase CT (TPCT) while immobilized in the stereotactic frame with abdominal compression using 4-dimensional technology to account for respiratory motion. The gross tumor volume (GTV) was defined as the gross disease in each phase of the TPCT and/or diagnostic MRI; with rare exceptions based on clinical suspicion, GTV = clinical target volume. The planning target volume included the GTV with a minimum 5-mm axial and 10-mm cranio-caudal expansion. In

patients with segmental portal vein thrombosis, the length of the thrombus with a 1-cm margin was included in the GTV. Multiple (range, 7-12) nonopposing, noncoplanar fields were designed to cover the planning target volume, with dose prescribed to the 80% to 90% isodose line. Normal tissue constraints and dose-escalation protocols have been previously described (2). Patients with multiple lesions were treated in one course.

Patients were evaluated for transplant at time of diagnosis of HCC, but because of medical comorbidities, substance abuse, low MELD score, or presence of segmental portal vein thrombus were not listed; 3 patients were diagnosed with HCC after being listed. After SBRT, patients were medically cleared, shown to have radiographic thrombus response, or developed higher MELD scores before successful appeal to undergo orthotopic liver transplantation (OLT) with methods previously described (7-11). Explants were sectioned and assessed pathologically for residual or new malignancy by a dedicated liver pathologist (R.S.). Pre-SBRT and pre-OLT imaging was compared to assess for radiographic response using criteria from the European Association for the Study of the Liver (EASL), World Health Organization (WHO), Response Evaluation Criteria in Solid Tumors (RECIST), and modified RECIST (mRECIST), with all grading performed by 2 clinical radiation oncologists (E.M., J.Z.) and verified by institutional abdominal radiologists (12-15). Pathologic and radiographic response concordance rates were assessed by the κ statistic. Stratification by imaging modality (CT or MRI) was done to assess for crude response agreement with pathologic grading. Sensitivity, specificity, and positive and negative predictive values (PPV, NPV) were tabulated for each radiographic grading criteria (response = complete and partial response, CR + PR; nonresponse = stable or progressive disease, SD or PD), using pathology as the gold standard. Radiographic and pathologic grading criteria are shown in Table 1. After stratifying by T stage and CPC, response was investigated against demographic and treatment variables using logistic regression. Local control was defined as absence of progression (CR + PR + SD).

Overall survival (OS) and disease-free survival (DFS; alive without evidence of recurrent disease) were estimated from the day of OLT using Kaplan-Meier methodology, with treatment failure documented by date, biopsy confirmation, site, and salvage therapy. Overall survival and DFS were studied by T stage, CPC, etiology of cirrhosis, pathologic confirmation of HCC, and total pathologic and radiographic response (by all 4 grading criteria), as well as the presence of any viable disease at explant (<CR residual + new HCC) using the log−rank test, signifying that the presence of viable disease would drive ultimate outcome. Patients were determined disease free according to the last surveillance imaging, oncology, or transplant hepatology appointment. Exploratory univariate analysis of demographic, treatment, and response variables against OS and DFS was undertaken for hypothesis generation. An analysis of those patients who failed SBRT + OLT against those who remained disease free was completed using logistic regression. All statistics were calculated using SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

Demographics

Thirty-eight patients are the subject of this retrospective report, with median follow-up of 4.8 years since OLT, when the mean age of the cohort was 58 years (range, 46-71 years). Of 38 patients, 16 (42%) were treated on the phase 1 to 2 protocols. Demographics are shown in Table 2. Seventy-one percent of patients did not have pathologically proven HCC. At SBRT, 55% of patients had CPC-B7. Seventy-one percent of patients had portal hypertension, and 16% were noted to have radiographic evidence of segmental portal vein thrombus. Seventy-four percent of patients had T1 disease. Seventy-six percent of patients were not listed owing to medical comorbidities or substance abuse. Mean sum longest dimension of tumors was 3.1 cm (range, 1.0-6.1 cm), and mean AFP level before SBRT was 197.2 IU/mL (range, 2.2-2996.2 IU/mL). Twenty-eight patients (74%) had 1 lesion, 7 (18%) had 2 lesions, and 3 (8%) had 3 lesions treated, for a total of 51 lesions.

Treatment

An SBRT dose of 16 Gy × 3 fractions was reserved for CPC-A patients and used in 10 patients (26%), whereas 8 Gy × 5 fractions was used most commonly, in 23 patients (61%),

Table 1 Radiographic and pathologic response grading criteria

Parameter	WHO	EASL	RECIST	mRECIST	Pathology
Measurement	Product of long dimensions	% with enhancement	Longest dimension	Longest enhancing dimension	% with necrosis
CR	Disappearance	Disappearance	Disappearance	Disappearance	≥90%
PR	50% decrease	50% decrease	30% decrease	30% decrease	1%-89%
SD	Not CR/PR/SD	Not CR/PR/SD	Not CR/PR/SD	Not CR/PR/SD	0%
PD	25% increase	25% increase	20% increase	20% increase	Enlargement

Abbreviations: CR = complete response; EASL = European Association for the Study of the Liver; mRECIST = modified RECIST; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; WHO = World Health Organization.

Table 2 Patient demographics

Variable	Value
Age at OLT (y)	58.5 (46-71)
Gender	
Female	10 (26)
Male	28 (74)
Race	
Caucasian	28 (74)
Non-Caucasian	10 (26)
KPS	
100	10 (38)
90	13 (50)
80	3 (12)
Etiology of cirrhosis	
Hepatitis B	4 (11)
Hepatitis C	28 (74)
NASH	7 (18)
Alcoholism	11 (29)
Cryptogenic	1 (3)
Child Pugh classification	
A (score 5-6)	17 (45)
B (score 7)	21 (55)
Pre-SBRT T-stage	
cT1	28 (74)
cT2	10 (26)
Presence of segmental PVT	6 (16)
Presence of portal hypertension	27 (71)
Pre-SBRT pathology (+)	11 (29)
Pre-SBRT AFP level (IU/mL)	197.2 (2.2-2996.2)
Individual tumor maximum dimension (cm)	2.4 (0.6-5.0)
Sum tumors maximum dimension (cm)	3.1 (1.0-6.1)
No. of lesions	
1	28 (74)
2	7 (18)
3	3 (8)
Reason not listed for OLT (n=35)	
Not medically cleared	24 (63)
Substance abuse	5 (13)
Low MELD score	6 (16)

Abbreviations: AFP = α-fetoprotein; KPS = Karnofsky performance status; MELD = model for end-stage liver disease; NASH = nonalcoholic steatohepatitis; OLT = orthotopic liver transplantation; PVT = portal vein thrombus; SBRT = stereotactic body radiation therapy.

Values are number (percentage) or mean (range).

including all CPC-B patients. Remaining dose-fractionation schedules (from the phase 1 dose-escalated cohort) used in CPC-A patients were 12 Gy × 3 (2 patients, 5%), 14 Gy × 3 (2 patients, 5%), and 9 Gy × 5 (1 patient, 3%).

Mean time from completion of SBRT until final pre-OLT imaging was 8.1 months or 242 days (range, 26-1207 days), with 35 of 38 patients imaged: 22 by TPCT (63%) and 13 by MRI (37%). Mean time from completion of SBRT until OLT was 8.8 months or 263 days (range, 13-1220 days). Before proceeding to OLT, laboratory evaluation revealed a 3-fold reduction in AFP to a mean 67.2 IU/mL (range, 2.6-860.7 IU/mL) and a shift in CPC as follows: A→A (34%), A→B (8%), A→C (3%), B→A (8%), B→B (29%), B→C (18%), resulting in 16 (42%) CPC-A, 14 (37%) CPC-B, and 8 (21%) CPC-C patients undergoing OLT. Although 63% of the patients' CPC status remained stable, 29% of patients' CPC declined by 1 category (26%) or 2 (3%). Of 10 patients transplanted <90 days after SBRT, 2 had declined CPC-B→CPC-C.

Explant pathology

Sectioned explanted livers revealed 16 patients (42%) had pT2 (14) or pT3 (2) disease, compared with just 10 patients (26%) having a maximum of cT2 disease at SBRT. Fifty percent of patients had no change in T stage, whereas 24% were downstaged at pathology, largely owing to 8 of 34 evaluable patients classified as pT0 (100% tumor kill and no new tumors). No patients were noted to have evidence of metastatic spread to porta hepatis lymph nodes, with 66% of patients confirmed pN0. Of 51 tumor locations, 19 were reported: ≤1 cm from capsule (15), >1 cm from capsule (3), and ≤1 cm from porta hepatis (1). In 6 patients initially with segmental portal vein thrombi, 50% had lymphovascular space invasion and 50% had new tumors at pathology, whereas 6 of 7 evaluable treated tumors showed pathologic CR or PR. New tumors were uncovered at pathology in 17 patients (45%), 41% of whom had more than 1 new tumor (2, 2, 3, 3, 6, 10, 10); this drove a 26% upstaging of T stage. Taking new HCC and treated HCC <pCR together reveals that 25 of 34 evaluable patients (74%) had viable tumor in their explant; 4 patients were unevaluable for this variable, 1 patient classified as a pT1/CR with 10% residual.

Response and local control

Pathologic response was documented in 44 of 51 lesions. Mean maximum dimension size for individual lesions was 2.4 cm (range, 0.6-5.0 cm). Taking complete (20 of 44, 45%) and partial (10 of 44, 23%) responses together yielded a crude pathologic response in 30 of 44 lesions (68%). No patients had pathologic progression of the treated lesion, with stable disease accounting for the remaining 32% of lesions; thus, crude pathologic local control was 100%. Pre-OLT CT or MRI evaluations of response were 86% by mRECIST, 82% by EASL, 56% by WHO, and 52% by RECIST. Only 2 patients demonstrated PD as assessed only by WHO criteria; neither received additional therapy. At imaging, mean maximum tumor dimension had decreased to 1.5 cm (range, 0.0-5.0 cm), for a mean 41% reduction. Univariate analysis of demographic and treatment variables revealed no significant predictors of radiographic response, with a diagnosis of hepatitis C associated with pathologic response ($P=.05$). Time from SBRT to pre-OLT imaging trended to significance for responses graded by mRECIST ($P=.06$), RECIST ($P=.07$), and WHO ($P=.09$). Assigning the worst lesion response to each patient reveals patient response values of 64% (pathologic), 47% (RECIST), 48% (WHO), 76% (EASL), and

82% (mRECIST). Pathologic responding patients' mean time from SBRT to OLT was 11.2 months (5% underwent OLT within 90 days of SBRT), compared with 7.1 months in patients exhibiting stable disease (50% underwent OLT within 90 days of SBRT).

Radiographic versus pathologic response grading

Analysis of each radiographic response scoring criteria against gold standard pathology is shown in Table 3. Sensitivity ranged from 54% (RECIST) to 90% (mRECIST), whereas specificity ranged from 18% (EASL, mRECIST) to 50% (WHO, RECIST). The PPV was similar among all criteria at 71% to 74%, whereas NPV ranged from 29% (EASL) to 40% (mRECIST). A weighted κ statistic used to analyze concordance ranged from 0.090 (RECIST) to 0.224 (mRECIST) and was unable to be calculated for WHO criteria owing to an imbalance in categories resulting from 2 patients judged as having PD by WHO. The CT agreement (22%-39%) and MRI agreement (31%-39%) with pathologic findings was poor, irrespective of radiographic criteria used.

Survival

Kaplan-Meier actuarial overall survival estimates at 1, 2, 3, and 5 years after OLT were, respectively, 92%, 86%, 77%, and 73% (Fig. 1). Median survival was not estimable. Univariate analysis failed to uncover demographic, treatment, or response variables significantly associated with OS. Kaplan-Meier actuarial DFS estimates at 1, 2, 3, and 5 years after OLT were, respectively, 91%, 85%, 74%, and 74% (Fig. 2). Stratification by CPC, pre-SBRT T stage, or by patient response assignment did not reveal significant differences in OS or DFS. Univariate analysis revealed a significant association between DFS and sum longest dimension of tumors (hazard ratio 1.93, $P = .026$).

Analysis of deaths and treatment failures

As summarized in Table 4, 10 of 38 patients (26%) were deceased at the time of this report, 6 without evidence of recurrent disease. The first peri-transplant death was due to cardiac arrest, with elevated liver function enzymes and Doppler-confirmed vessel and hepatic duct flow. The second peri-transplant death was in a patient with segmental nonobstructing portal venous clot whose posttransplant portal anastomosis thrombosed, leading to organ failure and immediate re-OLT without evidence of rejection or thrombus, with the patient dying thereafter of cardiac arrest. Neither peri-transplant death was attributed to SBRT. The patient who died of end-stage liver disease had recurrence of hepatitis C, inducing failure of the transplanted liver. In all, 9 of 38 patients (24%) had recurrent hepatocellular carcinoma, all pathologically confirmed. Seven of nine (78%) had hepatitis C, and 3 patients underwent biopsies before SBRT, 1 patient ultimately failing at the chest wall biopsy tract 5.5 years after OLT. Four patients were classified cT2, and 5 patients had CPC-B cirrhosis at SBRT. The CPC-A patients received 12 Gy × 3, 14 Gy × 3, and 2 received 16 Gy × 3. Four of

Table 3 Evaluation of radiographic response criteria versus pathologic gold standard

Parameter	WHO	EASL	RECIST	mRECIST
Sensitivity (%)	59	83	54	90*
Specificity (%)	50*	18	50*	18
Positive predictive value (%)	73	73	71	74*
Negative predictive value (%)	35	29	32	40*
Weighted κ statistic	†	0.174	0.090	0.224*

Abbreviations as in Table 1.
* Best value.
† Nonevaluable.

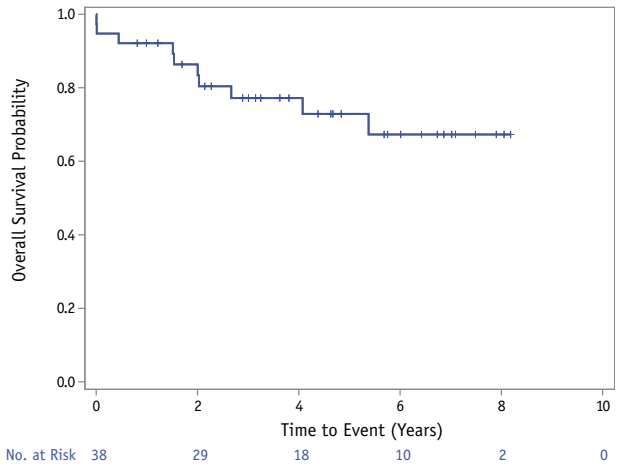

Fig. 1. Kaplan-Meier actuarial overall survival. Three- and 5-year estimates are 77% and 73%, respectively.

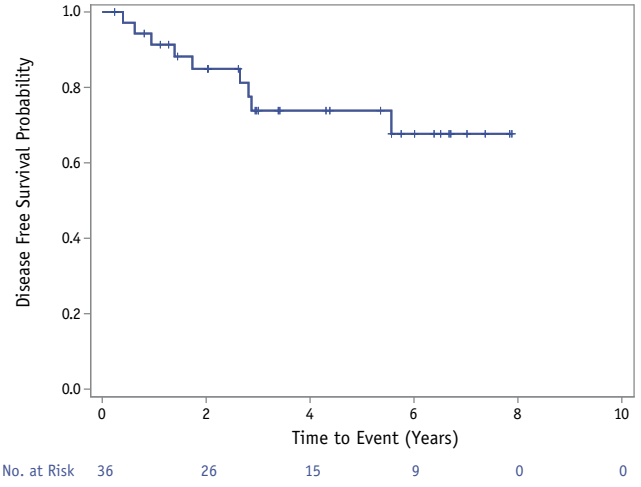

Fig. 2. Kaplan-Meier actuarial disease-free survival. Three- and 5-year estimate is 74%.

Table 4 Timeline and descriptors of treatment failures and deceased patients

ID	Time to failure (mo)	Failure site(s) (*biopsy site)	Salvage therapies	Time to death (mo)	Cause of death	Alive after OLT (mo)
1				<1	Peri-transplant	<1
2				<1	Peri-transplant	<1
3				18	End-stage liver disease	18
4				25	Lymphoma	25
5				34	Unknown	34
6				65	Subdural hematoma	65
7	4.5	Subcutaneous*, lung, liver, bone, spleen, adrenal	Palliative Care	5	Widespread metastases	5
8	16	Right middle lobe*	VATS metastatectomy	18	ARDS following VATS metastatectomy	18
9	17	Right middle lobe*, right upper lobe	VATS metastatectomy, SBRT	24	Unknown	24
10	36	Left adrenal gland*	Adrenalectomy	49	Small bowel obstruction	49
11	19	Left adrenal gland	Adrenalectomy			26
12	32	Clavicle*, T1	Palliative RT			42
13	34	Retroperitoneal LN*	Palliative Care			34
14	34	Manubrium*, T11, femur	Palliative RT, sorafenib, Phase I clinical trial			56
15	67	Chest wall*	Palliative RT			81

Abbreviations: ARDS = acute respiratory distress syndrome; RT = radiation therapy; SBRT = stereotactic body radiation therapy; VATS = video-assisted thoracopic surgery.

nine patients (44%) had >1 tumor targeted, and mean sum longest dimension of tumors was 4.0 cm (range, 1.7-6.1 cm), compared with 2.8 cm (range, 1.0-5.1 cm) in disease-free patients ($P = .014$). Mean AFP level fell from 60.3 IU/mL to 35.2 IU/mL over a mean 7.7 months between SBRT and OLT. Six patients declared pT2 at OLT. 8 of 9 (89%) patients had viable tumor in their explant: 3 PR, 3 SD, 5 patients with new tumors (1 patient with 3 tumors, another with 10 tumors). There was a trend toward higher percentage of lymphovascular space invasion appreciated in failure patients (44% vs 17%; $P = .07$) Only 1 patient initially with segmental portal venous thrombus failed.

Discussion

Modern SBRT provides the ability to spare uninvolved liver parenchyma, thereby reducing the incidence of radiation-induced liver disease, while providing an ablative dose to the tumor (2-5, 16, 17). Several clinical trials have demonstrated the safety, tolerability, and efficacy of SBRT for HCC, albeit in a nonrandomized fashion (3, 18, 19). In the cohort herein presented, patients with ≤CPC-B7 cirrhosis underwent SBRT before definitive OLT. Fifty-five percent had CPC-B7 cirrhosis, and just 29% of patients experienced a decline in CPC over a mean 8.8 months. At explant, 100% of tumors demonstrated pathologic local control, with 68% of tumors with at least a partial response, consistent with published radiographic local control data (3, 19, 20). The association between hepatitis C and pathologic response is unclear and needs further study. O'connor et al (21) reported on 10 patients who underwent SBRT followed by OLT, revealing no patients with pathologic PD (100% local control) and 3 of 10 (27%) with complete necrosis (all 3 received 18 Gy × 3). Facciuto et al (22) found 37% of explants to display at least 70% tumor necrosis after SBRT.

Three-fold reduction in AFP occurred between SBRT and OLT. Radiographic response rates (CR + PR) ranged from 52% (RECIST) to 86% (mRECIST), compared with a pathologic response of 68%. Using a lower SBRT dose and RECIST criteria, Facciuto et al (22) found a radiographic response rate of just 37%. Both TPCT and MRI demonstrated poor concordance with pathologic results. Radiographic grading criteria globally performed better in sensitivity (54%-90%) and PPV (71%-74%) than in specificity (18%-50%) or NPV (29%-40%); mRECIST did seem to be the most reliable, albeit with κ agreement of just 0.224. Time from SBRT to imaging trended with response for mRECIST, RECIST, and WHO. Forty-five percent of patients had new tumors uncovered at OLT, 41% of which were multifocal; 74% of evaluable patients had viable HCC in their explant, illustrating that until better staging studies exist to define any and all targets for local therapy, OLT will remain a critical part of the treatment algorithm.

Radiofrequency ablation has been shown to produce pathologic CR rates of 47% to 63%, with higher rates in tumors <3 cm and, like SBRT, was well tolerated (23, 24). Bland transarterial embolization has also shown efficacy as neoadjuvant therapy, with pathologic CR rates of 33% (25). Both transarterial chemoembolization and ^{90}Y embolization have shown a propensity for downstaging tumors, expanding OLT eligibility (26, 27), as demonstrated in patients with segmental portal vein thrombus reported here.

Randomized trials comparing these bridging modalities with SBRT are warranted.

Kaplan-Meier actuarial overall survival estimates at 1, 2, 3, and 5 years after OLT were 92%, 86%, 77%, and 73%, respectively. Published in 1996, Mazzaferro et al (7) found a 4-year OS of 85% when performing OLT in patients with cirrhosis and HCC limited to single tumors ≤5 cm or ≤3 nodules each ≤3 cm, no extrahepatic disease, and no vascular involvement. Despite our cohort's risk factors (expanded Milan criteria ≤6 cm and 16% segmental portal vein thrombus), results approach historical controls. Herein, sum longest tumor dimension was predictive of DFS (hazard ratio 1.93, $P = .026$). Failure patients had non−statistically significant higher rates of cT2 disease (44% vs 21%), ≥pT2 disease (67% vs 34%), multifocal tumors at SBRT (44% vs 21%), and less robust AFP response (−25 IU/mL vs −162 IU/mL).

Limitations include those inherent to retrospective analyses, namely selection bias because only patients treated with SBRT followed by OLT were analyzed. Additionally, SBRT prescription heterogeneity was evident in 5 of 38 patients (13%) from the phase 1 to 2 cohort. A significant limitation was the interpretation of "pathologic stable or progressive disease" on the basis of pretreatment clinical radiographs. However, this yielded 4 response categories, permitting more robust analysis of the radiographic criteria. Proposed reasons for poor concordance between pathologic and radiographic response include difficulty interpreting post-SBRT changes in the (cirrhotic) liver, no SBRT-specific grading criteria, and heterogeneity in time from SBRT until pre-OLT imaging and OLT. Notably, 50% of patients with pathologic stable disease were transplanted within 90 days of SBRT.

Concluding, this article illustrates the safety and efficacy of SBRT before OLT for patients with HCC in the setting of liver cirrhosis. With pathologic response rates of 68%, improved staging studies are needed to better delineate targets, and radiographic response criteria need refining. In this series, Kaplan-Meier 3-year estimates of OS and DFS were 77% and 74%, respectively. Determining which patients require therapy intensification remains a challenge, with our data suggesting stratification of patients according to initial burden of disease (AFP, sum longest tumor dimension), pathologic response of treated lesions, and presence of viable HCC in explanted livers.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65:5-29.
2. Cárdenes HR, Price TR, Perkins SM, et al. Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. *Clin Transl Oncol* 2010;12:218-225.
3. Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2011;81:e447-e453.
4. Price TR, Perkins SM, Sandrasegaran K, et al. Evaluation of response after stereotactic body radiotherapy for hepatocellular carcinoma. *Cancer* 2012;118:3191-3198.
5. Lasley FD, Mannina EM, Johnson CS, et al. Treatment variables related to liver toxicity in patients with hepatocellular carcinoma, Child-Pugh class A and B enrolled in a phase 1-2 trial of stereotactic body radiation therapy. *Pract Radiat Oncol* 2015;5:e443-e449.
6. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;42:1208-1236.
7. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693-699.
8. Mangus RS, Fridell JA, Vianna RM, et al. Comparison of histidine-tryptophan-ketoglutarate solution and University of Wisconsin solution in extended criteria liver donors. *Liver Transpl* 2008;14:365-373.
9. Tector AJ, Mangus RS, Chestovich P, et al. Use of extended criteria livers decreases wait time for liver transplantation without adversely impacting posttransplant survival. *Ann Surg* 2006;244:439-450.
10. Mangus RS, Fridell JA, Vianna RM, et al. No difference in clinical transplant outcomes for local and imported liver allografts. *Liver Transpl* 2009;15:640-647.
11. Mangus RS, Fridell JA, Vianna RM, et al. Use of the piggyback hepatectomy technique in liver transplant recipients with hepatocellular carcinoma. *Transplantation* 2008;85:1496-1499.
12. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001;35:421-430.
13. World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment. WHO offset publication no. 48. Geneva: WHO; 1979.
14. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-247.
15. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010;30:52-60.
16. Hawkins MA, Dawson LA. Radiation therapy for hepatocellular carcinoma: From palliation to cure. *Cancer* 2006;106:1653-1663.
17. Hoffe SE, Finkelstein SE, Russell MS, et al. Nonsurgical options for hepatocellular carcinoma: Evolving role of external beam radiotherapy. *Cancer Control* 2010;17:100-110.
18. Kwon JH, Bae SH, Kim JY, et al. Long-term effect of stereotactic body radiation therapy for primary hepatocellular carcinoma ineligible for local ablation therapy or surgical resection. Stereotactic radiotherapy for liver cancer. *BMC Cancer* 2010;10:475.
19. Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol* 2013;31:1631-1639.
20. Kang JK, Kim MS, Cho CK, et al. Stereotactic body radiation therapy for inoperable hepatocellular carcinoma as a local salvage treatment after incomplete transarterial chemoembolization. *Cancer* 2012;118:5424-5431.
21. O'Connor JK, Trotter J, Davis GL, et al. Long-term outcomes of stereotactic body radiation therapy in the treatment of hepatocellular cancer as a bridge to transplantation. *Liver Transpl* 2012;18:949-954.
22. Facciuto ME, Singh MK, Rochon C, et al. Stereotactic body radiation therapy in hepatocellular carcinoma and cirrhosis: Evaluation of radiological and pathological response. *J Surg Oncol* 2012;105:692-698.
23. Pompili M, Mirante VG, Rondinara G, et al. Percutaneous ablation procedures in cirrhotic patients with hepatocellular carcinoma submitted to liver transplantation: Assessment of efficacy at explant

analysis and of safety for tumor recurrence. *Liver Transpl* 2005;11: 1117-1126.

24. Mazzaferro V, Battiston C, Perrone S, et al. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: A prospective study. *Ann Surg* 2004; 240:900-909.
25. Tsochatzis E, Garcovich M, Marelli L, et al. Transarterial embolization as neo-adjuvant therapy pretransplantation in patients with hepatocellular carcinoma. *Liver Int* 2013;33:944-949.
26. Graziadei IW, Sandmueller H, Waldenberger P, et al. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. *Liver Transpl* 2003;9:557-563.
27. Kulik LM, Atassi B, van Holsbeeck L, et al. Yttrium-90 microspheres (TheraSphere) treatment of unresectable hepatocellular carcinoma: Downstaging to resection, RFA and bridge to transplantation. *J Surg Oncol* 2006;94:572-586.