Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: a retrospective dose response analysis

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Supplementary Material/Online Only Appendix

Patients and Methods

Patients

Inoperable disease was determined in hepatobiliary multidisciplinary tumor conferences based on radiographic or intraoperative evaluation and included findings such as the primary tumor involving the retrohepatic vena cava/hepatic vein confluence, both intrahepatic portal pedicles, extrahepatic portal vein or biliary bifurcation, and/or the hepatic parenchyma in such a way that resection would leave an inadequate liver remnant.[1] Patients with evidence of regional nodal disease, satellitosis involving the contralateral liver, or distant metastases were also considered oncologically inoperable.

Radiation Treatment

For the liver, the organ-at-risk was defined as the volume of liver minus the gross tumor volume (GTV), and standardized dose constraints were followed.[2] Our current normal tissue dose constraints are shown in Supplementary Table 1. Tumors within 2 cm of the porta hepatis were classified as central lesions and subject to stricter bile duct dose constraints based on the University of Tsukuba experience with treating hepatocellular carcinoma (HCC).[3,4] The dose to the gastric mucosa was limited to 45 Gy in 25 fractions when large volumes of mucosa were treated because of the risk of gastric bleeding.[5]

Radiation doses were assigned depending on the proximity to these normal structures and, in part, the treatment era. Before 2010, all 36 patients had been treated with conventional fractionation at 1.8-2.25 Gy per fraction, and after 2010, 34 of the 43 patients (79%) were treated

with hypofractionation. Definitions of target volumes (GTV and clinical target volume [CTV]) did not change over the course of the study period. Contour delineation was based on the same liver protocol CT imaging with similar image quality throughout the study period. Areas of potential microscopic extension (the CTV) were treated with a 0-10 mm expansion from the GTV. However, the planning target volume (PTV) margins used for patients treated with a 3D conformal technique (n=13, 16%) were slightly larger (15-mm margin from GTV to PTV) than the margins for patients treated with intensity-modulated radiation therapy (IMRT) or proton beam radiation (n=66, 84%, 5-15 mm margin from GTV to PTV). Also, the use of IMRT and proton beam radiation allowed the use of multiple PTVs with a simultaneous integrated boost (SIB) to deliver higher doses to the GTV and the hypoxic center of the tumor. In all cases, the prescription dose was normalized to the GTV dose.

For tumors within 1 cm of the luminal gastrointestinal (GI) organs, at least 25 fractions were used to optimally spare these structures while achieving the highest minimum dose to the tumor. A planning risk volume (PRV) was created by using a 5-mm margin around all luminal structures, and the PTV was subtracted from this region if there was overlap (Fig. 1). Tumors located on the inferior surface of the liver adjacent to the colon were treated in the same way using the more lenient dose constraint for the colon (Supplementary Table 1). For tumors within 2 cm of the porta hepatis, we used a dose of 58.05 Gy in 15 fractions extrapolated from the Tsukuba HCC data: no bile duct strictures were observed after 72.6 cobalt gray equivalents (CGE) in 22 fractions compared to 3 cases of strictures after 79.2 CGE in 16 fractions.[4] Therefore, 58.05 Gy in 15 fractions was thought to be sufficiently conservative to avoid the risk of stricture and was used initially for central tumors in the high-dose era (i.e., after 2010). Conservative doses were used to treat any grossly involved lymph nodes, as the regional lymph

nodes were often in close proximity to luminal GI organs. Typical doses for involved lymph nodes included 37.5 Gy in 15 fractions and 45 Gy in 25 fractions and elective nodal irradiation was not used. The doses to the gross lymph nodes did not vary by treatment era.

The choice between using IMRT or proton beam therapy was also based on anatomic considerations. Comparison IMRT vs. proton treatment plans were done for most patients and the best plan was selected for treatment. Patients with large tumors that were >2 cm from the luminal GI organs were treated with protons due to a greater ability to spare the normal liver. IMRT was used to treat tumors within 2 cm of adjacent stomach or bowel. Our ability to safely treat these tumors to higher doses was enhanced with daily CT-on-rails image guidance with inspiration breath hold gating set up to soft tissue. We do not currently have this technology available for protons and therefore we used IMRT for tumors close to critical structures requiring visualization of soft tissue anatomy for daily setup verification.

Biologically effective dose (BED) was calculated to compare total doses among patients treated with different fractionation schemes. An α/β value of 10 was used for tumor effect. For patients receiving the SIB/simultaneous integrated protection (SIP) dosing technique that included a higher dose to the hypoxic center of the tumor (n=13), the BED was calculated based on the dose delivered to at least 90% of the GTV.

Evaluation

Patients were seen 6 weeks after RT completion and then every 3 months with a contrast-enhanced CT or MRI. Treatment response was based on the Response Evaluation and Criteria in Solid Tumors (RECIST) revised guideline.[6] Local control (LC) was defined as the absence of new enhancement or RECIST-defined progressive disease at the primary site treated with RT;

this was further categorized as local in-field progression if it occurred within the >80% isodose volume or marginal if it occurred in an adjacent area receiving a lower radiation dose (within the 20-80% isodose volume). Progression outside the 20% isodose volume was defined as out of field. Evidence of local progression was verified independently by a radiologist.

Statistical Analyses

Overall survival (OS), LC, and progression-free survival (PFS) were calculated by the Kaplan-Meier method from the date of diagnosis to the occurrence of the considered event. Where noted, the duration of LC was also calculated from the start date of RT to the date of the event, which was defined as any new enhancement or RECIST-defined progressive disease at the primary site. The outcome event for OS was defined as death from any cause and the event for PFS was defined as progression/new local, satellite intrahepatic lesions, regional, or distant disease. Patients were censored if they did not experience the specified outcome event. Log-rank tests were used to assess differences between treatment and prognostic factors affecting survival, including RT dose and BED delivered, chemotherapy treatment, patient characteristics (age, sex, race, performance status), and baseline tumor characteristics (size of the primary tumor, presence of satellite intrahepatic metastasis, regional nodal or extrahepatic disease). Fisher's exact tests were used to assess differences between categorical variables for characteristics between subgroups of patients, and the nonparametric test of medians was used to assess differences in the medians of continuous variables. Patients with missing values were not included in the assessment of the *P* values. The Cox proportional hazards model was used for multivariate analyses and the proportional hazards assumption was tested by assessing the Schoenfeld residuals. The number of covariates selected for the LC and OS multivariate models

was about 1 for every 10 events. Statistical analyses were done with JMP 11 (SAS Institute, Cary, NC, USA) and Stata/MP 13.1 (StataCorp, College Station, TX, USA).

Results

Prognostic Factors

Radiation technique was a prognostic factor for OS, which was not surprising as all of the patients treated with higher RT doses had been treated with either IMRT or proton beam therapy. Univariate analysis showed a significant benefit from IMRT compared with a 3D technique for OS (hazard ratio [HR] 0.48, 95% confidence interval [CI] 0.25-0.97, P=0.04) and proton beam radiation vs. 3D technique (HR 0.26, 95% CI 0.11-0.61, P=0.002). However, no significant difference was found between proton beam radiation vs. IMRT (HR 0.54, 95% CI 0.24-1.1, P=0.10).

Concurrent chemotherapy was used for the majority of the patients treated with a BED >80.5 and for those treated with lower doses (58% and 65%, respectively, Table 2). Patients treated with concurrent chemotherapy received both conventional and hypofractionated RT regimens; 35 of the 50 patients (70%) who received concurrent chemotherapy were treated with conventional RT fractionation while 15 patients (30%) were treated with hypofractionation. The hypofractionation regimens given with concurrent chemotherapy included 75 Gy in 25 fractions (n=6), 58.05 Gy and 67.5 Gy in 15 fractions (n=6), 66 Gy in 20 fractions (n=2) and 70 Gy in 28 fractions (n=1). No significant benefit was found from concurrent chemotherapy in terms of either LC or OS when the patients were analyzed separately based on RT dose.

Causes of Death

When the causes of death were analyzed by the treatment era, hepatic failure related to progression of the primary tumor remained the dominant cause of death. Thirty-one of the 36 patients (86%) treated before 2010 died compared with 17 of the 43 (40%) treated after 2010. Of the known causes of death, 78% (n=21/27) of the patients treated before 2010 and 89% (n=8/9) of patients treated after 2010 died from hepatic complications related to disease progression.

Toxicity

Grade 1 toxicities included nausea/vomiting (n=23, 29%), fatigue (n=19, 24%), abdominal pain (n=14, 18%), loss of appetite/weight loss (n=11, 14%), skin reaction (n=13, 16%), and elevation of liver function tests (n=2, 3%). The only grade 2 acute toxicity was skin erythema, and no severe (grade ≥3) toxicity occurred. Eleven patients (14%) developed new ascites at some point after completing RT but only 2 required percutaneous drainage. The only difference in toxicity depending on era of treatment was the rate of gastric bleeding: 12 patients (15%) developed gastrointestinal bleeding prior to mid-2011 and no patients experienced bleeding after the new dose constraints to the stomach were implemented.[5]

Discussion

Current Treatment Recommendations

Our current treatment volumes for IMRT and proton therapy use an SIB technique with 3 different PTVs to include a microscopic dose, an SIB to the entire GTV, and a higher SIB to dose to the hypoxic center of the GTV. The SIB to the entire GTV (67.5 Gy in 15 fractions or 75 Gy in 25 fractions) is treated with a 0-5 mm PTV. We subtract a PRV for all luminal structures (created by taking the 4D contour of the luminal structure and adding 5 mm) from this high-dose

PTV, and then contract that volume by 10 mm to create the PTV to the hypoxic center. The hypoxic center of the tumor receives the higher dose of 75 Gy in 15 fractions (while the entire GTV receives 67.5 Gy in 15 fractions) or 100 Gy in 25 fractions (while the entire GTV receives 75 Gy in 25 fractions). The decision to use 0, 5 or 10 mm for the CTV or 0 vs 5 mm for the PTV of the microscopic dose is based on the liver minus GTV mean dose. We begin the planning process with the larger expansions and reduce the volumes rather than the total doses to achieve plans that are within liver tolerance. In our series, only 1 patient had a margin-only recurrence and in-field tumor progression was the dominant pattern of recurrence. Therefore, we recommend maintaining higher doses at the expense of using larger margins or adding the number of treatment fractions to meet dose constraints. Given our findings on the importance of RT dose on LC and OS, we recommend the more effective 67.5 Gy in 15 fractions for central lesions. If dose constraints cannot be met, we add fractions to the treatment but also increase the total RT dose, such as using 75 Gy in 25 fractions. Because we have not observed any complications or deaths related to progressive regional adenopathy, our standard is to continue to use conservative doses to treated gross lymph nodes to 37.5 Gy in 15 fractions or 45 Gy in 25 fractions. These doses also minimize the risk of mucosal bleeding, as the regional lymph nodes are often in close proximity to the duodenum.

Supplementary References

1. Vauthey JN, Pawlik TM, Abdalla EK, et al: Is extended hepatectomy for hepatobiliary malignancy justified? Ann Surg 239:722-30; discussion 730-2, 2004

2. McGinn CJ, Ten Haken RK, Ensminger WD, et al: Treatment of intrahepatic cancers with radiation doses based on a normal tissue complication probability model. J Clin Oncol 16:2246-52, 1998

3. Chiba T, Tokuuye K, Matsuzaki Y, et al: Proton beam therapy for hepatocellular carcinoma: a retrospective review of 162 patients. Clin Cancer Res 11:3799-805, 2005

4. Nakayama H, Sugahara S, Tokita M, et al: Proton beam therapy for hepatocellular carcinoma: the University of Tsukuba experience. Cancer 115:5499-506, 2009

5. Das P, Abboud MT, Haque W, et al: Gastric bleeding after radiation therapy for intrahepatic cholangiocarcinoma. Pract Radiat Oncol 3:344-8, 2013

6. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228-47, 2009

Supplementary/Online Only Table 1. Normal Tissue Radiation Dose Constraints

Organ	Standard Fractionation (1.8-2 Gy per fraction)	Hypofractionation (>2 Gy per fraction)
Liver minus GTV		
Mean dose	<28 Gy	<24 Gy
Absolute dose	>700 cm^3 receives <30 Gy	>700 cm^3 receives <25 Gy
Volumetric dose*	V_{30} <33%	V_{25} <33%
Bile Ducts		
Central lesions†	Max 85 Gy	Max 70 Gy for 15 fx; 60 Gy for 10 fx
Peripheral lesions	No constraint	No constraint
Stomach and Duodenum		
Maximum point dose	55 Gy	45 Gy for 25 fx; 40 Gy for 10-15 fx 30 Gy for 3-5 fx
Colon		
Maximum point dose	60 Gy	45 Gy for 15 fx; 40 Gy for 10 fx 30 Gy for 3-5 fx

Abbreviations: GTV, gross tumor volume; Gy, Gray; Fx, fraction
*Vx is defined as the volume of the liver that receives x Gy or more
† Defined as tumors within 2 cm of the porta hepatis

Supplementary/Online Only Table 2. Patient Characteristics by Era of Treatment

	All Patients (% or range)	Before 2010 (% or range)	After 2010 (% or range)	*P* Value*
Number of Patients	79	36	43	
Women	46 (58%)	17 (47%)	29 (67%)	.11
Men	33 (42%)	19 (53%)	14 (33%)	
Median Age, Years	63 (31-87)	62 (31-76)	63 (42-87)	.59†
Race/ethnicity				.82
White	66 (83%)	29 (80%)	37 (86%)	
Hispanic	7 (9%)	4 (11%)	3 (7%)	
Black	3 (4%)	2 (6%)	1 (2%)	
Arab	3 (4%)	1 (3%)	2 (5%)	
ECOG Performance Status				.03
0	37 (47%)	22 (61%)	15 (35%)	
1	37 (47%)	11 (31%)	26 (60%)	
2	5 (6%)	3 (8%)	2 (5%)	
3 or 4	0	0	0	
Tumor Markers				
Median CA 19-9, U/ml	97.6 (1-95,526)	75.9 (1-95,526)	129.7 (1-17,170)	.35†
Median CEA, µg/L	2 (0.4-85)	1.7 (1-83)	2.4 (0.4-85)	.52†
Median Size of Primary Tumor				
Maximum dimension, cm	7.9 (2.2-17)	8 (2.9-14.5)	7.9 (2.2-17)	.92†
Radiation Volumes (cm^3)				
Median gross tumor volume	198 (12-966)	321 (17-966)	149 (12-778)	.06†
Median planning target volume	548 (55-2012)	772 (55-2012)	378 (66-1599)	.001†
Total Number of Tumors, Median	1 (1-12)	1 (1-12)	1 (1-8)	.60
Pts with Satellite Intrahepatic Mets	31 (39%)	13	18	.65
Tumor Location				
Central	44 (56%)	16 (44%)	28 (65%)	.07
Peripheral	35 (44%)	20 (56%)	25 (35%)	
T Classification				.78
1	7 (9%)	2 (6%)	5 (12%)	
2	49 (62%)	22 (61%)	27 (63%)	
3	21 (26%)	11 (30%)	10 (23%)	
4	2 (3%)	1 (3%)	1 (2%)	
N Classification				.82
0	33 (42%)	14 (39%)	18 (42%)	
1	46 (58%)	22 (61%)	25 (58%)	
M Classification				.58
0	63 (80%)	30 (83%)	33 (77%)	
1	16 (20%)	6 (17%)	10 (23%)	

Overall Disease Stage				.18	Abb
I	4 (5%)	1 (5%)	3 (5%)		revi
II	17 (22%)	5 (17%)	12 (42%)		atio
III	11 (14%)	10 (37%)	1 (16%)		ns:
IV	47 (59%)	20 (41%)	27 (37%)		Pts,
					pati
					ents

; ECOG, Eastern Cooperative Oncology Group; CEA, carcinoembryonic antigen; Mets, metastasis

*P value calculated by Fisher's exact test unless noted

†P value calculated by the test of medians