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Scientific Article

Stereotactic body radiotherapy (SBRT) for locally advanced extrahepatic and intrahepatic cholangiocarcinoma

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Abstract

Objectives: We report single-institution clinical efficacy and safety outcomes for patients with unresectable locally advanced cholangiocarcinoma who were treated with stereotactic body radiation therapy (SBRT) and a subset of patients who received neoadjuvant SBRT and chemotherapy as part of an orthotopic liver transplantation (OLT) protocol.

Methods and materials: From October 2008 to June 2015, 31 consecutive patients with unresectable extrahepatic (n = 25) or intrahepatic (n = 6) cholangiocarcinoma were treated with SBRT and retrospectively analyzed. Four patients underwent liver transplantation, and 1 underwent resection. SBRT was delivered in 5 fractions with a median dose of 40 Gy. Toxicity was scored using the Common Terminology Criteria for Adverse Events Version 4.0. Overall survival (OS), time to progression, and local control were estimated using the Kaplan-Meier method.

Results: The median follow-up time was 11.5 months. The 1- and 2-year OS rates were 59% and 33%, respectively, with a median survival of 15.7 months. The 1- and 2-year freedom from progression was 67% and 34%, respectively. Median time to progression was 16.8 months. Nine patients had local failure. The actuarial 1- and 2-year local control rates were 78% and 47%, respectively. Among patients who also had OLT, the median OS was 31.3 months. Twenty-four patients (77%) experienced some form of acute grade 1-2 toxicity, most commonly fatigue or pain. Five patients (16%) experienced grade $\geq$3 toxicity.

Conflicts of interest: None.

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Conclusions: SBRT is a promising option for patients with unresectable or recurrent cholangiocarcinoma either as a component of neoadjuvant therapy prior to OLT or as part of definitive therapy for patients who are unresectable and not eligible for transplantation.

Introduction

Cholangiocarcinoma is a malignancy of the biliary duct epithelium and is typically classified as either intrahepatic or extrahepatic. Klatskin tumors arise at the bifurcation of the common bile duct and represent approximately 50% of cases.[1] Cholangiocarcinoma is uncommon, but there is some evidence that its incidence has been increasing over the past few decades.[2] Prognosis is generally poor; however, it is improved in patients who can undergo surgical resection. Unfortunately, few patients are candidates for resection at the time of presentation.[3] Treatment for unresectable or recurrent disease typically focuses on palliation with an overall survival (OS) less than 10% at 5 years and a median survival of approximately 7 months.[4]

Definitive radiation therapy, with or without chemotherapy, improves the median survival of patients who are unresectable from 2 to 4 months to 9 to 12 months.[5,6] Even with locoregional radiation therapy, local recurrence is commonly the first site of progression, and mortality is often associated with the consequences of local tumor growth. This has led to an interest in improving local control by escalating radiation therapy doses both with brachytherapy[7] and SBRT, both with encouraging results.

A retrospective series from Mayo Clinic reported 10 patients with unresectable primary or recurrent cholangiocarcinoma who underwent stereotactic body radiation therapy (SBRT) using a median dose of 55 Gy.[8] This study demonstrated 100% local control at a median follow-up of 14 months, but unfortunately, the toxicity was high. Recent retrospective data from MD Anderson demonstrated a dose-dependent improvement in local control and OS[9] when radiation therapy was delivered with a biologic effective dose of >80.5, which compared favorably with surgical resection. The toxicity profile in this study was favorable; however, the majority of patients had intrahepatic disease. Very few data are available on the use of SBRT in the treatment of patients with unresectable extrahepatic cholangiocarcinoma. Therefore, we sought to understand our institutional clinical outcomes utilizing SBRT and chemotherapy, both neoadjuvantly prior to orthotopic liver transplant (OLT) and definitively in patients who were not eligible for OLT.

Methods and materials

Patients and follow-up

Thirty-one patients with cholangiocarcinoma who underwent SBRT between October 2008 and June 2015 were included in the study. Our institutional review board approved the study, and retrospectively acquired data were de-identified in accordance with Health Insurance Portability and Accountability Act of 1996 guidelines. A subset of patients was part of a single-institution prospective study to evaluate the use of neoadjuvant SBRT with chemotherapy followed by OLT for patients with unresectable or recurrent cholangiocarcinoma. Eighteen of 31 patients were included in the study and evaluated for transplant: 14 patients who were listed for and 4 patients who ultimately underwent OLT.

Inclusion and exclusion criteria

Consecutive patients who were treated with SBRT for either intrahepatic or hilar cholangiocarcinoma were included. Patients were diagnosed by malignant stricture on cholangiography or biopsy/cytology results that demonstrate malignancy, cancer antigen (CA) 19-9 >100 U/mL, or aneuploidy. Patients were excluded from the study if they had an uncontrolled infection, a lesion >8 cm on imaging scans, medical conditions or other malignancies that preclude liver transplantation, or extrahepatic malignancy. All patients underwent a complete staging workup that typically consisted of positron emission tomography (PET) with computed tomography (CT) and magnetic resonance imaging (MRI). Patients with locoregional nodal involvement were included in the study if the location was adjacent to the primary tumor and thus amenable to inclusion in the high-dose SBRT volume group. All patients were treated and seen during the follow-up period by the same radiation oncologist (P.L.). All patients underwent a surgical staging operation prior to OLT.

SBRT treatment planning

All planning CT scans were obtained with a Siemens SOMATOM Definition AS scanner (Siemens Healthcare

Diagnostics, Los Angeles, CA) with intravenous contrast. A 4-dimensional CT scan was performed under free-breathing conditions. Images were acquired during the portal venous phase. Data from PET-CT and/or MRI scans with Eovist were incorporated in the target definition when available and helpful. For each case, the gross tumor volume, normal liver, right and left kidneys, spinal cord, esophagus, stomach, duodenum near the gross tumor volume, and bowel bag were segmented. An internal target volume was generated with the maximum-intensity projection derived from the 4-dimensional CT scan to derive the tumor's motion envelope. The internal target volume was then expanded to 5 to 8 mm to generate a planning target volume (PTV).

The volume of normal liver (ie, total liver minus PTV) receiving 15 Gy was maintained at <1000 mL, the spinal cord and kidneys were limited to a maximum of 2.5 Gy per fraction, the volumes of bowel bag and stomach receiving 20 Gy were maintained at <20 mL. The volume of duodenum receiving 20 Gy was kept at <9 mL, which was adapted from research by Murphy et al.[10] Our liver constraint, which was more conservative than current guidelines, was adapted using the principles outlined by Schefter et al.[11] The bowel and stomach constraints were used per Rwigema et al[12] in which patients with abdominal and pelvic metastases were treated with SBRT using these constraints with minimal small bowel and stomach toxicity. With the single fraction constraint from Murphy et al as a guide, we relaxed the constraint slightly to account for a fractionated regimen but stay as conservative as possible given the high rates of duodenal toxicity in this patient population.

The biliary tree was not routinely segmented. Biliary toxicity in this patient population is an area of ongoing research, and some studies show acceptable levels of biliary toxicity with a dose of 40 Gy in 5 fractions.[13] Additionally, many of our patients had biliary stents placed prior to radiation, which was thought to potentially mitigate biliary tree fibrosis and stenosis due to the disease or radiation. SBRT was delivered in 5 fractions, typically every other day, with total doses ranging from 25 to 50 Gy. Nearly all patients (26 of 31) received a total dose of 40 Gy in 5 fractions. All patients who proceeded to treatment with surgery underwent 40 Gy in 5 fractions. Two patients had involved portal nodes, which were included in the SBRT treatment volume. Patients who received treatment earlier in the study were treated with a lower dose (25-30 Gy in 5 fractions) when we had less experience with the technique and were more cautious. One patient received 50 Gy in 5 fractions. The reason for escalation of the dose in this patient was young age (30s), ineligibility for liver transplantation, and our ability to safely meet constraints at the higher dose. The PTV was normalized and plans were designed such that 95% of the PTV received the full prescription dose (Table 1). The average maximum dose (D_{max}) was 111% of the prescribed dose (range, 98-118%).

Table 1 Patient and treatment characteristics

Characteristic	Number (%)
Patients	31
Target volume (cc)	
Median	59.3
Range	13.8-174.5
Total dose (gray)	
Median	40
Range	25-50
Number of fractions	5
Dose to planning target volume (gray)	
Average maximum dose	42.60
Average mean dose	39.84
Average minimum dose	33.54
Chemotherapy received	
Chemotherapy	23 (74)
No chemotherapy	8 (26)
Chemotherapy regimen	
Gemcitabine/cisplatin	19 (83)
Gemcitabine alone	2 (9)
Gemcitabine/oxaliplatin	1 (4)
Capecitabine/oxaliplatin	1 (4)
Chemotherapy duration (weeks)	
Median	23.7
Range	2.6-112
Age, y	
Median	63
Range	32-94
Gender	
Male	19 (61)
Female	12 (39)
Tumor Location	
Intrahepatic	6 (19)
Extrahepatic	25 (81)
Treatment Location	
Tumor alone	29 (94)
Tumor and portal node	2 (6)
Pertinent history	
Inflammatory Bowel Disease	2 (6)
Chronic hepatitis	3 (10)
Hemochromatosis	1 (3)
Pretreatment cancer antigen 19-9	
Average	1876
Range	<1 to 23,000
Tumor size (cm)	
Median	2.7
Range	1-7.3

The average mean dose to the PTV was 104% of the prescribed dose (range, 91-107%).

Statistical analysis

Follow-up time was calculated from the last day of radiation therapy to either the last date of contact or death. Local progression and OS were calculated from the last day of radiation therapy to the date of local progression

on imaging or death, respectively. Local progressive disease on imaging was defined using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 if applicable, or as increase in fluorodeoxyglucose (FDG) avidity on PET compared with fluorodeoxyglucose prior to SBRT. The Kaplan-Meier method was used to ascertain the 1- and 2-year OS, local progression, and freedom-from-progression rates as well as the median survival times. The survival plots were generated using the Kaplan-Meier method. Analysis was performed using SAS Version 9.4 (SAS Institute, NC).

Results

Baseline patient and disease-specific characteristics are described in Table 1. Thirty-one consecutive cases of unresectable cholangiocarcinoma treated with SBRT between October 2008 and June 2015 were analyzed. The median patient age at diagnosis was 63 years. Three patients had a history of chronic viral hepatitis, 2 patients had inflammatory bowel disease, and 1 patient had hemochromatosis. Four cases were recurrent; of these, two received prior chemoradiotherapy initially. Of these 2 cases, both received 54 Gy previously. One patient had undergone a Whipple procedure alone and another a Whipple procedure followed by adjuvant chemotherapy. The median post-treatment follow-up time ranged from 1 to 44 months with a median follow-up time of 11.5 months. One patient had resection after SBRT, and 4 had OLT.

Local control

In total, 9 patients suffered a local recurrence. Of note, one of these 9 patients had disease progression after transplant at the site of the porta hepatis. The remainder of the local recurrences were in patients who were treated nonsurgically. All local recurrences were in the high-dose SBRT field. The actuarial local control rate was 78% at 1 year and 47% at 2 years (Fig 1). Of the patients who underwent liver transplant or resection (n = 5), all had a favorable tumor response to SBRT at the time of OLT. Most commonly, the pathology from the ex-plant showed extensive radiation fibrosis with small and intermediate vascular radiation changes. Negative margins were achieved in all surgeries, including that for the patient who underwent resection instead of OLT. Pathologic features are summarized in Table 2.

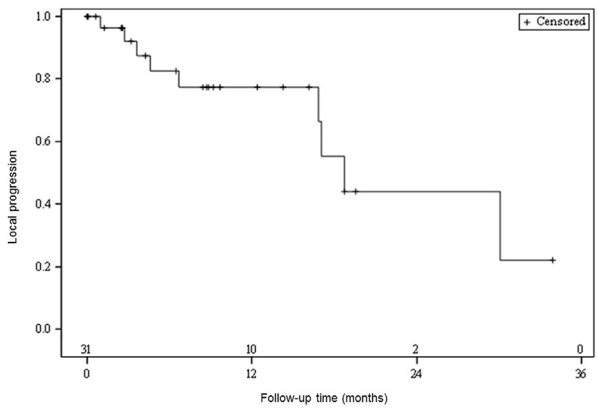

Figure 1 Kaplan-Meier curve demonstrating time to local tumor progression.

Survival and progression

The 1- and 2-year OS rates were 59% and 33%, respectively, with a median survival of 15.7 months (Fig 2). The 1- and 2-year freedom-from-progression rates were 67% and 34% respectively. The overall median time to progression was 16.8 months. Of the patients who underwent OLT, one died 18 weeks after transplantation, one survived 30 months after transplantation, and 2 others were still alive at the time of the last follow-up (11 and 15 months from transplant). The patient who underwent resection (of liver segments 4B and 5) was alive at the time of the last follow-up (28 months after resection). Of the patients who underwent any type of surgery, median OS by Kaplan-Meier method was 31.3 months (Table 2). For patients who were treated nonsurgically, median OS was 12.7 months. Two patients progressed regionally, including one patient who had an intrahepatic failure out of the SBRT field and one patient who had a regional recurrence in a periportal lymph node. One patient progressed both regionally and distantly to the liver and retroperitoneal lymph nodes. Two patients progressed distantly with metastases to lung and ureter, respectively.

Toxicity

Twenty-four patients (77%) experienced some form of acute grade 1-2 toxicity from SBRT based on Common Terminology Criteria for Adverse Events Version 4.0. with mild fatigue or abdominal pain being the most common. One patient developed grade 3 duodenal obstruction acutely 2 months after radiation. Five patients (16%) experienced severe late toxicity, of whom 2 developed grade 3 duodenal obstruction, 2 experienced grade 3 duodenal hemorrhage, and 1 had grade 4 duodenal hemorrhage. One patient also had long-term abdominal pain (Table 3).

All patients who experienced severe late toxicity were prescribed a dose of 40 Gy in 5 fractions. Of the 5 patients, 3 had maximum duodenal doses of >40 Gy and 2 had maximum doses of 33.5 Gy and 3 Gy.

Discussion

Patients with unresectable cholangiocarcinoma typically have a very poor prognosis of 7 to 12 months when

Table 2 Treatment and outcomes of surgical patients

Patient Number	Neoadjuvant Treatment/Date of completion	Date of surgery (months post-SBRT)	Pathologic findings	Outcome (months post-SBRT)
1	SBRT followed by chemo, 3/17/10	1 month (OLT)	Extensive fibrosis, +residual carcinoma	Death 6 months
2	SBRT alone, 12/21/09	5 months (OLT)	Residual carcinoma	Local progression 19.5 months, death 33.5 months
3	SBRT followed by chemo, 9/24/12	5.5 months (resection)	No residual carcinoma	Alive at last follow-up at 33.5 months
4	SBRT followed by chemo, 8/16/13	18 months (OLT)	Extensive fibrosis, no residual carcinoma	Alive at last follow-up at 28.5 months
5	SBRT followed by chemo, 4/21/14	6 months (OLT)	Extensive fibrosis, +residual carcinoma	Alive at last follow-up at 20 months

SBRT, stereotactic body radiation therapy; OLT, orthotopic liver transplantation.

treated with fractionated radiation therapy with or without chemotherapy, often with a palliative intent. Metastatic disease is uncommon, and survival is usually dictated by local progression.[14,15]

A small series of patients with unresectable cholangiocarcinoma who were treated with SBRT have shown promising rates of local control but with variable toxicity.[8,16,17] In one of the earliest published series, Kopek et al described the results of 27 patients with unresectable cholangiocarcinoma (26 of 27 patients with Klatskin type) who were treated with 45 Gy in 3 fractions.[16] The patients showed a median progression-free survival of 6.7 months and OS of 10.6 months. Local control was excellent, and only 2 patients failed locally with an actuarial 1-year local control rate of 84%. However, gastrointestinal toxicity was high (30%), with 6 patients developing severe duodenal ulceration and 3 developing duodenal stenosis. Of note, the treatment margins in this series were rather large (5 mm radially and 10 mm cranial-caudal) compared with the commonly used 5 mm in all directions.

Three subsequent studies evaluated similar regimens. The first used a dose of 30 Gy in 3 fractions in a series of 10 patients, all of whom were diagnosed with a Klatskin tumor.[18] The study reported a high local failure rate with 6 of 10 patients experiencing a local progression. The median OS was 35.5 months in this cohort. The authors did not report any grade 3 or 4 toxicities. The lower dose may explain both the decreased toxicity and the high rate of local progression. In the Mayo Clinic series, the doses ranged from 45 to 60 Gy in 3 to 5 fractions.[8] The study reported a 12-month OS of 73%. Two patients (20%) in that study had severe late toxicity, including 1 patient with grade 3 biliary stenosis and 1 patient with grade 5 liver failure. Similar to the patients in our study, treatment margins of approximately 5 mm were used. The third study was a larger series that was published in 2014 and included 58 patients (half with primary tumors and half with recurrent disease) who were treated with SBRT.[19] The rates of local control at 1- and 2-year follow-up were 85% and 72%, respectively. The 1- and 2-year OS rates were 53% and 28%, respectively, with a median OS of 13 months. The study reported only 6 patients (10%) with grade $\geq$3 toxicity. It is important to note that the vast majority of patients in this series had intrahepatic disease. Intrahepatic tumors tend to result in lower rates of high-grade toxicity (<10%) as reported in series of patients with hepatocellular carcinoma treated with SBRT[20,21] due to a favorable location

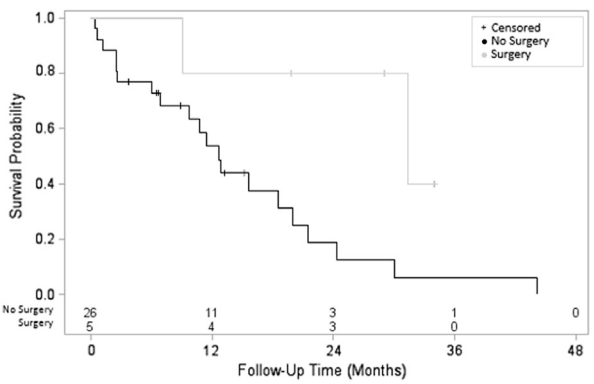

Figure 2 Kaplan-Meier curve demonstrating overall survival, stratified by surgical and nonsurgical patients.

Table 3 Toxicity

Toxicity	Number (%)
Acute (<3 months post-RT)	
Fatigue	11 (35)
Pain	7 (23)
Nausea	3 (10)
Duodenal obstruction	1 (3)
Other	3 (10)
Late (>3 months post-RT)	
Duodenal ulcer (Gr 3)	2 (6)
Duodenal ulcer (Gr 4)	1 (3)
Duodenal obstruction (Gr 3)	2 (6)

RT, radiation therapy.

that is often removed from serial structures such as the stomach, duodenum, and jejunum. Also of note, the treatment margins were smaller in this series at 2 mm radially and 4 mm cranial-caudal.

Given the high rates of duodenal toxicity in this patient population, it is worthwhile to compare the results with SBRT in patients with pancreatic cancer because the pancreas is also an organ that is intimately associated with the duodenum. Herman et al conducted a phase 2 multi-institutional trial to evaluate SBRT (33 Gy in 5 fractions) after gemcitabine in patients with unresectable pancreas adenocarcinoma.[22] In that series, the researchers observed 6 cases of severe late toxicity (13%). Three patients had grade 3 ulceration, one had grade 4 fistula, one died due to gastrointestinal bleeding from direct tumor extension into the duodenum, and one died due to secondary bleeding from stent migration. These rates of toxicity are similar to those in our study, again emphasizing the challenges of minimizing toxicity when delivering SBRT close to the duodenum.

In our current study, we observed a median OS of 12.7 months among patients who did not undergo OLT. Nine of 31 patients experienced local progression with a 1-year actuarial local control rate of 78%, which compares very favorably with other series that report outcomes for extrahepatic disease when balanced against high risk for toxicity in treating at this location. Specifically, we observed 5 of 31 patients (16%) with late grade $\geq$3 toxicity, 3 with duodenal ulcer and 2 with duodenal strictures. When comparing this percentage with the doses and toxicity rates cited above, we feel this is an acceptable toxicity especially given the patients' overall poor prognosis and lack of treatment options. Efforts towards reducing duodenal toxicity are ongoing and may be achieved with using techniques that offer more compact dosimetry, better image-guidance techniques, or other means. Duodenal toxicity is not well understood and remains a subject of ongoing investigation. Indeed, 2 of our patients who had severe late toxicity had modest or very small doses to the duodenum, suggesting that other factors such as the possibility of severe toxicity that results from damage to the biliary tree, which is often under-reported, may be contributing.

Excellent outcomes have been reported for patients with unresectable cholangiocarcinoma who undergo neoadjuvant chemoradiation followed by OLT with up to 70% recurrence-free survival at 5 years.[23,24] A series of 132 patients with cholangiocarcinoma conducted at UCLA[25] showed improved recurrence-free survival in patients who underwent OLT versus patients in the resection group (33% vs 0% at 5 years). Among patients who underwent transplants, survival rates were improved for those patients who received neoadjuvant and adjuvant therapy versus adjuvant alone or no additional therapy. In the current study, we showed very favorable rates of survival in patients who underwent transplants with a median OS of 31.3 months. However, the numbers are very small and definitive conclusions cannot be made.

Limitations

Our study has several limitations, including a retrospective study design, small sample size, and relatively limited follow-up time of approximately 1 year. However, cholangiocarcinoma is a relatively rare and rapidly fatal disease; therefore, a 1-year median follow-up does provide meaningful results, especially since many patients were enrolled in a prospective clinical trial with good follow up.

Conclusions

To our knowledge, this is the largest report on patients with primarily extrahepatic cholangiocarcinoma who were treated with SBRT. Our local control and OS compare favorably with those reported in the literature, especially when considering that many of the published series are small and include patients with primarily intrahepatic cholangiocarcinoma. This technique appears to have good primary tumor control that is comparable to other dose-escalation methods. Using SBRT before transplant or resection appears to offer a high survival rate in a limited number of eligible patients and may be potentially curative. More patients and longer follow up time is necessary to validate these results. Importantly, significant grade 3 or higher toxicity persists and typically includes duodenal ulcers or obstruction. In the future, more advanced image-guided approaches such as MRI-guidance and tracking coupled with adaptive radiation therapy may further improve local tumor control with SBRT and decrease late toxicity in this patient population.

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