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CLINICAL INVESTIGATION **Liver**

EXTERNAL-BEAM RADIOTHERAPY FOR LOCALIZED EXTRAHEPATIC CHOLANGIOCARCINOMA

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Purpose: The role of radiation therapy (RT) in extrahepatic cholangiocarcinoma (EHCC) is not clear and only limited reports exist on the use of this modality. We have reviewed our institutional experience to determine the pattern of failure in patients after potentially curative resection and the expected outcomes after adjuvant RT and in unresectable patients.

Methods and Materials: After institutional review board approval, 81 patients diagnosed with EHCC (gallbladder 28, distal bile duct 24, hilar 29) between June 1986 and December 2004 were identified and their records reviewed. Twenty-eight patients (35%) underwent potentially curative resection with R0/R1 margins. Fifty-two patients (64%) were unresectable or underwent resection with macroscopic residual disease (R2). All patients received three-dimensional planned megavoltage RT. The dose for each patient was converted to the equivalent total dose in a 2 Gy/fraction, using the linear-quadratic formalism and α/β ratio of 10. The median dose delivered was 58.4 Gy (range, 23–88.2 Gy). 54% received concomitant chemotherapy.

Results: With a median follow-up time of 1.2 years (range, 0.1–9.8 years) 75 patients (93%) have died. Median overall survival (OS) and progression-free survival (PFS) were 14.7 (95% CI, 13.1–16.3) and 11 (95% CI, 7.6–13.2) months, respectively. There was no difference among the three disease sites in OS ($p = 0.70$) or PFS ($p = 0.80$). Complete resection (R0) was the only predictive factor significantly associated with increase in both OS and PFS ($p = 0.002$), and there was no difference in outcomes between R1 and R2 resections. The first site of failure was predominantly locoregional (68.8% of all failures).

Conclusion: Local failure is a major problem in EHCC, suggesting the need for more intense radiation schedules and better radiosensitizing strategies. Because R1 resection appears to convey no benefit, it appears that surgery should be contemplated only when an R0 resection is likely. Borderline-resectable patients might be better served by neoadjuvant therapy. © 2006 Elsevier Inc.

Radiation therapy, Extrahepatic cholangiocarcinoma, Gallbladder carcinoma, Hilar carcinoma.

INTRODUCTION

Extrahepatic cholangiocarcinoma (EHCC) is an uncommon disease, accounting for 7500 new cases in 2005 in the United States and 3300 deaths (1). These tumors arise from the epithelial cells of the extrahepatic bile ducts and can be further divided into hilar (also known as Klatskin tumor), distal bile duct, and gallbladder origin. Most patients will present with locally advanced, unresectable disease from a tendency for extensive spread beyond the gross tumor margins at diagnosis (2, 3). Gallbladder carcinoma tends to invade through the gallbladder wall into the liver or neighboring structures and to spread to distant organs (4). Although complete resection of these tumors is the most effective and the only potentially curative treatment (5), many patients cannot undergo surgery because of their advanced stage at diagnosis (6).

The overall prognosis for EHCC is poor, with 5–19% of patients alive at 5 years and a median survival time of 6–9 months (5, 7–10). Several centers have reported improved outcome with 5-year survival rate of up to 56% in a selected patient group using an aggressive surgical approach, including partial hepatectomy (11–14).

Chemotherapy as a treatment modality for adjuvant or palliative treatment for EHCC is largely ineffective, and an extensive literature review of 65 clinical trials documented no survival benefit (15). Generally, 5-fluorouracil and mitomycin C, alone or combined with doxorubicin, carmustine

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(CCNU), or other drugs elicited a low response rate and no survival benefit (15). Other, newer drugs such as capecitabine and gemcitabine, alone or combined with cisplatin, appear to be somewhat more effective (16, 17).

Little is known about the use of modern three-dimensional (3D) radiation alone or in combination with chemotherapy as adjuvant treatment after surgical resection or as primary therapy of unresectable disease (15, 18–24). At the University of Michigan, we have routinely used radiation therapy (with or without systemic or intrahepatic infusion of chemotherapy) for locally advanced EHCC and adjuvantly in patients with ≥T2 or $N+$ disease. We have reviewed our experience during the 3D treatment planning era to determine the pattern of failure after potentially curative resection and adjuvant RT and the expected outcomes in the adjuvant and unresectable settings.

METHODS AND MATERIALS

Between June 1986 and December 2004, 81 patients diagnosed with invasive, nonmetastatic EHCC were treated in the Department of Radiation Oncology at the University of Michigan. After Institutional Review Board approval, their medical records were reviewed for the following characteristics: age, sex, race, presenting symptoms, surgical procedures, histologic features, stage, resection-margin status, radiation treatment details, chemotherapy treatment details, acute and late toxicity, pattern of failure, and survival. Patients were staged by the AJCC, 5th edition (25). Acute toxicity was scored according the Common Terminology Criteria for Adverse Events v3.0 (26), and late events were assessed using the Radiation Therapy Oncology Group and the European Organization for Research and Treatment Criteria (27). Patients with intrahepatic cholangiocarcinoma and patients diagnosed with metastatic disease at presentation are not included in this analysis.

The primary clinical endpoints for this retrospective study were progression-free survival (PFS), overall survival (OS), and acute and late radiation-induced toxicities. Both PFS and OS were estimated using the product-limit method of Kaplan and Meier. Time to progression or death was calculated from the date of cancer diagnosis. Estimates for the median, 1- and 2-year PFS and OS were stratified by residual disease status and by disease site and reported separately. Cox proportion hazards regression was used to test for significant associations between PFS and the clinical characteristics abstracted across all disease sites. Separate analyses for each site were not attempted because of the small sample size. Clinical characteristics were compared between disease sites, residual disease status, and by the occurrence of acute or late radiation induced toxicity by use of the chi-square test statistic, the Fisher's exact test statistic (when cell counts were small), and the Kruskal-Wallis test statistic (for continuous data, such as age and RT dose). For all statistical tests, p values ≤0.05 were considered to be significant.

RESULTS

Patient characteristics

Patient and disease characteristics are summarized in Table 1. There were 28 patients with gallbladder cancer, 24 with distal bile duct tumors and 29 with hilar carcinoma. The median age at diagnosis was 62.9 years (range, 26–86 years). There was no difference between the groups in terms of follow-up time, age, gender, and race. All but 8 patients (9%) had tissue diagnosis established by needle biopsy or at time of surgery. In these 8 patients, repeated biopsy at-

Table 1. Patient and disease characteristics

	All patients	Distal extrahepatic cholangiocarcinoma	Hilar	Gallbladder
Group size	81	24	29	28
Clinical follow-up				
Median: years (range)	1.2 (0.1–9.8)	1.3 (0.3–9.8)	1.0 (0.1–7.5)	1.2 (0.3–7.1)
Alive at last follow-up: N (%)	6 (7.4)	1 (4.2)	1 (3.5)	4 (14.3)
Age at diagnosis: years				
Median (range)	62.9 (25.8–86.4)	59.6 (44.9–83.6)	65.7 (25.8–81.6)	60.4 (37.2–86.4)
Gender				
Male *n* (%)	42 (51.9)	15 (62.5)	15 (51.7)	12 (42.9)
Race:				
Caucasian *n* (%)	74 (91.4)	22 (91.7)	26 (89.7)	26 (92.9)
Other *n* (%)	7 (8.6)	2 (8.3)	3 (10.3)	2 (7.1)
Stage				
Resected patients (RO, R1)				
IB	6	3	—	3
IIA	10	4	1	5
IIB	10	4	3	3
III	—	—	—	—
Unresectable or R2				
IB	3	—	2	1
IIA	22	8	12	2
IIB	13	2	5	6
III	15	4	7	4
Unknown	2	—	1	1

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