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CONCURRENT CHEMORADIOOTHERAPY IN RESECTED EXTRAHEPATIC CHOLANGIOCARCINOMA

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Abstract

Purpose—Extrahepatic cholangiocarcinoma is a rare malignancy. Despite radical resection, survival remains poor, with high rates of local and distant failure. To clarify the role of radiotherapy with chemotherapy, we performed a retrospective analysis of resected patients who had undergone chemoradiotherapy.

Methods and Materials—A total of 45 patients (13 with proximal and 32 with distal disease) underwent resection plus radiotherapy (median dose, 50.4 Gy). All but 1 patient received concurrent fluoropyrimidine-based chemotherapy. The median follow-up was 30 months for all patients and 40 months for survivors.

Results—Of the 45 patients, 33 underwent adjuvant radiotherapy, and 12 were treated neoadjuvantly. The 5-year actuarial overall survival, disease-free survival, metastasis-free survival, and locoregional control rates were 33%, 37%, 42%, and 78%, respectively. The median survival was 34 months. No patient died perioperatively. Patient age ≥ 60 years and perineural involvement adversely affected survival on univariate analysis. Patients undergoing R0 resection had a significantly improved rate of local control but no survival advantage. Despite having more advanced disease at presentation, patients treated neoadjuvantly had a longer survival (5-year survival 53% vs. 23%, $p = 0.16$) and similar rates of Grade 2–3 surgical morbidity (16% vs. 33%, $p = 0.24$) compared with those treated in the postoperative setting.

Conclusion—These study results suggest a possible local control benefit from chemoradiotherapy combined with surgery in patients with advanced, resected biliary cancer.

Furthermore, our results suggest that a treatment strategy that includes preoperative chemoradiotherapy might result in improved tumor resectability with similar surgical morbidity compared with patients treated postoperatively, as well as potentially improved survival outcomes. Distant failure remains a significant failure pattern, suggesting the need for more effective systemic therapy.

Keywords

Biliary cancer; Radiotherapy; 5-Fluorouracil; Surgical resection; Adjuvant therapy

INTRODUCTION

Carcinoma of the extrahepatic biliary system is a rare malignancy, with 3,000 cases estimated to occur in the United States in 2008 (1, 2). Most patients with biliary cancer present with locally unresectable or metastatic disease, resulting in a 5-year survival rate of <10% (3–6). The range of overall survival (OS) is 2–3 months in patients receiving medical management alone, 6–12 months for patients undergoing palliative surgical biliary bypass, and 12–24 months for resected patients. Surgery is the only potentially curative treatment. However, the resectability rate ranges from 10% to 35% (3, 4). Even in patients undergoing radical resection, the prognosis remains poor, with local failure rates >50% in contemporary series with associated morbidity and mortality (5, 7). Given these poor outcomes, adjuvant therapy should be considered for these patients. However, given the rarity of this malignancy, the role of radiotherapy (RT) and chemotherapy in resectable patients is poorly defined. An analysis evaluating combined RT and chemotherapy in patients who underwent potentially curative surgery at Duke University was undertaken.

METHODS AND MATERIALS

The Duke University institutional review board approved this retrospective study. All patients who had undergone resection with curative intent and RT for localized adenocarcinoma of the extrahepatic biliary system in the Duke University Health System between 1992 and 2006 were included. Patients with carcinoma of the intrahepatic bile ducts, liver, gallbladder, pancreas, ampulla of Vater, and duodenum were excluded. Patients treated with palliative procedures (*e.g.*, palliative bypass, stent placement) were likewise excluded.

Histologic disease confirmation was obtained for all patients before the initiation of adjuvant or neoadjuvant therapy. The surgical margin status and completeness of resection (R0, uninvolved margins; R1, microscopically involved margins/no gross residual disease; and R2, involved margins/gross residual disease) were determined by reviewing the operative notes and pathology report for each case.

Multifield external beam RT techniques were used to treat the tumor bed and locoregional lymph nodes (*i.e.*, porta hepatis, pericholedochal, celiac, pancreaticoduodenal) to a median dose of 50.4 Gy (range, 10.8–54) using 1.8–2 Gy daily fractions. The field arrangements included anteroposterior–posteroanterior and anteroposterior–posteroanterior with lateral fields. Brachytherapy, using ^{192}Ir (dose rate, 45–150 cGy/h) prescribed to a depth of 5–7

mm by way of percutaneous catheters, was delivered in 1 patient (43.5 Gy) who did not undergo external beam RT and as a boost (mean dose, 29 Gy) to external beam RT in 4 patients. Fluoropyrimidine-based chemotherapy was delivered concurrently with RT in all but 1 patient (as a continuous infusion for 26 patients, a bolus for 8, and orally for 10). No patient had evidence of distant metastases at treatment. Of the 45 patients, 20 received adjuvant chemotherapy after chemoradiotherapy and surgery, using varying regimens including capecitabine, gemcitabine, irinotecan, paclitaxel, oxaliplatin, cisplatin, bevacizumab, doxorubicin, and eniluracil. No clear pattern of chemotherapy use was discernable from the information available for review.

Local, regional, and distant failure patterns were determined by follow-up clinical examination, radiographic imaging, endoscopy, and autopsy data. Local and regional failure was defined as any evidence of recurrence in the tumor bed or locoregional lymph node basins, including the celiac, porta, or hepatic parenchyma immediately adjacent to the resection bed. Distant failure was defined as the appearance of disease outside of these areas. Patients were generally followed every 3 months with physical examination, laboratory assessments of liver function tests and tumor markers, and computed tomography after treatment completion.

The Kaplan-Meier method was used to determine the OS, median survival, disease-free survival, metastasis-free survival, and local control rates for the entire cohort. Univariate regression analysis was performed to evaluate the effect of selected variables (age >60 years, gender, tumor location proximal or distal to the cystic duct, surgery type [pancreaticoduodenectomy vs. segmental resection], nodal status, lymphovascular invasion, histologic differentiation, perineural invasion, radiation dose 50 Gy, two-dimensional vs. three-dimensional treatment planning, brachytherapy use, and use of post-RT chemotherapy) on the clinical endpoints (8).

RESULTS

A total of 45 patients (29 men and 16 women) underwent resection plus RT. Of the 45 patients, 33 received adjuvant RT, and 12 were treated neoadjuvantly. Of the 12 neoadjuvantly treated patients, 10 were deemed to have borderline resectable disease or unresectable disease as determined by laparotomy ($n = 5$) or abdominal computed tomography ($n = 5$). The remaining 2 patients were treated neoadjuvantly because of physician preference. The median age was 60 years (range, 32–79). The median follow-up of all patients and of the surviving patients was 30 months (range, 3–178) and 40 months (range, 7–178), respectively. Of the 45 patients, 36 (80%) underwent a complete resection with negative microscopic margins, 6 (13%) had microscopically involved margins, and 3 (7%) had gross residual disease. The disease was classified as well differentiated in 8 (18%), moderately differentiated in 26 (58%), and poorly differentiated in 11 (24%). The patient characteristics are listed in Tables 1 and 2.

Of the 45 patients treated, 16 patients were alive, with 14 exhibiting no evidence of disease at their last follow-up visit. The most common chemoradiotherapy toxicities were fatigue (80%), nausea (65%), anorexia (50%), and abdominal pain (30%). No treatment-related

deaths occurred. One patient who was undergoing preoperative RT discontinued treatment after 10.8 Gy, opting for immediate surgical treatment. Five patients required a reduction in the chemotherapy dose because of treatment-related effects (nausea/vomiting in 4, hand/foot/mouth reaction in 1). All remaining patients completed the prescribed course of chemoradiotherapy.

Clinical endpoints

The 5-year actuarial overall survival, disease-free survival, metastasis-free survival, and locoregional control rates were 33%, 37%, 42%, and 78%, respectively (Figs. 1 and 2). The median overall survival, disease-free survival, and metastasis-free survival duration was 34, 41, and 41 months, respectively.

On univariate analysis, age ≥ 60 years and perineural involvement adversely affected survival (perineural involvement, yes vs. no, 5-year OS rate of 21% vs. 48%, respectively, $p = 0.01$; age >60 vs. ≤ 60 years, 5-year OS rate of 50% vs. 12%, respectively, $p = 0.03$). Patients with poorly differentiated tumors showed a trend toward inferior 5-year survival (27%) compared with patients with well-differentiated (42%, $p = 0.07$) or moderately differentiated (33%, $p = 0.11$) disease. Patients with lymph node involvement also showed a trend toward lesser survival, although the difference was not statistically significant (5-year OS rate, 35% vs. 27%, respectively, $p = 0.10$). Patients with negative resection margins (R0 vs. R1 or R2) had a significantly improved local control rate at 5 years (82% vs. 60%, respectively, $p = 0.02$), but this did not convey a survival benefit (5-year OS rate, 36% vs. 32%, respectively, $p = 0.7$). However, patients achieving local control appeared to experience a survival benefit in our series (5-year survival rate, 35% vs. 17%, $p = 0.06$). Tumor location (proximal vs. distal), surgery type, gender, nodal status (N0 vs. N+), lymph vascular invasion radiation dose (≥ 50 Gy), radiation planning method, and the use of post-RT chemotherapy did not significantly affect survival in our series. No benefit was seen with the use of brachytherapy, with patients receiving brachytherapy showing inferior 5-year survival (20% vs. 34%, $p = 0.05$), possibly because of a patient selection bias, although a review of such failed to identify disproportionate adverse prognostic factors in this group.

Of the 6 patients who underwent R1 resection, 1 lived >3 years, without evidence of recurrence. Surprisingly, of the 3 patients who underwent R2 resection, 2 were long-term survivors at 6 and 7 years, respectively, without evidence of recurrence. Of the 12 patients who received neoadjuvant chemoradiotherapy, 10 were judged to have borderline resectable or unresectable malignancies as determined by either preoperative imaging or the initial exploratory laparotomy. Despite this, these patients showed a trend toward improved survival (5-year survival rate, 53% vs. 23%, $p = 0.16$). Of the 12 neoadjuvantly treated patients, 3 were found to have a pathologic complete response, and 9 had varying degrees of histologic response. In addition, 11 (91%) of these 12 patients underwent R0 resection.

Of the 45 patients included in this study, 2 patients in the neoadjuvant group (17%) and 11 in the adjuvant group (33%) experienced Grade 2–3 surgical complications ($p = \text{NS}$) (9). These included abdominal abscess in 11 patients, pancreatic leak in 1, and cardiac arrhythmia in 1 patient. The mean hospital stay after definitive surgical resection was similar between the adjuvantly and neoadjuvantly treated patients (Table 3).

Failure patterns

Distant failure dominated in this cohort after a period of clinical complete response. Sixteen patients experienced distant failure as the first site of failure and 5 developed locoregional failure as the site of first failure; 3 of these 5 then developed systemic failure. Conversely, only 1 patient with initial distant failure subsequently developed local failure. For the entire group, the most common site of distant failure was the liver ($n = 10$), followed by distant nodal failure ($n = 5$), lungs ($n = 3$), and the peritoneal cavity ($n = 1$).

DISCUSSION

The outcome of patients with extrahepatic cholangiocarcinoma is poor. Because most patients with biliary cancer present with unresectable or metastatic disease, the overall 5-year survival rate has been 10% (3, 4). Although surgery is the only potentially curative option for patients with biliary carcinoma, only a minority are surgical candidates at presentation. Even for patients who undergo resection with curative intent, the prognosis remains poor, and additional therapy should be considered for these patients.

Patterns of failure analyses after surgery alone for extrahepatic cholangiocarcinoma have been limited. The available data suggest that locoregional recurrence is underreported, common, and ultimately leads to death, usually from complications of biliary obstruction and liver failure. In patients surviving long term after resection, the local recurrence rates remain high, even after 5 years (10–12). Extrahepatic cholangiocarcinoma is commonly divided into proximal (disease arising at the confluence of the right and left hepatic ducts; *i.e.*, Klatskin or hilar tumors) and distal common bile duct tumors. A large, contemporary experience from Memorial Sloan-Kettering Cancer Center showed that in patients undergoing extended resection for hilar cholangiocarcinoma, locoregional recurrence developed in 58% (7). In a series reported by Korean investigators, radical resection was performed in 83 patients with extrahepatic biliary tumors. Most had uninvolved lymph nodes and negative surgical margins. Despite this, >50% experienced locoregional tumor relapse (13). In patients with distal common bile duct cancers undergoing radical resection alone, the local recurrence rates have ranged from 35% to 74% (14, 15). This high incidence of locoregional failure might be overlooked once patients have developed metastatic disease, likely underestimating the true incidence of local failure in many series (including the present series). With the development of metastatic disease, many patients do not undergo follow-up imaging or autopsy. In addition, the role that persistent locoregional disease plays in the subsequent development of distant metastases is uncertain. Given the patterns of failure in biliary tract malignancies and the morbidity and mortality associated with such, the use of RT is rational.

The use of 5-fluorouracil-based chemotherapy in association with RT has been extrapolated from the survival benefit demonstrated in patients with other gastrointestinal malignancies (16–18). A few other studies have reported the use of RT concurrent with chemotherapy after surgery (Table 4). A recent series from Johns Hopkins Hospital analyzed 34 patients with distal common bile duct cancer who received adjuvant chemoradiotherapy after pancreaticoduodenectomy. The median survival duration and 5-year survival rate were 37 months and 35%, respectively. Compared with a group of patients from the same institution

who had undergone pancreaticoduodenectomy alone (and who collectively had more favorable histologic features), survival was significantly improved in the adjuvantly treated group (median survival, 37 vs. 22 months, $p < 0.05$) (19). We observed a similar median survival of 34 months in our study. Kim *et al.* (20) reported a 5-year survival rate of 31% in 84 patients who had undergone postoperative RT (40–45 Gy), most of whom received concurrent chemotherapy. The investigators concluded that long-term survival can be achieved in patients undergoing resection and postoperative chemoradiotherapy (20). The limitations of these studies (including the present study) included small sample sizes, possible group imbalance with regard to completeness of resection and adverse histologic features, and varying RT techniques.

The potential advantages of neoadjuvant chemoradiotherapy include the delivery of therapy with an intact vascular supply, downstaging of borderline resectable tumors, a reduction of tumor seeding and locoregional dissemination during surgery, and selection of patients for surgery according to their response to therapy (21). However, experience with this strategy in biliary tumors is limited. A report from the M.D. Anderson Cancer Center described 9 patients (5 with hilar and 4 with distal common duct cholangiocarcinoma) treated with preoperative chemoradiotherapy. The patients received continuous infusion 5-fluorouracil with concurrent external beam RT. Of the 9 patients, 3 experienced a pathologically complete response and 6 had varying degrees of histologic response. The rate of margin-negative resection was 100% for the preoperative chemoradiotherapy group compared with 54% for the patients receiving surgery alone ($p < 0.01$). Additionally, the patients receiving preoperative treatment did not experience any significant treatment-related complications (22). In the present series, 12 patients with primarily borderline or unresectable tumors underwent neo-adjuvant chemoradiotherapy. Three of the 12 experienced a pathological complete response, and 11 of 12 underwent R0 resection. No stent revisions were required in this group of patients during the neoadjuvant treatment period. At pathologic analysis, no patients in the neoadjuvantly treated group had lymph node metastases. Despite the clinical impression that the neoadjuvantly treated patients had more advanced local disease, these patients showed a trend toward improved survival compared with the adjuvantly treated patients. However, the number of patients receiving neoadjuvant treatment was small, making definitive conclusions speculative.

One concern of the use of neoadjuvant chemoradiotherapy is the perception that this therapy will enhance surgical morbidity and mortality. This was not observed in the present study. The mean hospital stay was similar in both groups for all patients (15 days, range, 8–47 for the adjuvant group; and 16 days, range, 7–53 for the neoadjuvant group). No perioperative deaths occurred. Of the 12 patients treated neoadjuvantly, 2 (17%) experienced a postoperative complication requiring additional surgical intervention with prolongation of the hospital stay or readmission. This compares favorably with that for the 33 patients who underwent surgery before chemoradiotherapy, of whom, 11 (33%) experienced similarly defined surgical complications ($p = \text{NS}$). Similar findings were reported by Cheng *et al.* (23), who retrospectively examined the surgical morbidity in 79 patients who had undergone either neoadjuvant or adjuvant chemoradiotherapy combined with pancreaticoduodenectomy. They reported a marked reduction in the pancreatic leak and

leak-associated morbidity and mortality rates in patients treated neoadjuvantly (23). Furthermore, neoadjuvant therapy has not been shown to increase perioperative morbidity compared with adjuvant treatment in patients with other gastrointestinal malignancies (24).

The presence of perineural invasion portended for inferior OS in our series ($p = 0.01$). This has also been observed in other series of resectable cholangiocarcinoma (25, 26). This finding emphasizes the need for careful investigation of the pathologic specimens, the findings of which could be used to guide treatment decision-making regarding adjuvant therapy.

The role of brachytherapy in the treatment of cholangiocarcinoma remains controversial. Published studies have reported conflicting results regarding the value of this modality. In the present analysis, 5 patients received brachytherapy and had inferior outcomes. Given the small patient subset and the range of the treatments given, it was difficult to assess the role of brachytherapy in this setting.

Because of the poor prognosis of patients with resected cholangiocarcinoma, innovative treatment strategies have been investigated. Investigators from the Mayo Clinic reported on a strategy of neoadjuvant RT and chemotherapy and, in selected patients, hepatic transplantation. A total of 71 patients with cholangiocarcinoma underwent neoadjuvant chemoradiotherapy, including a brachytherapy boost. Of these, 61 subsequently underwent operative staging, followed by hepatic transplantation in 38. Of these 38 patients, 16 (42%) showed no evidence of residual tumor, suggesting that cholangiocarcinoma (compared with pancreatic cancer) is a more radiosensitive malignancy. The survival rate for all 71 patients was 58% at 5 years and was 82% for the patients who underwent transplantation (26). Despite the highly selected nature of the patients treated with this approach, these results are encouraging, and this strategy is under active investigation.

CONCLUSION

Extrahepatic cholangiocarcinoma is a rare malignancy. Despite the advanced disease at presentation, our data suggest a possible local control benefit from chemoradiotherapy combined with surgery. These results also support the role of preoperative chemoradiotherapy in enhancing tumor resectability and survival, with acceptable morbidity and mortality. Systemic metastases remain a significant mode of failure, suggesting the need for more effective systemic therapy. The integration of novel therapeutic strategies for this disease is indicated, including additional investigation of combined modality therapy with hepatic transplantation, as well as the use of novel systemic agents that double as radiosensitizers.

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Fig. 1.
Overall survival and disease-free survival in all patients.

Fig. 2.
Local control and metastasis-free survival in all patients.

Table 1

Patient characteristics

Characteristic	Patients (n)
Gender	
Male	29 (64)
Female	16 (36)
Race	
African American	6 (13)
Caucasian	37 (82)
Other	2 (5)
Presenting sign/symptom *	
Laboratory abnormalities	45 (100)
Stool/urine discoloration	42 (93)
Jaundice	41 (91)
Pruritus	38 (84)
Abdominal pain	26 (58)
Weight loss (>10 lb)	19 (42)
Nausea/vomiting	4 (9)
Diagnostic procedure	
Laparotomy	26 (58)
ERCP/brush	14 (31)
Percutaneous biopsy	5 (11)
Bile duct segment	
Proximal	13 (29)
Distal	32 (71)

Abbreviation: ERCP = endoscopic retrograde cholangiopancreatography.

Data in parentheses are percentages.

* Some patients had >1 presenting symptom/sign.

Table 2

Treatment characteristics

Characteristic	Patients (n)
Surgery performed	
Whipple	28 (62)
Bile duct excision $\pm$ partial hepatectomy	15 (33)
Liver transplantation	2 (5)
Resection completeness	
R0	36 (80)
R1	6 (13)
R2	3 (7)
Nodal status*	
N0	34 (75)
N+	11 (25)
Stage group [†]	
Adjuvant-pathologic	
Ia	1 (2)
Ib	13 (29)
IIa	8 (18)
IIb	6 (13)
III	5 (11)
Neoadjuvant-pathologic/clinical	
Ia	0 (0)
Ib	1 (2)
IIa	1 (2)
IIb	9 (20)
III	1 (2)
RT	
EBRT (Gy)	44 (98)
<45	2 (5)
45–50.4	37 (84)
>50.4	5 (11)
Brachytherapy	5 (11)
Boost	4 (9)
Primary therapy	1 (2)
Treatment timing	
Neoadjuvant	12 (27)
Adjuvant	33 (73)
Chemotherapy	
Concurrent 5-FU	44 (98)
Bolus	8 (18)
Continuous infusion	26 (59)

Characteristic	Patients (n)
Oral	10 (22)
Adjuvant chemotherapy	20 (44)

Abbreviations: 5-FU = 5-fluorouracil; RT = radiotherapy; EBRT = external beam RT.

Data in parentheses are percentages.

* Includes patients treated preoperatively.

[†] American Joint Committee on Cancer 2002 staging system.

Table 3

Surgical complications

		<u>Hospital stay (d)</u>	
Radiation therapy	<i>n</i>	Mean	Range
Adjuvant			
All patients	33	15	8–47
Grade 2–3 complications	11	25	13–47
Uncomplicated	22	11	8–22
Neoadjuvant			
All patients	12	16	7–53
Grade 2/3 complications	2	41	29–53
Uncomplicated	10	12	7–20

Table 4

Concurrent chemoradiotherapy for resected biliary carcinoma

Investigator	Patients (n)	Chemotherapy	Median radiation dose (Gy)/fraction	Median survival (mo)	LC rate (%)	5-y Survival rate (%)
Present study	45	5-FU	50.4/1.8	34	78	33
Hughes <i>et al.</i> (19)*	34	5-FU [†]	50.4/1.8	37	82	35
Kim <i>et al.</i> (20)	84	5-5U [‡]	NS	NS	NS	31

Abbreviations: LC = local control; 5-FU = 5-fluorouracil; NS = not stated.

* Distal common bile duct tumors only.

[†] Combination of 5-FU with LV, cisplatin, mitomycin, or interferon[‡] Of 84 patients, 85% received concurrent chemotherapy.