Chemoradiotherapy for Extrahepatic Bile Duct Cancer with Gross Residual Disease after Surgery

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Abstract. *Background: The purpose of the present study was to analyze the outcome of chemoradiotherapy for extrahepatic bile duct (EHBD) cancer patients with gross residual disease after surgical resection. Patients and Methods: We retrospectively analyzed 30 patients with EHBD adenocarcinoma who underwent chemoradiotherapy after palliative resection (R2 resection). Postoperative radiotherapy was delivered to the tumor bed including residual tumor and regional lymph nodes (range=40-55.8 Gy). Most patients underwent chemoradiotherapy concurrently with 5-fluorouracil (5-FU) or gemcitabine. Results: The 2-year locoregional progression-free, distant metastasis-free and overall survival rates were 33.3%, 42.4% and 44.5%, respectively. High radiation dose ≥50 Gy had a marginally significant impact on superior locoregional progression-free survival compared to 40 Gy (p=0.081). One patient developed grade 3 late gastrointestinal toxicity. Conclusion: Adjuvant chemoradiotherapy for EHBD cancer patients with gross residual disease after surgery was well-tolerated. There could be a chance for durable locoregional control and even long-term survival in selected patients.*

Extrahepatic bile duct (EHBD) cancer is a rare neoplasm representing less than 3% of all gastrointestinal tract malignancies (9). Surgical resection with negative margins is considered the only possibility for cure for EHBD cancer but only about one-third of patients present with resectable disease (3, 8). Although recent advance in imaging modalities has enabled more accurate assessment of resectability in EHBD cancer preoperatively, the diagnostic accuracy of resectability does not exceed 60-90% even with magnetic resonance imaging (MRI) and MR cholangiography (15, 21, 24). Therefore, some patients are found to be unresectable at exploration or have gross residual disease after surgical procedure (R2 resection) due to main hepatic artery and/or portal vein invasion.

The incidence of R2 resection is reported to be 9-22% and it is well-known that their overall survival is extremely dismal (4, 11, 12, 19, 20). A number of retrospective studies have suggested the benefit of adjuvant radiotherapy after incomplete surgery, especially R1 resection (11, 20, 23). However, the role of adjuvant radiotherapy after R2 resection has rarely been evaluated separately. Moreover, few studies have reported the pattern of failure or analyzed prognostic factors influencing survival outcomes in these palliatively resected patients.

In the present study, we retrospectively analyzed the outcome of adjuvant chemoradiotherapy for EHBD cancer patients with gross residual disease after surgery and identified the prognostic factors for these patients.

Patients and Methods

Study population. At our institution, incomplete resection (R1 or R2 resection) and locoregionally advanced disease (≥T2 disease or involved lymph node) have been used as tentative indications for adjuvant chemoradiotherapy for resected EHBD cancer.

After Institutional Review Board approval, a retrospective review was conducted on EHBD adenocarcinoma patients operated at Seoul National University Hospital between August 2000 and October 2011. We included patients who underwent postoperative chemoradiotherapy after R2 resection, which meant partial resection with grossly visible tumor left behind. The patients who underwent bypass surgery or explorative laparotomy without tumor resection were not eligible in this study. Patients with any kind of neoadjuvant treatment prior to surgery, metastatic disease at the time of diagnosis or history of any other malignancy were excluded from analysis. A patient diagnosed as EHBD cancer and early gastric cancer concurrently was included. A patient who had second R2 resection

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after first R2 resection due to local disease progression was also included and his base of follow-up was the date of second surgery. Patients who developed postoperative mortality or had less than 6 months of follow-up period due to follow-up loss were also excluded. Thirty patients were the subjects of this study.

Chemoradiotherapy. At a median of 46 days (range, 35-145) after surgery, all patients underwent postoperative radiotherapy. The planning target volume encompassed the tumor bed including residual tumor and regional lymph nodes, such as the porta hepatic, pericholedochal, retrocaval, aortocaval, celiac axis and superior mesenteric artery lymph nodes according to the location of primary tumor. All patients underwent individualized computer-based treatment planning.

Eight patients received a total dose of 40 Gy, which was delivered using 2 Gy/fraction, 5 days per week, with 2 weeks of planned rest after 20 Gy. Concomitant 5-fluorouracil (5-FU, 500 mg/m^2/day, intravenous (*i.v.*) bolus) was administered for the first 3 days of each 2 weeks of radiotherapy. Twenty-two patients received continuous courses of radiotherapy and the total dose ranged from 50 Gy to 55.8 Gy in conventional fractionation. Of 22 patients, 16 patients received concomitant 5-FU (500 mg/m^2/day, *i.v.* bolus for 3 days) on weeks 1 and 5 of radiotherapy. Three patients were given gemcitabine (300 mg/m^2/day, *i.v.* bolus, weekly) during radiotherapy, while no concomitant chemotherapy was given in 3 patients. The radiotherapy technique was 2-dimensional radiotherapy in 5 patients, 3-deminsional conformal radiotherapy in 22 patients and intensity-modulated radiotherapy in 3 patients.

Maintenance chemotherapy was administered to 17 patients after the completion of concurrent chemoradiotherapy. Nine patients received combination chemotherapy of 5-FU and leucovorin, one received 5-FU and cisplatin and 3 received 5-FU monotherapy. Three patients received gemcitabine and one had enteric-coated tegafur/uracil. Maintenance chemotherapy was not offered in 13 patients due to following reasons: disease progression after radiotherapy with or without chemotherapy in 5 patients, patients' refusal in 4 patients, poor performance status after chemoradiotherapy in 2 patients and others in the remaining 2 patients. The scheduled duration of maintenance chemotherapy was 6-12 months.

The details of treatment characteristics are summarized in Table I.

Statistical analysis. Survival was calculated from the date of surgical resection. Statistical analysis was done using the SPSS software (release version18; SPSS Inc. Chicago, IL, USA). Actuarial locoregional progression-free survival (LRPFS), distant metastasis-free survival (DMFS) and overall survival (OS) rates were calculated according to the Kaplan-Meier method, while comparisons between groups were performed using log-rank tests. A *p*-value lower than 0.05 was regarded statistically significant.

Results

Patients' characteristics. In the study 17 males and 13 females were included. The median age of all patients was 64 years (range=24-79). As for the location of the tumor, 24 patients had perihilar tumors and 6 patients had distal common bile duct tumors (Table I). The resection type was dependent on the location and extent of the tumor. Among 24 patients with perihilar tumors, 15 had bile duct resection, 8 had bile duct resection with partial hepatectomy and one had pancreatoduodenectomy. Among 6 patients with distal bile duct tumors, 5 had bile duct resection and one had pancreatoduodenectomy. All but two patients underwent lymph node dissection. Disease stage was determined according to the American Joint Committee on Cancer (AJCC) staging system, 6th edition. With regard to pathological T classification, 4 patients had T1, 12 patients had T2, 12 patients had T3 and 2 patients had T4 disease. Twelve patients showed pathological lymph node involvement.

Table I. *Patients, tumors and treatment characteristics*.

Characteristics	Number (%)
Age	
≤60Y	12 (40.0%)
>60Y	18 (60.0%)
Gender	
Male	17 (56.7%)
Female	13 (43.3%)
Tumor location	
Perihilar	24 (80.0%)
Distal	6 (20.0%)
Type of resection	
Perihilar tumor	
Bile duct resection	15 (50.0%)
Bile duct resection with partial hepatectomy	8 (26.7%)
Whipple's operation	1 (3.3%)
Distal tumor	
Bile duct resection	5 (16.7%)
Pancreatoduodenectomy	1 (3.3%)
Treatment modality	
2D-radiotherapy	5 (16.7%)
3D-radiotherapy	22 (73.3%)
Intensity-modulated radiotherapy	3 (10.0%)
Radiation dose	
40 (20+20) Gy	8 (26.7%)
50-54 Gy	16 (53.3%)
55-55.8 Gy	6 (20.0%)
Combined chemotherapy	
Radiotherapy alone	3 (10.0%)
Concurrent CRT	8 (26.7%)
Concurrent CRT + Maintenance chemotherapy	19 (63.3%)

CRT, Chemoradiotherapy.

Patterns of failure. At a median follow-up period of 15.7 months (range=5.0-114.8), 25 patients experienced disease progression. Locoregional progression (LRP) occurred in 19 patients and most of them arose within 24 months (range=2.63-27.34) (Figure 1A). Distant metastasis (DM) occurred in 17 patients and 11 of them had LRP as well. Synchronous LRP and DM (within 1 month) occurred in 6 patients. LRP preceded DM in 2 patients and DM preceded

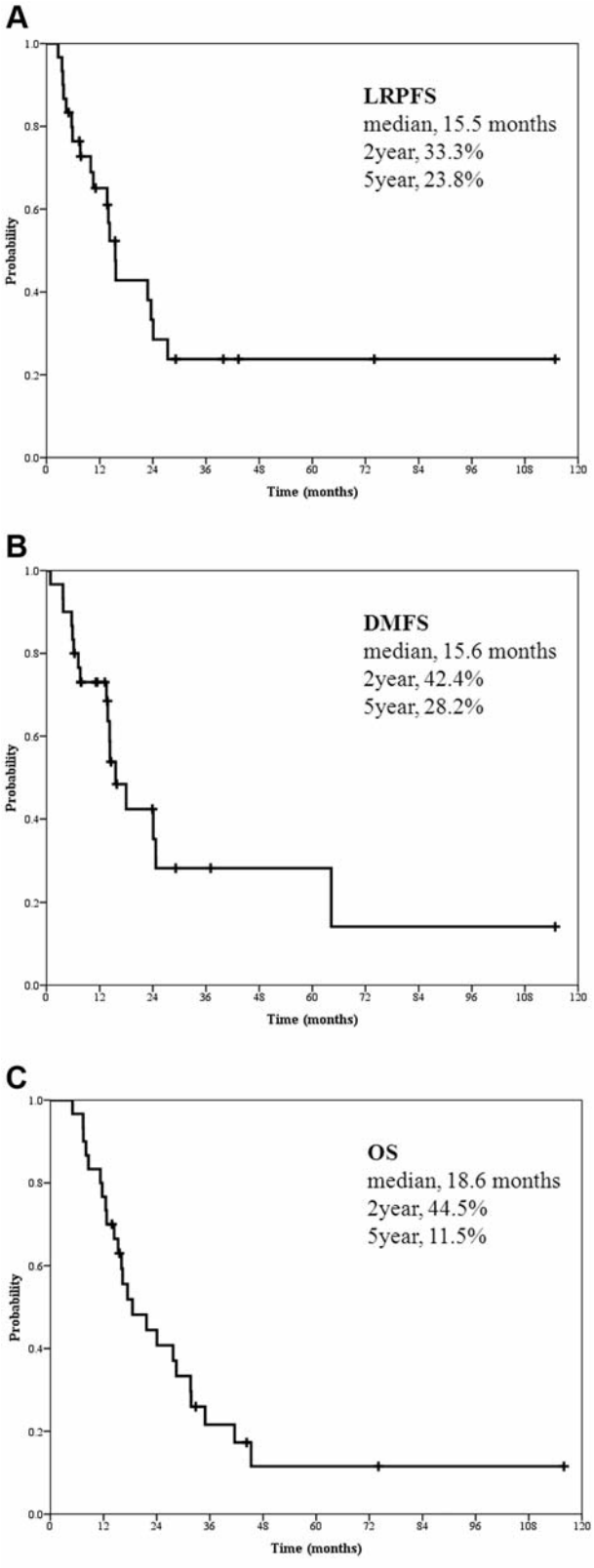

Figure 1. *The locoregional progression-free, distant metastasis-free and overall survival curves. A. Locoregional progression-free survival. B. Distant metastasis-free survival. C. Overall survival.*

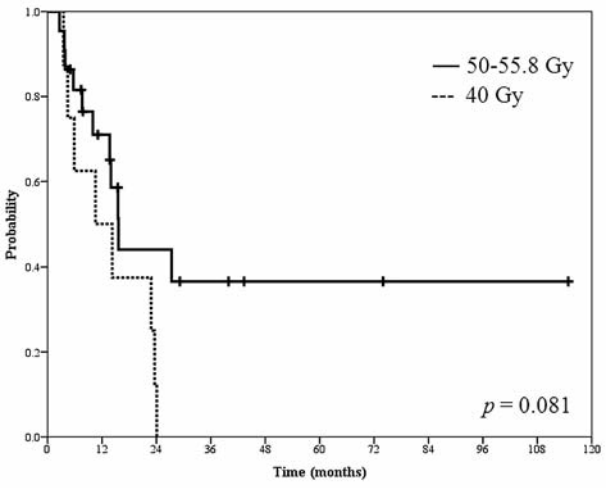

Figure 2. *Locoregional progression-free survival curve according to radiation dose.*

LRP in 3 patients. The most common sites of DM were the liver (n=6) and peritoneal seeding (n=6), followed by lung (n=5) and abdominal wall (n=1).

Twenty-four patients had died at the time of analysis and all deaths came from disease progression. The median follow-up period for 6 survivors was 36.3 months (range, 13.8-114.8). Five patients who were alive without disease progression received high dose continuous radiotherapy (50 Gy in 1, 50.4 Gy in 1, 54 Gy in 2 and 55.8 Gy in 1 patient). Four of them were given radiotherapy with concomitant chemotherapy and 3 of them were treated with maintenance chemotherapy after completion of chemoradiotherapy.

Outcome and prognostic factors. The 2-year LRPFS, DMFS and OS rates were 33.3%, 42.4% and 44.5%, respectively. The 5-year LRPFS, DMFS and OS rates were 23.8%, 28.2% and 11.5%, respectively (Figure 1). The results of univariate analysis are shown in Table II. None of the variables, such as age at diagnosis, tumor location, radiation dose and addition of concomitant and/or maintenance chemotherapy to radiotherapy did affect LRPFS, DMFS or OS. However, high radiation dose ≥50 Gy had a marginally significant impact on superior LRPFS compared to 40 Gy split-course radiation (p=0.081) (Figure 2). The 2-year LRPFS were 12.5% and 43.9%, while the median LRPFS were 10.6 months and 15.6 months in the high-dose (≥50 Gy) and low-dose (40 Gy) radiation group, respectively.

Toxicity of chemoradiotherapy. Radiation morbidity was evaluated using the Radiation Therapy Oncology Group criteria. Regarding acute treatment-related morbidity during chemoradiotherapy, the most common toxicity was nausea or

Table II. *Univariate analysis for locoregional progression-free, distant metastasis-free and overall survival.*

Variables	No. of patients	2-year LRPFS (%)	*p*	2-year DMFS (%)	*p*	2-year OS (%)	*p*
Age							
≤60 y	12	38.9	0.647	45.7	0.161	55.6	0.538
>60 y	18	28.4		39.7		37.0	
Tumor location							
Perihilar	25	35.7	0.219	41.6	0.723	47.3	0.078
Distal	5	22.2		41.7		33.3	
Radiation dose							
40 (20+20) Gy	8	12.5	0.081	17.5	0.208	37.5	0.744
50-55.8 Gy	22	43.9		53.7		48.1	
Concurrent chemotherapy							
Radiotherapy alone	3	50.0	0.473	33.3	0.868	33.3	0.839
Concurrent CRT	27	31.1		42.4		45.6	
Maintenance chemotherapy							
(–)	11	30.0	0.957	35.4	0.502	36.4	0.763
(+)	19	35.8		48.5		48.2	

LRPFS, Locoregional progression-free survival; DMFS, distant metastasis-free survival; OS, overall survival; CRT, chemoradiotherapy.

Table III. *Summary of contemporary series of R2 resection for extrahepatic bile duct cancer.*

				Extent of resection			Survival for R2 resection			
	Year	No. of patients	RT dose	R0	R1	R2	Median	5-year LRPFS	5-year DMFS	5-year OS
Kim *et al*. (11)	2002	84 (op+RT)	40 Gy	47	25	12	13mo	NR	NR	0%
Oh *et al*. (10)	2007	60 (op+RT)	45 Gy	24	23	13	NR	NR	NR	0%
Nelson *et al*. (9)	2009	45* (op+RT)	50.4 Gy	36	6	3	NR	NR	NR	NR
Park *et al*. (16)	2011	101 (op+RT)	50 Gy	52	37	12	15mo†	23%†	0%	0%
Li *et al*. (8)	2011	215 (op)	0	141	46	28	12mo	NR	NR	NR
Cho *et al*. (7)	2012	105‡ (op)	0	74	22	9	19mo	NR	NR	0%
This study	2013	30 (op+RT)	50.4 Gy	0	0	30	19mo	15.1%	12.7%	11.5%

RT, Radiotherapy; R0, no residual disease; R1, microscopic residual disease; R2, gross residual disease; NR, not reported; op, operation. *Thirty-three patients underwent adjuvant radiotherapy and 12 underwent neoadjuvant radiotherapy. †estimated from presented figure. ‡Eight patients underwent neoadjuvant treatment.

vomiting, which developed in 11 patients with grade 2. Grade 2 abdominal pain was recorded in one patient. No patient experienced grade 3 or higher toxicity. According to the World Health Organization criteria, grade 3 and grade 2 hematological toxicities developed in 3 patients and 7 patients during concurrent chemoradiotherapy, respectively. Regarding late treatment-related morbidity, one patient receiving 50.4 Gy had grade 3 gastrointestinal obstruction requiring surgery.

Discussion

The resection margin status is a well-established prognostic factor predicting OS for patients with EHBD cancer (6, 8, 13, 18). Complete resection with negative margin (R0 resection) can achieve the best survival (median=40-44 months) (8, 18) and is accepted as the only possibility for cure. Incomplete resection with microscopic disease at resected margin (R1 resection) has been generally recognized to have worse treatment results than complete resection. However, recent retrospective studies suggested that R1 resection could have comparable OS to R0 resection with addition of adjuvant radiotherapy (10, 20, 22). A previous study from our Institution also reported that adjuvant chemoradiotherapy after resection resulted in a similar long-term survival in both R0 and R1 resection (10). On the other hand, survival outcome of patients with macroscopic disease after surgery (R2 resection) is much inferior to that of R0 or R1 resection and was never compensated with postoperative

radiotherapy and/or chemotherapy (11, 22). Contemporary studies reported that median survival time of R2 resection was 12-19 months regardless of adjuvant treatment, which is comparable to our result (Table III) (4, 11, 12, 19, 20). However, these studies did not report other end points such as LRPFS or DMFS, for the R2 resection subgroup. Therefore, we have little information about the pattern of failure, locoregional control or even specific actuarial survival in this group of patients. Our analysis provided valuable data about these patients.

The survival of unresected EHBD cancer patients is dismal. Their median survival approximates 7-12 months and there were only a few long-term survivors with or without radiotherapy (2, 5, 16). However, there are some reports showing the impact of surgery along with radiotherapy, even though the extent of resection was not complete (7, 16). Fritz *et al*. investigated the effectiveness of combined external beam radiation therapy (EBRT) and intraluminal brachytherapy with or without surgery. They reported a longer median survival in 9 patients who underwent palliative resection compared with 21 patients who did not undergo surgery (12.1 *vs*. 7.9 months) (7). Morganti *et al*. also evaluated the effect of chemoradiation plus intraluminal brachytherapy with or without surgery. Four of 20 patients received partial resection and median survival was 27 months in the partially resected group and 13 months in unresected group (16). In addition, Brunner *et al*. compared stenting plus chemoradiation to stenting alone in 98 unresectable EHBD cancer patients and their median survival was 16.5 months and 9.3 months, respectively (p=0.22). They found that only small tumors (≤40 mm) may benefit from the addition of chemoradiation to stenting (p=0.01). These observations may implicate that the lower tumor burden of EHBD cancer might have positive impact on improved survival, whether they received palliative tumor resection or not.

As for the long-term survival in R2 resection, the aforementioned studies in Table III showed 0% 5-year OS or no data presented. Though, Nelson *et al*. reported that 2 out of 3 patients who underwent R2 resection and adjuvant/neoadjuvant radiotherapy were long-term survivors at 6 and 7 years without evidence of recurrence (19). A similar finding was observed in the current study; 2 patients survived more than 5 years (74 and 116 months) and 5-year OS was 11.5%. These long-term survivors were achieved with palliative resection and high-dose radiotherapy more than 50 Gy in both studies, even with gross tumor existed.

Regarding the pattern of failure, LRP (19 of 30 patients) was slightly more than DM (17 of 30 patients) in our study. The previous study from our institution analyzing R0 and R1 resection reported DM as a predominant failure, rather than LRP (10). This difference suggests that macroscopic residual tumors need more intensified radiation than microscopic tumors to control. Previous studies already suggested the benefit of dose escalation by adding brachytherapy to EBRT (1, 14). Our analysis showed marginal LRPFS gain with high radiation dose ≥50 Gy over 40 Gy split course radiation (p=0.081). Although this finding failed to reach statistical significance due to the small number of patients, the absolute difference of 2-year LRPFS was 31.4% (12.5% *vs*. 43.9%) and that of median LRPFS was 5 months (10.6 months *vs*. 15.6 months). This difference did not affect overall survival but locoregional control for 5 more months is still meaningful considering LRP can be associated with symptom development in EHBD cancer patients.

Despite the addition of radiation ≥50 Gy after R2 resection, 2-year LRPFS was 43.9% and there was only one late toxicity requiring surgery. Therefore, there is room for dose escalation to enhance local control. Dose escalation with EBRT has become possible without increasing the risk of treatment-related toxicity. Advanced technology such as intensity-modulated radiotherapy or image-guided radiotherapy enables to deliver high dose radiation, while sparing organ-at-risk. Stereotactic radiotherapy can also ablate gross residual tumor in a few fractions. Additionally, more potent radiosensitizers, other than 5-FU, can be applied concomitantly with radiation to further enhance tumor control. DM was also the major failure pattern. However, the need of intensified systemic treatment and the issue of maintenance chemotherapy are beyond the scope of discussion in the present study.

It is important to recognize the limitations of this study. First, it is a single-arm retrospective study with a small number of patients. Therefore, conclusions drawn from this study require cautious interpretation and need further validation through another patient cohort and, possibly, through a prospective trial. Secondly, regional lymph node metastasis is one of the most important prognostic factors predicting OS of patients with EHBD cancer (11, 17, 20). However, our study is not appropriate to address this issue because the patients did not undergo lymph node dissection with curative aim and some of them did not at all.

In conclusion, adjuvant chemoradiotherapy for EHBD cancer patients with gross residual disease after surgery was well-tolerated. However, the locoregional control and survival were still dismal. High-dose radiation ≥50 Gy resulted in promising locoregional control and suggested the possible benefit of dose escalation. There could be a chance for durable locoregional control and even long-term survival in selected patients considered to tolerate palliative surgery and intensified radiotherapy regimen.

Conflicts of Interest

None.

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