Original Article

Radiat Oncol J 2014;32(1):7-13
http://dx.doi.org/10.3857/roj.2014.32.1.7
pISSN 2234-1900 · eISSN 2234-3156

ROJ Radiation Oncology Journal

Postoperative radiotherapy dose correlates with locoregional control in patients with extra-hepatic bile duct cancer

Jung Ho Im, MD[1], Jinsil Seong, MD[1], Jeongshim Lee, MD[1], Yong Bae Kim, MD[1], Ik Jae Lee, MD[3], Jun Sung Park, MD[4], Dong Sup Yoon, MD[4], Kyung Sik Kim, MD[2], Woo Jung Lee, MD[2]

Departments of [1]Radiation Oncology, [2]Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul; Departments of [3]Radiation Oncology, [4]Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Purpose: To evaluate the results of postoperative radiotherapy in patients with extra-hepatic bile duct cancer (EHBDC) and identify the prognostic factors for local control and survival.

Materials and Methods: Between January 2001 and December 2010, we retrospectively reviewed the cases of 70 patients with EHBDC who had undergone curative resection and received postoperative radiotherapy. The median radiation dose was 50.4 Gy (range, 41.4 to 54 Gy). The resection margin status was R0 in 30 patients (42.9%), R1 in 25 patients (35.7%), and R2 in 15 patients (21.4%).

Results: The 5-year rates of overall survival (OS), event-free survival (EFS), and locoregional control (LRC) for all patients were 42.9%, 38.3%, and 61.2%, respectively. The major pattern of failure was distant relapses (33 patients, 47.1%). A multivariate analysis showed that the postradiotherapy CA19-9 level, radiation dose (≥50 Gy), R2 resection margins, perineural invasion, and T stage were the significant prognostic factors for OS, EFS, and LRC. OS was not significantly different between the patients receiving R0 and R1 resections, but was significantly lower among those receiving R2 resection (54.6%, 56.1%, and 7.1% for R0, R1, and R2 resections, respectively).

Conclusion: In patients with EHBDC who had undergone curative resection, a postoperative radiotherapy dose less than 50 Gy was suboptimal for OS and LRC. Higher radiation doses may be needed to obtain better LRC. Further investigation of novel therapy or palliative treatment should be considered for patients receiving R2 resection.

Keywords: Bile duct neoplasms, Adjuvant radiotherapy, Radiotherapy dosage

Introduction

Extra-hepatic bile duct cancer (EHBDC) is a relatively rare malignancy that is predominantly fatal [1,2]. Complete surgical resection is associated with long-term survival [3,4], but local regional occurrence is a major pattern of failure, even after complete resection [5,6].

Adjuvant treatment for patients with EHBDC may decrease

Received 28 December 2013, Revised 13 January 2014, Accepted 13 February 2014.

Correspondence: Ik Jae Lee, MD, PhD, Department of Radiation Oncology, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 135-720, Korea. Tel: +82-2-2019-3152, Fax: +82-2-2019-4855, E-mail: ikjae412@yuhs.ac

*The abstract of this study was accepted for poster presentation at the 54th Annual Meeting of the American Society for Radiation Oncology, Boston, MA (October, 2012).

locoregional recurrence and improve survival; however, such treatment is administered according to the physician's preference or institutional policy. Because EHBDC is relatively rare, there are few randomized controlled trials evaluating treatment options, and most of the relevant reports are from retrospective studies. The benefits of adjuvant radiotherapy (RT) and/or chemotherapy in resectable patients are therefore poorly defined. Several reports suggest that adjuvant RT has no effect on survival [7,8]. However, some reports suggest that adjuvant RT could improve locoregional control and survival [9-17].

We analyzed single-institutional outcomes for patients with resected EHBDC who underwent adjuvant RT to evaluate the effects of adjuvant RT and identify survival rates, patterns of treatment failure, and prognostic factors.

Materials and Methods

1. Study design and patient characteristics

Between January 2001 and December 2010, 78 patients with EHBDC underwent curative resection and postoperative RT at the Severance Hospital or Gangnam Severance Hospital in Seoul, Korea. The eligibility criteria for this study were pathologically confirmed EHBDC adenocarcinoma, no distant metastasis, no other previous or current malignancies or newly developed malignancies after curative resection, a maximum Eastern Cooperative Oncology Group performance status of two, and a radiation dose greater than 40 Gy. Patients who died after surgery from postoperative complications or comorbidities and those with carcinoma of the intrahepatic bile ducts, gallbladder, or ampulla of Vater were excluded. A total of eight patients were excluded, and 70 patients were retrospectively analyzed.

The disease stage for all patients was determined according to the sixth edition of the American Joint Committee on Cancer (AJCC) system. The resection margins were classified as negative resection margins (R0), microscopic residual tumor (R1), or macroscopic residual tumor (R2).

The characteristics of the 70 patients are summarized in Table 1. The median age was 63 years (range, 37 to 79 years), and there were 42 males and 28 females. The location of the primary tumor was the perihilar bile duct in 26 patients and distal in 44 patients. Fifty-two patients (74.3%) and 12 patients (17.1%) had a serum carbohydrate antigen (CA) 19-9 level greater than the upper normal limit (37 U/mL) before resection and after radiotherapy, respectively.

Table 1. Patient characteristics

Characteristic	No. of patients (%)
Age (yr), median (range)	63 (37–79)
Sex	
Male	42 (60.0)
Female	28 (40.0)
Tumor location	
Perihilar	26 (37.1)
Distal	44 (62.9)
Preoperative CA19-9 (U/mL)	
<37	18 (25.7)
≥37	52 (74.3)
Postradiotherapy CA19-9 (U/mL)	
<37	58 (82.9)
≥37	12 (17.1)
Surgical procedure	
Bile duct resection	31 (44.3)
Liver lobectomy with bile duct resection	15 (21.4)
PPPD	24 (34.3)
Concurrent chemotherapy	
Yes	38 (54.3)
No	32 (45.7)
Radiation dose (Gy)	
<50	28 (40.0)
≥50	42 (60.0)
Residual tumor	
R0 resection	30 (42.9)
R1 resection	25 (35.7)
R2 resection	15 (21.4)
Histologic grade	
Well differentiated	17 (24.3)
Moderately differentiated	43 (61.4)
Poorly differentiated	8 (11.4)
Not specified	2 (2.9)
Perineural invasion	
Yes	20 (28.6)
No	50 (71.4)
Lymphovascular invasion	
Yes	55 (78.6)
No	15 (21.4)
T stage	
T2	37 (52.9)
T3	25 (35.7)
T4	8 (11.4)
N stage	
N0	39 (55.7)
N1	31 (44.3)

CA, carbohydrate antigen; PPPD, pylorus-preserving pancreaticoduodenectomy.

http://dx.doi.org/10.3857/roj.2014.32.1.7

Resection was limited to the bile duct alone in 31 patients because of old age, comorbidity, limited tumor extent, or poor liver function. Fifteen patients underwent bile duct resection with liver resection, and 24 patients underwent pylorus-preserving pancreaticoduodenectomy. Thirty-two patients (45.7%) received postoperative RT alone, and 38 patients (54.3%) underwent postoperative RT and concurrent chemoradiotherapy. Thirty patients (42.9%), 25 patients (35.7%), and 15 patients (21.4%) had R0, R1, and R2 resection margins, respectively. Regional lymph node metastasis was found after lymph node dissection in 31 patients (44.3%).

2. Adjuvant therapy

Postoperative RT is typically recommended for patients who have positive resection margins. Patients with negative resection margins received postoperative RT according to the physician's preference. The RT was generally started 4 to 6 weeks (median, 40 days) after resection. All the patients were treated with three-dimensional conformal radiotherapy (3DCRT). The clinical target volume included the primary tumor bed with a 1- to 2-cm margin and the regional lymphatics. The planning target volume included the clinical target volume and a uniform 0.5-cm margin. External beam RT (EBRT) was delivered with multiple fields using megavoltage photon beams at 1.8 Gy daily for 5 days each week. A total radiotherapy dose is determined by not margin status (Table 2) but the physician's preference or organ-at-risk (duodenum, stomach). All treatment plans were determined individually, considering the planning target volume and organs-at-risk (e.g., duodenum, liver, and kidney). The median radiation dose was 50.4 Gy (range, 41.4 to 54 Gy), and 42 patients (60%) received a dose of 50 Gy or more. Concomitant 5-fluorouracil-based or gemcitabine-based chemotherapy was administered concurrently by the referring physician's preference. Two cycles of 5-fluorouracil (1,000 mg/m^2/day) and leucovorin (20 mg/m^2/day) was administered for 4 days in the first and last week of RT. Gemcitabine was administered at 1,000 mg/m^2 weekly during RT.

Table 2. Association between resection margin and radiation dose

	Radiation dose (Gy)		p-value
	<50	≥50	
Resection margin			0.543
R0 resection	14 (50.0)	16 (38.1)	
R1 resection	8 (28.6)	17 (40.5)	
R2 resection	6 (21.4)	9 (21.4)	

Values are presented as number (%).
The p-value was calculated by chi-square test.

3. Statistical analysis

Survival was calculated from the date of surgical resection. The time of each recurrence event was measured from the date of the surgery to the date of the recurrence. Locoregional recurrence was defined as any recurrence in the primary tumor bed and regional lymphatic areas. Distal recurrence was defined as the appearance of disease in the systemic organ, peritoneum, or distant lymph nodes.

Resection margin and radiation dose were compared using the chi-square test. The survival rates were calculated using Kaplan-Meier methods. The assessment of prognostic factors for survival was performed using the log-rank test and the Cox proportional hazards model.

Results

1. Survival

The median follow-up time was 63 months (range, 30 to 127 months) for the surviving patients. Of the 70 patients, 21 (30.0%) survived at least until the end of the follow-up period. The median overall survival time was 45 months. The 5-year overall survival (OS), event-free survival (EFS), and locoregional control (LRC) rates were 42.9%, 38.3%, and 61.2%, respectively (Fig. 1).

2. Patterns of failure

The site of recurrence was evaluated in all patients over the entire follow-up period (Table 3). There were a total of 55 failures in 39 patients (55.7%), and distant metastasis was the dominant type of failure. Locoregional recurrence occurred in 22 patients (31.4%), and distant metastasis occurred in 33 patients (47.1%). Locoregional recurrences were the first event in 20 patients (28.6%), and distant relapse occurred first in 31 patients (44.3%). Sixteen patients had both locoregional relapse and distant metastasis during the follow-up period. The liver was the most common primary metastatic recurrence site (13 patients).

3. Prognostic factors

The results of the univariate analysis of OS, EFS, and LRC are summarized in Table 4. The univariate analysis showed

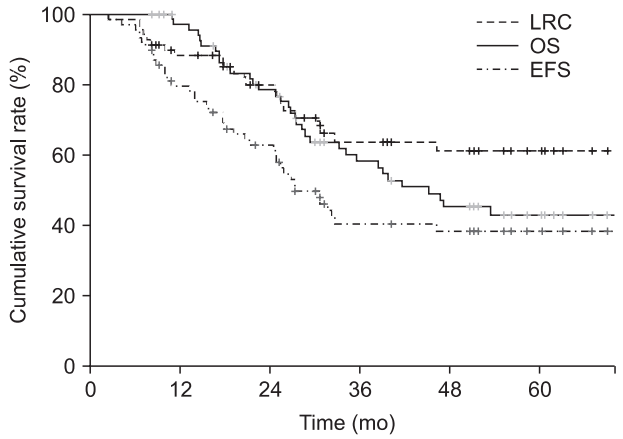

Fig. 1. Overall survival (OS), event-free survival (EFS), and locoregional control (LRC) rates for all 70 patients who underwent postoperative radiotherapy.

that a postradiotherapy CA19-9 level of at least 37 U/mL, the resection margin, and perineural invasion were independent prognostic factors for OS ($p < 0.05$). The postradiotherapy CA19-9 level, the resection margin, and the N stage were significant prognostic factors for EFS ($p < 0.05$). The postradiotherapy CA19-9 level, the radiation dose, the resection margin, and the lymphovascular invasion were significant prognostic factors for LRC ($p < 0.05$).

The results of the multivariate analysis of OS, EFS, and LRC are shown in Table 5. A postradiotherapy CA19-9 level of at least 37 U/mL, a radiation dose of at least 50 Gy, the perineural invasion, and the T stage were significant prognostic factor for OS, EFS, and LRC ($p < 0.05$).

The patients with R0 and R1 resection margins had similar 5-year OS, EFS, and LRC rates (54.6% and 56.1%, 48.8% and 50.9%, and 81.9% and 78.2%, respectively). The patients with R2 resection margins had significantly lower 5-year OS, EFS, and LRC rates (7.1%, 6.7%, and 10.0%, respectively) (Table 4). R2 resection was a significant prognostic factor for OS ($p = 0.001$), EFS ($p < 0.001$), and LRC ($p < 0.001$) in the multivariate analysis (Table 5).

Discussion and Conclusion

We retrospectively analyzed 70 patients with EHBDC who had undergone curative resection and adjuvant radiotherapy. Distant metastases were more common than locoregional failures. The postradiotherapy CA19-9 level, the radiation dose, the resection margin, the perineural invasion, and the T stage were independent prognostic factors for OS, EFS, and LRC.

Table 3. Patterns of first and total recurrence over the entire follow-up period (n = 70)

	First recurrence	Total recurrence
LRF	20 (28.6)	22 (31.4)
DF	31 (44.3)	33 (47.1)
LRF + DF	12 (17.1)	16 (22.9)

Values are presented as number (%).
LRF, locoregional failure; DF, distant failure.

Locoregional recurrence can cause bile duct obstruction and hepatic failure and subsequently lead to mortality. Adjuvant RT may increase EFS and OS by improving locoregional disease control. A previous study found that 59% of patients with hilar cholangiocarcinoma experienced locoregional recurrence [6]. In another study, locoregional relapse occurred in 54.7% of patients with middle and distal bile duct cancers [18]. These results suggest that locoregional disease recurrence rates following surgery alone were high. Postoperative RT with or without chemotherapy has been used to decrease locoregional recurrence rates. The first recurrence event was locoregional in 20 patients (28.6%) in the present study. Other studies found that the locoregional relapse rate for patients undergoing adjuvant RT was 17% to 24% [9,12,14-16,19,20]. These findings suggest that adjuvant RT reduces the locoregional recurrence rate.

Our findings that the 5-year OS and LRC rates were 42.9% and 61.2%, respectively, are comparable to those of several other recent retrospective studies. Several investigators reported that the 5-year LRC rate for patients receiving adjuvant RT was 59% to 70% [12,14,16,19,20], and the 5-year OS was 35% to 45% [12,14,16,19,20].

In our study, the major pattern of recurrence was distant metastasis. Other studies also reported that distant metastasis was the major pattern of recurrence (44% to 52%) in patients undergoing adjuvant RT [15,19,20]. Oh et al. [21] reported that failures caused by distant metastasis occurred in 42% of patients. Among patients undergoing surgery alone, however, the most common failure pattern was locoregional [14,15]. Adjuvant RT, therefore, appears to shift the major cause of treatment failure from locoregional recurrence to distant metastasis. These findings suggest that more effective systemic chemotherapies should be considered to decrease distant metastasis in patients undergoing adjuvant RT.

Several studies have shown that there were no significant differences in the 5-year OS rates between patients receiving

http://dx.doi.org/10.3857/roj.2014.32.1.7

Table 4. Univariate analysis of prognostic factors

Prognostic factor	No.	5-yr survival rate (%)					
		OS	p-value	EFS	p-value	LRC	p-value
Age (yr)			0.956		0.926		0.364
≤60	24	40.1		37.9		53.5	
>60	46	44.7		38.5		66.1	
Sex			0.254		0.776		0.656
Male	42	37.8		40.1		57.8	
Female	28	52.1		35.5		65.5	
Tumor location			0.092		0.180		0.254
Perihilar	26	30.4		31.3		57.9	
Distal	44	50.4		43.4		64.6	
Preoperative CA19-9 (U/mL)			0.197		0.083		0.712
<37	18	49.7		53.3		60.4	
≥37	52	40.2		32.6		62.0	
Postradiotherapy CA19-9 (U/mL)			<0.001		0.001		0.001
<37	58	50.2		44.3		66.6	
≥37	12	9.1		9.5		34.3	
Concurrent chemotherapy			0.158		0.123		0.984
Yes	38	48.7		46.6		61.1	
No	32	36.9		29.2		61.0	
Radiation dose (Gy)			0.109		0.115		0.043
<50	28	34.6		32.8		50.8	
≥50	42	48.0		42.3		68.5	
Resection margin			0.028		0.028		<0.001
R0 resection	30	54.6		48.8		81.9	
R1 resection	25	56.1		50.9		78.2	
R2 resection	15	7.1		6.7		10.0	
Histologic grade			0.968		0.749		0.454
WD/MD	60	42.5		36.8		58.5	
PD	8	50.0		56.3		87.5	
Perineural invasion			0.031		0.138		0.099
Yes	50	35.0		35.6		56.4	
No	20	63.2		47.0		74.6	
Lymphovascular invasion			0.432		0.114		0.034
Yes	15	35.7		26.7		40.4	
No	55	45.2		41.6		67.0	
T stage			0.072		0.114		0.264
T2	37	46.3		42.2		63.6	
T3-4	33	38.9		33.4		58.5	
N stage			0.083		0.034		0.275
N0	39	48.6		45.2		63.7	
N1	31	35.2		30.3		58.9	

OS, overall survival; EFS, event-free survival; LRC, locoregional control; CA, carbohydrate antigen; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.

R0 resections and those receiving R1 resections [19-21]. These reports suggest that adjuvant RT might help to control microscopic residual tumors, which translates into OS benefits. Our results support such a hypothesis. However, LRC in patients receiving R2 resection was poor [19,22]. Koh et al. [22] found that 2-year and median LRC in patients with gross residual disease were 37% and 15.5 months, respectively. Park et al. [19] reported that 5-year LRC and OS for patients with R2 resection were 0.0%. Todoroki et al. [9] reported that 13 of 14 patients with R2 resection received adjuvant

Table 5. Multivariate analysis of prognostic factors

Variable	5-yr OS		5-yr EFS		5-yr LRC	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Tumor location (perihilar duct)	1.899 (0.868–4.155)	0.108	-	-	-	-
Preoperative CA19-9 (≥37 U/mL)	-	-	1.963 (0.791–4.871)	0.146	-	-
Postradiotherapy CA19-9 (≥37 U/mL)	3.154 (1.358–7.324)	0.008	2.606 (1.171–5.799)	0.019	7.638 (2.513–23.218)	<0.001
Radiation dose (≥50 Gy)	0.278 (0.126–0.615)	0.002	0.290 (0.139–0.607)	0.001	0.144 (0.053–0.396)	<0.001
Resection margin						
R1 resection	1.443 (0.530–3.926)	0.473	1.911 (0.815–4.482)	0.136	2.128 (0.516–8.780)	0.296
R2 resection	4.132 (1.739–9.818)	0.001	4.980 (2.152–11.522)	<0.001	39.943 (9.109–175.141)	<0.001
Perineural invasion (positive)	4.620 (1.829–11.671)	0.001	2.515 (1.067–5.925)	0.035	13.271 (3.214–54.798)	<0.001
Lymphovascular invasion (positive)	-	-	-	-	0.754 (0.224–2.534)	0.648
T stage (T3-4)	2.810 (1.265–6.239)	0.011	2.091 (1.026–4.260)	0.042	3.832 (1.066–13.784)	0.040
N stage (N1)	-	-	1.593 (0.775–3.275)	0.205	-	-

HR, hazard ratio; CI, confidence interval; OS, overall survival; EFS, event-free survival; LRC, locoregional control; CA, carbohydrate antigen.

EBRT alone (2 patients) or intraoperative RT (IORT) alone (6 patients), or EBRT + IORT (5 patients). The 5-year OS was 0.0% [9]. Our multivariate analysis showed that R2 resection was a significant prognostic factor for OS ($p = 0.001$), EFS ($p < 0.001$), and LRC ($p < 0.001$). The 5-year OS rate was only 7.1% among patients receiving R2 resection. We therefore suggest that clinical trials using updated modalities, such as intensity-modulated radiotherapy (IMRT) and targeted agent or palliative treatment, is needed for these patients.

The effect of higher radiation doses in patients receiving EBRT has rarely been analyzed. Todoroki et al. [9] reported that for patients receiving R1 resection, treatment with EBRT and intraoperative RT yielded the best 5-year survival rate compared with treatment with either intraoperative RT or EBRT alone. All of the patients in our study received EBRT alone, and the multivariate analysis showed that the radiation dose was a significant prognostic factor for OS, EFS, and LRC ($p < 0.05$ for each measure); a radiation dose less than 50 Gy was associated with suboptimal LRC and OS. We therefore suggest using a radiation dose greater than 50 Gy for adjuvant RT in patients with EHBDC. When adjuvant RT is delivered at a dose greater than 50 Gy, we recommend using conformal treatment (3DCRT or IMRT) to reduce normal tissue complications through organ-at-risk sparing.

Park et al. [19] found that the CA19-9 level was an important prognostic indicator after surgery or postoperative RT in patients with EHBDC. Likewise, we also found that the postradiotherapy CA19-9 level was a significant prognostic factor. Park et al. [19] suggested that more aggressive treatment should be considered for patients in whom the CA19-9 level remains elevated after postoperative RT. These patients likely need additional strategies to improve their outcomes.

There are some limitations to our study. The study is retrospective in nature, and unrecognized biases could not be considered. In addition, the RT volume and radiation dose were applied according to the physician's preference. The chemotherapy regimen was also determined according to the physician's preference. Therefore, heterogeneous treatments might be a confounding factor. We did not analyze treatment-related toxicity.

In conclusion, adjuvant RT for patients with EHBDC undergoing curative resection can reduce locoregional recurrence, which can translate into an OS benefit. Furthermore, adjuvant RT with a dose higher than 50 Gy might improve local control. The 5-year OS rate in patients with

http://dx.doi.org/10.3857/roj.2014.32.1.7

R2 resection was very low, and we therefore recommend further investigation of adjuvant therapies (IMRT and targeted agent) in prospective studies or palliative treatment for these patients.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

This work was supported by a faculty research grant from Yonsei University College of Medicine for 2011 (No. 6-2011-0127) and by a National Research Foundation of Korea (NRF) grant funded by the Korean government (No. 2011-0005633).

References

1. Jung KW, Won YJ, Kong HJ, Oh CM, Seo HG, Lee JS. Cancer statistics in Korea: incidence, mortality, survival and prevalence in 2010. Cancer Res Treat 2013;45:1-14.
2. Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD. Cholangiocarcinoma. Lancet 2005;366:1303-14.
3. Reding R, Buard JL, Lebeau G, Launois B. Surgical management of 552 carcinomas of the extrahepatic bile ducts (gallbladder and periampullary tumors excluded): results of the French Surgical Association Survey. Ann Surg 1991;213:236-41.
4. Nakeeb A, Pitt HA, Sohn TA, et al. Cholangiocarcinoma: a spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996;224:463-73.
5. Kim JK, Ha HK, Han DJ, Auh YH. CT analysis of postoperative tumor recurrence patterns in periampullary cancer. Abdom Imaging 2003;28:384-91.
6. Jarnagin WR, Ruo L, Little SA, et al. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. Cancer 2003;98:1689-700.
7. Pitt HA, Nakeeb A, Abrams RA, et al. Perihilar cholangiocarcinoma: postoperative radiotherapy does not improve survival. Ann Surg 1995;221:788-97.
8. Sagawa N, Kondo S, Morikawa T, Okushiba S, Katoh H. Effectiveness of radiation therapy after surgery for hilar cholangiocarcinoma. Surg Today 2005;35:548-52.
9. Todoroki T, Ohara K, Kawamoto T, et al. Benefits of adjuvant radiotherapy after radical resection of locally advanced main hepatic duct carcinoma. Int J Radiat Oncol Biol Phys 2000;46:581-7.
10. Todoroki T, Kawamoto T, Koike N, Fukao K, Shoda J, Takahashi H. Treatment strategy for patients with middle and lower third bile duct cancer. Br J Surg 2001;88:364-70.
11. Gerhards MF, van Gulik TM, Gonzalez DG, Rauws EA, Gouma DJ. Results of postoperative radiotherapy for resectable hilar cholangiocarcinoma. World J Surg 2003;27:173-9.
12. Hughes MA, Frassica DA, Yeo CJ, et al. Adjuvant concurrent chemoradiation for adenocarcinoma of the distal common bile duct. Int J Radiat Oncol Biol Phys 2007;68:178-82.
13. Cheng Q, Luo X, Zhang B, Jiang X, Yi B, Wu M. Predictive factors for prognosis of hilar cholangiocarcinoma: postresection radiotherapy improves survival. Eur J Surg Oncol 2007;33:202-7.
14. Borghero Y, Crane CH, Szklaruk J, et al. Extrahepatic bile duct adenocarcinoma: patients at high-risk for local recurrence treated with surgery and adjuvant chemoradiation have an equivalent overall survival to patients with standard-risk treated with surgery alone. Ann Surg Oncol 2008;15:3147-56.
15. Gwak HK, Kim WC, Kim HJ, Park JH. Extrahepatic bile duct cancers: surgery alone versus surgery plus postoperative radiation therapy. Int J Radiat Oncol Biol Phys 2010;78:194-8.
16. Kim TH, Han SS, Park SJ, et al. Role of adjuvant chemoradiotherapy for resected extrahepatic biliary tract cancer. Int J Radiat Oncol Biol Phys 2011;81:e853-9.
17. Matsuda T, Fujita H, Harada N, et al. Impact of adjuvant radiation therapy for microscopic residual tumor after resection of extrahepatic bile duct cancer. Am J Clin Oncol 2013;36:461-5.
18. Choi SB, Park SW, Kim KS, Choi JS, Lee WJ. The survival outcome and prognostic factors for middle and distal bile duct cancer following surgical resection. J Surg Oncol 2009;99:335-42.
19. Park JH, Choi EK, Ahn SD, et al. Postoperative chemoradiotherapy for extrahepatic bile duct cancer. Int J Radiat Oncol Biol Phys 2011;79:696-704.
20. Kim K, Chie EK, Jang JY, et al. Adjuvant chemoradiotherapy after curative resection for extrahepatic bile duct cancer: a long-term single center experience. Am J Clin Oncol 2012;35:136-40.
21. Oh D, Lim DH, Heo JS, et al. The role of adjuvant radiotherapy in microscopic tumor control after extrahepatic bile duct cancer surgery. Am J Clin Oncol 2007;30:21-5.
22. Koh HK, Park HJ, Kim K, Chie EK, Min HS, Ha SW. Molecular biomarkers in extrahepatic bile duct cancer patients undergoing chemoradiotherapy for gross residual disease after surgery. Radiat Oncol J 2012;30:197-204.