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FULL PAPER

Salvage radiotherapy for locoregionally recurrent extrahepatic bile duct cancer after radical surgery

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Objective: This study evaluated the outcome of salvage radiotherapy for locoregionally recurrent extrahepatic bile duct cancer.

Methods: We performed a retrospective review of 23 extrahepatic bile duct cancer patients who underwent radiotherapy with or without concomitant chemotherapy for isolated locoregional recurrence after radical surgery between August 2001 and September 2013. The median disease-free interval was 11.8 months. Salvage radiotherapy was delivered to the recurrent tumour with or without initial operation bed up to a median dose of 54 Gy (range, 45–60). 18 patients received concomitant chemotherapy.

Results: The median follow-up period was 14.2 months for all patients, and 48.8 months for survivors. The median overall survival and progression-free survival (PFS) were 18.4 (range, 4.4–114.6) and 15.5 months (range, 1.6–114.6), respectively. On multivariate analysis, the use of concomitant chemotherapy was a favourable prognostic factor for PFS (p = 0.027), and prolonged disease-free interval (≥1 year) was associated with a significantly poor overall survival (p = 0.047). Grade 3 or higher toxicities did not occur in follow-up period.

Conclusion: Salvage radiotherapy showed promising survival outcomes in locoregional recurrence of extrahepatic bile duct cancer. Our results indicated that concomitant chemotherapy was associated with improved PFS. Concurrent chemoradiotherapy can be a viable salvage treatment option in selected patients.

Advances in knowledge: Locoregional recurrence is the most common pattern of failure after radical resection in extrahepatic bile duct cancer. In this study, salvage radiotherapy showed favourable survival outcomes without severe complications in locoregionally recurrent extrahepatic bile duct cancer patients.

INTRODUCTION

Cholangiocarcinoma is a rare neoplasm arising from bile duct epithelium, and classified as intrahepatic or extrahepatic depending on the loci of the lesion. Extrahepatic cholangiocarcinoma occurs in perihilar or distal bile duct, and it is more common than intrahepatic lesion.[1] Although surgical resection provides the only chance for cure, reported resection rates for perihilar and distal bile duct cancer were 56 and 91%, respectively.[2] Even after radical surgery, locoregional failure was the most frequent site of relapse with reported rates ranging from 40 to 80%.[3–7] While some retrospective studies reported the benefit from adjuvant radiotherapy, the evidence of adjuvant treatment has not yet been established due to the lack of randomized controlled trials.[8–11]

The standard treatment for locoregionally recurrent extrahepatic bile duct cancer is still controversial. Re-operation and radiotherapy with or without concomitant chemotherapy could be considered as a local treatment. Few studies have reported the outcomes of surgery or chemotherapy in recurrent cholangiocarcinoma.[12–15] Previous studies included intrahepatic cholangiocarcinoma and systemic recurrence, so, information about the treatment outcomes for isolated locoregional recurrence of extrahepatic bile duct cancer is limited. Therefore, further investigations are needed to identify the role of salvage radiotherapy for these patients.

The purpose of this retrospective study was to evaluate the efficacy of salvage radiotherapy on locoregionally recurrent

disease without distant metastasis, and to define subgroups with favourable outcomes.

METHODS AND MATERIALS

Patients

Between August 2001 and September 2013, 23 patients with isolated locoregional recurrence of extrahepatic bile duct cancer after radical surgery received salvage radiotherapy. After resection, all patients were routinely followed-up with serum tumour marker and abdominal CT scan, which was taken 1 week after resection and then repeated every 3–6 months. Locoregional recurrence was defined as a recurrence in resected bed or regional lymph node area, and only cases determined as unresectable and/or inoperable by the attending surgeon were referred for salvage radiotherapy. The inclusion criteria were as follows: (1) initially resected extrahepatic bile duct cancer under curative intention without adjuvant radiotherapy, (2) clinically confirmed locoregional recurrence, (3) no evidence of distant metastasis and (4) curative aim radiotherapy for recurrent tumour. Recurrence was diagnosed by CT, MRI, 18-fluoro-deoxyglucose positron emission tomography-CT (PET-CT) and/or tumour marker such as carbohydrate antigen 19–9 (CA 19–9) and carcinoembryonic antigen (CEA).

Treatment

Initially, all patients underwent radical surgery including bile duct resection (n = 4), extended hemihepatectomy (n = 8), and pancreaticoduodenectomy (n = 11). All patients did not receive adjuvant radiotherapy, while five patients received adjuvant chemotherapy. After the recurrence, salvage radiotherapy was individually planned. The gross tumour volume was defined as the recurrent lesion on CT or PET-CT. The clinical target volume was defined as the gross tumour volume plus a 0.5–1.0 cm margin ± regional lymph nodal areas based on the tumour location at the discretion of the attending physician. The planning target volume was defined as the clinical target volume plus a 1.0–2.0 cm margin. Radiotherapy was administered with three-dimensional conformal technique. The total dose was 45 to 60 Gy, delivered in daily fractions of 1.8 or 2 Gy, 5 days per week. Concomitant chemotherapy was given to 18 patients (78.3%). Chemotherapy regimens were 2 cycles of 5-fluorouracil (5-FU) for three consecutive days on 1st and 5th weeks of radiotherapy (n = 10), weekly gemcitabine (n = 4), daily capecitabine (n = 3) or tegafur/uracil (n = 1). Maintenance chemotherapy was administered after completion of radiation in seven patients (30.4%). Four patients received tegafur/uracil, and three patients received cisplatin-based chemotherapy.

Statistical analysis

Locoregional progression-free survival (LRPFS), progression-free survival (PFS), and overall survival (OS) were calculated from the initiation of radiotherapy to the event. Survival was estimated with the Kaplan-Meier method. The log-rank test and the Cox proportional hazard model were used for univariate and multivariate analyses, respectively. Multivariate analysis was performed on variables with a p-value < 0.1 in univariate analysis. Factors with a p-value < 0.05 were regarded as statistically significant. All statistical analyses were performed with PASW Statistics for Windows, Version 23.0 (SPSS Inc., Chicago, IL).

Table 1. Patient and tumour characteristics

Variables	N	(%)
Gender		
Males	14	(60.9)
Females	9	(39.1)
Age, median (range, year)	60	(44–81)
Primary tumour location		
Proximal	10	(43.5)
Distal	13	(56.5)
Initial T stage		
T1-2	7	(30.4)
T3-4	16	(69.6)
Initial N stage		
N0	12	(52.2)
N1	11	(47.8)
Initial CA 19–9 (U ml^{-1})		
≤37	9	(39.1)
>37	14	(60.9)
Initial CEA (ng ml^{-1})		
<5	21	(91.3)
≥5	2	(08.7)
Resection margin		
Negative	17	(73.9)
Positive	6	(26.1)
Adjuvant chemotherapy		
No	18	(78.3)
Yes	5	(21.7)
Disease-free interval, median (range, month)	11.8	(1.2–101.1)
Recurrence site		
Regional lymph node	13	(56.5)
Operation bed	10	(43.5)

CA 19–9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

RESULTS

Patient and tumour characteristics

The patient and tumour characteristics are listed in Table 1. There were 14 males (60.9%) and 9 females (39.1%) with median age of 60 years (range, 44–81). For primary tumour location, 10 patients had proximal tumour and 13 patients had distal tumour. As regard to initial TNM stage, 16 patients (69.6%) had T3-4, and 11 patients (47.8%) had node-positive disease. In addition, there were five patients with early stage; one patient with T1N0

and four patients with T2N0. Resection margin was microscopically involved in six patients. The median disease-free interval was 11.8 months (range, 1.2–101.1). Of the 10 patients with local recurrence, 6 recurred in the anastomotic sites and 4 recurred in the resection bed. And, there were 13 patients with regional nodal recurrence, and 5 of them had multiple nodal station involved. Location of recurrent lymph nodes were periaortic (n = 4), pericaval (n = 4), portocaval (n = 3), superior mesentery artery (n = 3), portal vein (n = 3) and celiac axis (n = 2).

Survival and prognostic factors

The median PFS and OS were 15.5 months (range, 1.6–114.6) and 18.4 months (range, 4.4–114.6), respectively. The 1-year LRPFS, PFS and OS rates were 59.3%, 56.3, and 62.6%, respectively. The 2-year LRPFS, PFS and OS rates were 54.7%, 49.3, and 44.8%, respectively. The results of univariate and multivariate analyses of PFS and OS are shown in Table 2. On univariate analysis, initial T1-2 stage and disease-free interval ≥12 months were the adverse prognostic factors for OS. When age at recurrence, initial T stage, disease-free interval and concomitant chemotherapy were incorporated into Cox proportional hazard model, disease-free interval was the only significant prognostic factor (p = 0.047, Figure 1a). Although the use of concomitant chemotherapy was not a significant prognostic factor for OS, it was associated with improved PFS on multivariate analysis (p = 0.027, Figure 1b).

Table 3 provides the characteristics of the patients who survived >5 years after salvage radiotherapy. All patients had received concurrent chemoradiotherapy with 5-FU (n = 3) or gemcitabine (n = 1). Two patients showed recurrence in operation bed, and two patients showed the regional lymph node recurrence.

Patterns of failure

The median follow-up time was 14.2 months (range, 2.4–114.6) for all patients, and 48.8 months (range, 5.1–114.6) for survivors. Treatment failure occurred in 14 patients (60.9%). 11 patients failed locoregionally, and 7 of them showed simultaneous distant metastasis. The locoregional failure sites were periaortic lymph node (n = 3), hepaticojejunostomy (n = 3), portocaval lymph node (n = 2), celiac axis lymph node (n = 2) and choledocojejunostomy (n = 1). Among 11 patients with locoregional failures, 9 patients had recurrences within the irradiated area. 10 patients failed systemically, and 3 of them showed isolated distant metastasis. The site of distant metastasis was peritoneum (n = 5), lung (n = 3), liver (n = 1) and bone (n = 1).

Treatment toxicities

Treatment-related toxicity was evaluated using the Common Terminology Criteria for Adverse Events ver. 4.03. Acute Grade 2 abdominal pain or diarrhea occurred in two patients, and Grade 2 radiation hepatitis occurred in one patient. During the follow-up, late Grade 2 gastrointestinal toxicity including duodenal ulcer and pyloric stenosis developed in 3 patients (13%).

DISCUSSION

This study reported the clinical outcomes of salvage radiotherapy with or without chemotherapy in locoregional recurrence of extrahepatic bile duct cancer patients after radical surgery. Median OS and PFS were 18.4 and 15.5 months, respectively, and these were significantly associated with concomitant chemotherapy and short disease-free interval (<12 months). Although there is no standard treatment for locoregionally recurrent extrahepatic bile duct cancer, our results suggest that concurrent chemoradiotherapy may be one of the salvage treatment options.

Treatment strategy for recurrent extrahepatic bile duct cancer after radical surgery is controversial. As for chemotherapy, a large randomized controlled trial for unresectable, recurrent or metastatic biliary tract cancer patients showed that gemcitabine plus cisplatin was associated with a significant survival benefit compared with gemcitabine alone.[15] The median OS and PFS of cisplatin-gemcitabine group were 11.7 and 8.0 months, respectively. The 1- and 2 -year OS rates were 37.3 and 8.3%, respectively. However, this study included patients with intrahepatic/extrahepatic cholangiocarcinoma, gallbladder cancer or ampullary cancer. Recently, several investigators reported the outcomes of surgery for recurrent biliary duct cancer.[12–14] Miyazaki et al[13] reported that surgical resection showed significant survival benefits in recurrent biliary tract cancer patients. The 5-year survival after recurrence was 19% in patients treated with surgery, and this was significantly better than the survival outcome after chemotherapy. According to a systematic review of the literatures, 5-year survival of patients who underwent surgical resection for recurrent biliary tract cancer was 29%.[13]

Regarding radiotherapy for recurrent cholangiocarcinoma, Jung et al[16] reported the outcomes of unresectable or recurrent bile duct cancer patients treated with stereotactic body radiotherapy (30–60 Gy/3–5 fx, median 45 Gy/3 fx). In the recurrent tumour group, 2-year OS was 28%. Although 6 (10%) of 58 patients showed severe complications above Grade 3, 3 of those 6 patients received the salvage stereotactic ablative radiotherapy after initial external radiotherapy. Kim et al[17] also demonstrated that salvage radiotherapy was feasible for isolated local recurrence of extrahepatic cholangiocarcinoma. 2-year PFS and OS rates were 44 and 55%, respectively. Acute haematologic toxicities of Grade 3 occurred in 3 patients (12%), and Grade 3 gastrointestinal toxicities were not observed. Current study also showed similar PFS and OS rates with acceptable toxicities. Given these observations, radiotherapy seems to be a viable salvage treatment option for locoregional recurrence of extrahepatic bile duct cancer, although a comparison between different treatment modalities is difficult due to the potential selection bias.

Previous studies demonstrated that long disease-free interval was a favourable prognostic factor in recurrent cholangiocarcinoma patients. Takahashi et al[12] showed that recurrence-free interval >2 year was associated with better survival in patients treated with salvage surgical resection. Among patients undergoing salvage radiotherapy, Jung et al[16] noted that patients with disease-free interval >1 year showed improved OS (p = 0.026). However, Kim et al[17] failed to demonstrate the significance of disease-free interval in survival outcomes. In the present study, patients with a longer disease-free interval had rather poor prognosis. This correlation may have resulted in the following observation of

Table 2. Univariate and multivariate analyses of progression-free survival and overall survival after recurrence

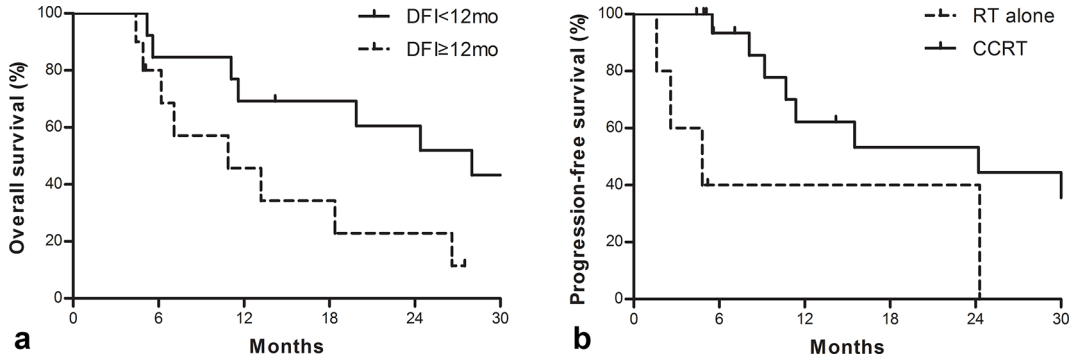
Variables	*n*	Progression-free survival			Overall survival		
		2- year rate (%)	*p*-value (uni)	*p*-value (multi)	2-year rate (%)	*p*-value (uni)	*p*-value (multi)
Gender			0.865			0.652	
Males	14	57.5			57.1		
Females	9	35.6			37.5		
Age (yr)			0.076			0.553	
<60	11	64.9			54.5		
≥60	12	35.7			45.8		
Location			0.562			0.319	
Proximal	10	57.1			16.4		
Distal	13	44.0			36.9		
Initial T stage			0.083	NS		0.036	NS
T1-2	7	34.3			14.3		
T3-4	16	53.9			58.9		
Initial N stage			0.648			0.702	
N0	12	47.1			36.7		
N1	11	53.0			54.5		
Resection margin			0.388			0.912	
Negative	17	48.5			49.4		
Positive	6	53.3			33.3		
Adjuvant CTx			0.569			0.781	
No	18	44.9			39.8		
Yes	5	66.7			60.0		
DFI (mo)			0.038	NS		0.038	0.047
<12	13	65.3			60.6		
≥12	10	20.0			22.9		
RT dose (Gy)			0.604			0.453	
≤54	12	40.2			30.0		
>54	11	58.3			61.4		
Concomitant CTx			0.017	0.027		0.180	
No	5	40.0			20.0		
Yes	18	53.3			52.1		
Maintenance CTx			0.357			0.753	
No	16	49.2			46.2		
Yes	7	50.0			42.9		

CTx, chemotherapy; DFI, disease-free interval; NS, not significant; RT, radiotherapy.

our study, which also seems paradoxical: the mean disease-free interval of patients with initial T3-4 diseases was shorter than that of patients with initial T1-2 diseases ($p = 0.041$, data not shown), patients with early T stages had a worse survival rate following recurrence compared to those with advanced T stages although statistically insignificant on multivariate analysis. According to the study by Miyazaki et al[13] which analysed patients with recurrent biliary tract cancer, the 3-year survival rates after recurrence were 0% in patients with T1-2 diseases and 12% in those with T3-4 diseases, and there was no significant association between survival and initial T stage, which was similar to our results.

As the possible explanations for our results, one may argue that there is uncertainty about the clinical diagnosis of locoregional

Figure 1. (a) Overall survival according to disease-free interval and (b) progression-free survival according to the use of concomitant chemotherapy. DFI, disease-free interval; RT, radiotherapy; CCRT, concurrent chemoradiotherapy.



recurrence without histologic confirmation. Early presentation of a suspicious lesion in the operation bed may be a postoperative reactive change rather than a true recurrence. However, there have been several studies about the efficacy of PET to assess the recurrent and metastatic biliary tract cancer.[18–20] According to Jadvar et al,[18] the sensitivity and specificity of PET were 94 and 100% for detection of recurrent and metastatic cholangiocarcinoma, respectively. Another study by Lee et al[20] also noted that an additional PET-CT showed significantly higher sensitivity in the assessment of the recurrent biliary tract cancer. Considering 15 of 23 patients underwent PET-CT and the rest had regular serial CT scans (data not shown), the uncertainty of clinical diagnosis might not significantly contribute the 'unusual' finding of the present study.

Another possible explanation for our results comes from the selection bias of the study population, that is, "isolated" locoregional recurrence. Although the major patterns of failure of extrahepatic cholangiocarcinoma are locoregional recurrences when adjuvant radiotherapy is not given, a considerable number of patients experience combined locoregional recurrences and distant metastases.[4] Because our study population consisted of only patients with isolated locoregional recurrences, those patients with rapid clinical course might have been excluded. Among patients with relatively indolent disease, early detection of recurrence could be correlated with better clinical outcomes, as in our results. Further studies are needed to fully elucidate the association between disease-free interval and the prognosis in this clinical setting.

Four patients were still alive beyond years after the diagnosis of recurrence in current study. All four patients received salvage concurrent chemoradiotherapy. Although chemoradiotherapy was not associated with improved OS, it was a favourable prognostic factor for PFS. Regarding the role of concomitant chemotherapy, Wilkowski et al[21] reported that chemoradiotherapy was a promising treatment option in patients with local recurrence after primary resection of pancreatic cancer. Kim et al[17] also noted that chemoradiotherapy achieved a longer PFS and OS rates compared with radiotherapy alone in patients with isolated local recurrence of extrahepatic cholangiocarcinoma. Taken together that all 4 patients were of disease-free interval <12 months, concurrent chemoradiotherapy can achieve a long-term survival in selected patients, even if the disease-free interval is relatively short.

Although the outcomes of salvage radiotherapy for isolated locoregional recurrence were promising, a significant number of enrolled patients experienced locoregional failures within irradiated area with simultaneous distant metastases after salvage treatment. Therefore, the optimal strategy on "adjuvant" treatment should be revisited. Role of adjuvant chemotherapy with capecitabine has been recently reported.[22] However, role of adjuvant radiotherapy has not been elucidated. Considering the risk of locoregional failure, impact of additional locoregional modality should be validated through a prospective randomized trial.

The current study is not free from the typical shortcomings from retrospective study design with only small number

Table 3. List of patients with long-term survival after recurrence

No.	Initial tumour location	Initial surgery	Initial stage	Resection margin	Recurrence site	DFI (mo)	Concomitant CTx	RT dose (Gy)	OS (mo)
1	Distal	PPPD	pT3N0	Negative	Operation bed	1.4	Yes	55.8	114.6
2	Proximal	Extended hepatectomy	pT3N1	Positive	Regional LN	1.6	Yes	54	85.7
3	Distal	PPPD	pT3N1	Negative	Regional LN	10.6	Yes	59.4	71.2
4	Proximal	Extended hepatectomy	pT3N0	Positive	Operation bed	11.7	Yes	50.4	60.5

CTx, chemotherapy; DFI, disease-free interval; LN, lymph node; OS, overall survival; PPPD, pylorus-preserving pancreaticoduodenectomy; RT, radiotherapy.

of patients: low statistical power, selection bias, and so on. However, due to the rarity of results reporting the efficacy of salvage radiotherapy for recurrent tumour, this study may provide valuable data regarding the therapeutic strategy for the locoregional recurrence of extrahepatic bile duct cancer.

In conclusion, the present study showed favourable clinical outcomes with salvage radiotherapy for locoregional recurrence of extrahepatic bile duct cancer after radical surgery, especially in those patients receiving concomitant chemotherapy. Concurrent chemoradiotherapy can be a viable salvage treatment option in selected patients.

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