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MINIREVIEWS

Radiation therapy for extrahepatic bile duct cancer: Current evidences and future perspectives

Taeryool Koo, Hae Jin Park, Kyubo Kim

Taeryool Koo, Department of Radiation Oncology, Hallym University Sacred Heart Hospital, Anyang 14068, South Korea

Hae Jin Park, Department of Radiation Oncology, Hanyang University College of Medicine, Seoul 04763, South Korea

Kyubo Kim, Department of Radiation Oncology, Ewha Womans University College of Medicine, Seoul 07985, South Korea

Corresponding author: Kyubo Kim, MD, PhD, Associate Professor, Department of Radiation Oncology, Ewha Womans University College of Medicine, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 07985, South Korea. kyubokim.ro@gmail.com
Telephone: +82-2-2650-5334
Fax: +82-2-2654-0363

ORCID number: Taeryool Koo (0000-0002-6646-0937); Hae Jin Park (0000-0003-3891-8952); Kyubo Kim (0000-0001-6093-1294).

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Abstract

Extrahepatic bile duct cancer (EBDC) is a rare malignancy that involves neoplastic changes extending from both hepatic ducts to the common bile duct. The treatment of choice is surgical resection, but the predominant pattern of initial treatment failure is locoregional recurrence. Accordingly, adjuvant radiotherapy has been administered after surgical resection based on these rationales. At this time, there is minimal evidence supporting adjuvant radiotherapy, because there have been no phase III trials evaluating its benefit. Relatively small retrospective studies have tried to compare outcomes associated with EBDC treated with or without radiotherapy. We aimed to review studies investigating adjuvant radiotherapy for resected EBDC. Because less than one-third of EBDC cases are amenable to curative resection at diagnosis, other locoregional treatment modalities need to be considered, including radiotherapy. The next aim of this review was to summarize reports of definitive radiotherapy for unresectable EBDC. Patients with advanced EBDC often experience biliary obstruction, which can lead to jaundice and progress to death. Biliary stent insertion is an important palliative procedure, but stents are prone to occlusion after subsequent ingrowth of the EBDC. Radiotherapy can be effective for maintaining the patency of inserted stents. We also reviewed the benefit of palliative radiotherapy combined with the biliary stent insertion. Lastly, we discuss the existing gaps in the evidence supporting radiotherapy in the management of EBDC.

Key words: Extrahepatic bile duct cancer; Patterns of failure; Adjuvant radiotherapy; Definitive radiotherapy; Palliative radiotherapy; Biliary stent

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Core tips: Radiotherapy has been administered for extrahepatic bile duct cancer patients in adjuvant, definitive, or palliative settings. The evidence in support of radiotherapy is derived from retrospective studies because there is a lack of randomized controlled trials. This review aimed to summarize contemporary series involving radiotherapy treatment for extrahepatic bile duct cancer. These data and findings were then used to propose strategies for generating robust evidence for or against the use of radiotherapy for this disease.

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INTRODUCTION

Extrahepatic bile duct cancer (EBDC) accounts for 3% of all gastrointestinal malignancies[1]. EBDC is traditionally divided into proximal and distal tumors, and the hallmark feature is a confluence of the cystic duct and common hepatic duct. The treatment of choice is surgical resection: combined hepatic and hilar resection for proximal tumors and pancreaticoduodenectomy for distal tumors. The bile duct system is deeply situated between surrounding critical organs and major vessels, which makes complete resection with pathologically negative margins difficult to achieve[2]. The 5-year survival rates are up to 50% after complete surgical resection, but survival dramatically decreases to as low as 0% after incomplete resection or without resection[3-6]. Adjuvant chemotherapy has been applied to increase survival among patients with bile duct malignancies, including cancers involving intrahepatic bile ducts, extrahepatic bile ducts, or the gallbladder. Phase III trials of gemcitabine alone[7] or gemcitabine plus oxaliplatin[8] failed to show a survival benefit of adjuvant chemotherapy alone compared with observation. In a palliative setting for unresectable bile duct cancer, cisplatin plus gemcitabine was associated with better survival than gemcitabine alone[9].

Another potential approach for improving EBDC treatment outcomes is the addition of radiotherapy (RT). Theoretically, adjuvant RT can complement locoregional control (LRC) after incomplete resection. Definitive RT can be applied with curative intent for inoperable patients, or palliative RT can be used for symptom control and for maintaining the patency of biliary stents in advanced cases. Nonetheless—owing to the rareness of the disease—to the best of our knowledge, there is no high-level evidence, including published reports of randomized controlled trials, supporting the use of RT for EBDC. However, there are a few published reports of relatively small retrospective studies demonstrating the efficacy of RT. In this review, we discuss patterns of EBDC treatment failure after curative resection to illustrate the rationale of adjuvant RT. We also discuss the role of RT in definitive treatment and palliative care settings. We searched literatures about RT for EBDC in PubMed, and then reviewed the literatures published between 1995 and 2018.

PATTERNS OF TREATMENT FAILURE

Locoregional failure (LRF) has been reported as the most common type of initial EBDC treatment failure. Two Korean studies[10,11] reported the patterns of initial treatment failure among EBDC patients who underwent curative resection. Choi *et al*[10] analyzed the patterns of failure among 93 EBDC patients who underwent gross total resection and no adjuvant RT. Tumor recurrence occurred in 54 patients: isolated LRF in 18 (19%), both LRF and distant metastasis (DM) in 20 (22%), and DM alone in 16 (17%). Another study showed a similar result in 97 EBDC patients after curative resection without adjuvant treatment[11]. Initial treatment failure was noted in 46 patients (47%): isolated LRF in 24 (25%), both LRF and DM in 13 (13%), and DM alone in 9 (9%). In terms of LRF sites, all of these studies reported similar distributions. The commonly involved LRF sites were tumor beds and lymph nodes (LNs) around the hepatoduodenal ligament, celiac artery, and superior mesenteric vein. Considering the higher proportion of LRF in initial treatment failures, a potential role for adjuvant RT to prevent LRF had been proposed.

EBDC is more commonly associated with LRF than other biliary malignancies. Jarnagin *et al*[12] analyzed 80 patients with gallbladder cancer (GBCA) and 76 patients with hilar cholangiocarcinoma (HCCA). All patients underwent potentially curative resection, and 11% of patients (11 with GBCA and 7 with HCCA) received adjuvant therapy. Recurrence occurred in 52 HCCA patients (68%), and the rates of initial LRF and DM were 65% and 36%, respectively. In contrast, 53 GBCA patients (66%) experienced tumor recurrence, and the rates of initial LRF and DM were 28% and 72%, respectively. The authors also noted the resection margin (RM), hilum, and bilioenteric anastomosis as sites of local recurrence. The LRF sites were concordant with those found in the aforementioned studies[10,11].

EBDC has two patterns of tumor progression: superficial spread and submucosal infiltration[13]. Consequently, biliary duct extension, liver atrophy, or portal vein involvement frequently occur, especially with proximal EBDC. Because of the natural history of proximal EBDC, hepatectomy is typically required to achieve negative RMs[14]. Additionally, an adequate radial margin should be obtained for mid-distal EBDC, although the bile duct is surrounded by major vascular structures[15]. Owing to the surgical complexity, the reported incidence of positive RMs ranges from 10% to 48% after potentially curative resection for EBDC[2-6,12,14]. Positive RMs are generally associated with poorer survival, and adjuvant RT is a potential solution to this problem.

ADJUVANT RT

The use of adjuvant RT for EBDC has been associated with a change in the patterns of treatment failure. Several studies investigating EBDC patients undergoing adjuvant RT have reported enhanced LRC, with DM identified as a significant pattern of failure. The 5-year locoregional–recurrence-free survival (LRFS) and overall survival (OS) rates are up to 80% and 46%, respectively, in patients with negative RMs[16-18]. In terms of initial failure sites, DM alone reportedly occurs in 58% to 76% of cases, LRF alone in 12% to 24%, and both LRF plus DM in 19% to 21%[16-18]. Conflicting results can also be found, for example, LRF reported as the predominant site of failure and the median OS reported as less than 20 mo[19,20]. Interestingly, the studies reporting lower LRFS used concomitant chemotherapy (20%-54%) less frequently than those reporting improved LRFS (84%-97%). The use of concomitant chemotherapy with adjuvant RT might increase LRC via a radiosensitizing effect. SWOG S0809, a phase II trial[21] used an intensified adjuvant treatment regimen—four cycles of gemcitabine and capecitabine followed by concurrent capecitabine and RT (54-59.4 Gy)—for EBDC (n = 54) and GBCA (n = 25) patients after curative resection. With a median follow-up time of 35 mo, the 2-year OS rates were 67% and 60% for R0- and R1-resected patients (not significantly different), respectively, and the 2-year local recurrence rates were 9% and 16% for corresponding patients. Regarding initial failure, distant failure (n = 24) was more frequent than local failure (n = 14). This was positive evidence, suggesting a high level of local control with the intensified adjuvant chemoradiotherapy (CRT) regimen.

In the absence of randomized controlled trials comparing adjuvant RT *vs* no RT after curative resection, we reviewed retrospective studies investigating potential survival and LRC benefits associated with adjuvant RT for EBDC. In earlier reports, the association between the use of adjuvant RT and improved outcomes was equivocal. Pitt *et al*[22] compared adjuvant RT *vs* no RT for proximal EBDC (n = 50). Adjuvant RT was not associated with improved outcomes, and median OS was not significantly different between the groups. These findings should be interpreted cautiously, however, because curative resection was frequently insufficient. In the resection subgroup (n = 31), gross total resection was achieved for only 21 patients, and 10 underwent partial resection. Two studies using the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute[23,24] also concluded there was no definitive evidence for improved survival with the addition of adjuvant RT for resected EBDC. However, the registries in these studies had no information about the extent of resection, and the study period (1973-2004) was too long to reflect the trend of surgery or RT.

According to recently reported studies based on a multi-institutional database, adjuvant therapy is associated with improved survival for patients with resected EBDC[25-27]. In particular, adjuvant CRT is more beneficial than adjuvant chemotherapy or RT alone. As detailed methods for these studies were not provided, it is worthwhile to review retrospective studies. Selected series are summarized in Table 1.

Improved survival or LRC after adjuvant CRT was reported after several studies investigating the treatment of EBDC with resection and adjuvant therapy with curative intent[28-34]. Kim *et al*[30] performed survival analyses of EBDC patients who underwent curative resection and compared an adjuvant CRT group *vs* a no-CRT group. The median RT dose was 45 Gy in 25 fractions, and 5-fluorouracil (5-FU)-based chemotherapy was concurrently administered (99.1%). The CRT group had significantly longer 5-year LRFS (58.5% *vs* 44.4%, *P* = 0.007), disease-free survival (DFS; 32.1% *vs* 26.1%, *P* = 0.041), and OS (36.5% *vs* 28.2%, *P* = 0.049) than the no-CRT group. Gwak *et al*[31] reported the usefulness of adjuvant RT by comparing a surgery-alone group *vs* an adjuvant-RT group; LRF decreased (61.7% *vs* 35.6%, *P* = 0.02) and DFS increased among patients who underwent incomplete resection (4.1% *vs* 13.9%, *P* = 0.042). In contrast, no significant differences were found in the 5-year OS rates (12% *vs* 21%, *P* > 0.5), and less use of chemotherapy (51.6%) for the adjuvant RT group might be one of the reasons (Table 1).

To determine the patients most likely to benefit, adjuvant RT has been considered in cases with unfavorable disease characteristics. In this context, several studies have suggested that adjuvant RT or CRT yield equivalent even with apparently unfavorable baseline clinical features, such as advanced stage, LN-positive, or RM-positive disease[35-37]. Borghero *et al*[35] divided 65 patients who underwent curative resection into surgery-alone (RM-negative, *n* = 23) and adjuvant CRT (RM-positive or pN1, *n* = 42) groups. The median RT dose was 55 Gy (45 Gy to primary field and 10 Gy to boost field), and all patients with adjuvant RT received chemotherapy (5-FU in 52.4% and capecitabine in 47.6%). Even with unfavorable baseline clinical features, the surgery-alone and adjuvant CRT groups showed similar 5-year OS (36% *vs* 42%, *P* = 0.6) and LRFS (38% *vs* 37%, *P* = 0.13) (Table 1).

DEFINITIVE RT

Although resection is the most important treatment modality for EBDC, less than one-third of patients are amenable to curative resection at the time of diagnosis[38]. For patients with such advanced disease, an alternative option for LRC must be considered. Definitive CRT has been reported to be feasible and tolerable among patients with unresectable and non-metastatic EBDC[39,40]. In studies using the SEER database or National Cancer Database, CRT has been associated with improved survival, unlike RT alone[41] or chemotherapy alone[42]. Definitive CRT with intensified chemotherapy was a candidate strategy to improve LRC. In a phase I/II trial performed in Germany[43], 18 EBDC patients (7 resected cases and 11 unresectable cases) underwent CRT up to 49.6 Gy with gemcitabine followed by 66 cycles of gemcitabine and capecitabine. In patients with unresectable tumors, the median OS was 7.9 mo, and four patients experienced grade 3 to 4 cholangitis. Considering high toxicity, the authors did not recommend their protocol to patients with unresectable tumors.

Another option for improving LRC is increasing the RT dose. Because of the anatomic location of EBDCs, a higher RT dose can give rise to frequent and severe adverse events, such as duodenal ulcers, stenosis, and bowel perforation. In this context, a combination of external-beam RT (EBRT) and intraluminal brachytherapy (ILBT) has been tried. ILBT doses are prescribed at 0.5 to 1.5 cm from the center of the source, so the RT dose theoretically can be escalated within a manageable toxicity range. Due to the relative scarcity of studies guiding ILBT, various schemes for ILBT are used in practice, and patients receiving ILBT are frequently analyzed as a subgroup in EBDC studies[44-46]. In Italy, a phase II trial of definitive CRT with gemcitabine for unresectable EBDC was conducted[47]. Twenty-seven patients received 50 Gy of EBRT, and six patients were given 15 to 20 Gy of ILBT. After a median follow-up time of 16 mo, the 2-year LRFS and OS rates were 29% and 27%, respectively. Gastrointestinal toxicity was tolerable, and grade 3 and 4 toxicities occurred in four patients and one patient, respectively. Also, patients who received an ILBT boost appeared to have a better LRC than those who did not receive the boost (the 2-year LRFS rates, 53% *vs* 25%).

Several studies reported improved treatment outcomes in patients with unresectable EBDC after combination therapy with EBRT and ILBT[46,48-50]. Takamura *et al*[48] prescribed 27 to 50 Gy (mean, 39.2 Gy) of ILBT following 50 Gy of EBRT (*n* = 93). The median OS was 12 mo, and the 1-year and 2-year OS rates were 49.5% and 15.1%, respectively. Grade 3 gastroduodenal complications occurred in 10 patients (10.8%), grade 3 biliary complications in five patients (5.4%), and treatment-related biliary fistulas in eight patients (8.6%). However, results from studies comparing combined

Table 1 Contemporary series of adjuvant radiotherapy for resected extrahepatic bile duct cancer

Ref.	Study period	Study design	No. of pts	RT dose (median)	Concurrent chemo-therapy	Subgroup	5-yr overall survival	
Kim *et al*[16]	1995-2002	Retrospective	86	40 Gy	5-FU (96.5%)	R0 (n = 58)	46.3%	P = 0.6641
						R1 (n = 28)	41.4%	
Park *et al*[17]	1998-2007	Retrospective	101	50 Gy	5-FU (84%)	R0 (n = 52)	44%	P = 0.2779
						R1 (n = 37)	33%	
Borghero *et al*[35]	1984-2005	Retrospective	65	55 Gy	5-FU (52.4%), Cap (47.6%)	RT[1] (n = 42)	36%	P = 0.6
				-		No RT (n = 23)	42%	
Gwak *et al*[31]	1997-2005	Retrospective	78	50.4 Gy	FP or FL (51.6%)	RT (n = 31)	21.0%	P > 0.5
				-	-	No RT[2] (n = 47)	11.6%	
Kim *et al*[30]3	2001-2009	Retrospective	168	45 Gy	FL (99.1%)	RT (n = 115)	36.5%	P = 0.049
				-	-	No RT (n = 53)	28.2%	
Ben-Josef *et al*[21]4	2008-2012	Phase 2	79	54-59.4 Gy	4 cycles of GemCap followed by concurrent Cap	R0 (n = 54)	67%[5]	P = NS
						R1 (n = 25)	60%[5]	

[1]Received adjuvant chemotherapy before chemoradiotherapy in 17% of patients;
[2]Received adjuvant chemotherapy in 17% of patients;
[3]Includes ampullary cancer as well (18.4%);
[4]Includes gallbladder cancer as well (31.6%);
[5]2-yr overall survial rate. RT: Radiotherapy; 5-FU: 5-fluorouracil; Cap: Capecitabine; FL: 5-FU plus leucovorin; GemCap: Gemcitabine plus capecitabine; NS: Not significant.

EBRT and ILBT *vs* EBRT alone are somewhat conflicting[49,50]. Shin *et al*[49] compared treatment outcomes among 17 patients who underwent EBRT alone (median, 50.4 Gy) and 14 patients who underwent EBRT and ILBT (15 Gy). The combination group had a better OS than the EBRT-alone group (at 2 years, 21% *vs* 0%, P = 0.015), but LRF rates were similar (36% *vs* 53%, P > 0.05). Yoshioka *et al*[50] performed a propensity-score matched-pair analysis of 209 patients (153 who underwent EBRT alone and 56 who received EBRT and ILBT). OS was similar between the groups (at 2 years, 31% for the ILBT(+) group *vs* 40% for the ILBT(-) group; P = 0.862), and there was a trend toward improvement of LRC in the ILBT(+) group (at 2 years, 65% for the ILBT(+) group *vs* 35% for the ILBT(-) group; P = 0.094). After sensitivity analysis, it was concluded that ILBT had no significant impact on OS but was associated with enhanced LRC. Selected studies for definitive RT are listed in Table 2.

With the development of new RT techniques, including sophisticated dose delivery and image guidance, intensity-modulated radiation therapy (IMRT) or stereotactic body radiation therapy (SBRT) have been noted as alternatives to ILBT. SBRT can deliver high doses within a narrower safety margin than would be possible with three-dimensional conformal RT. SBRT could be useful in terms of invasiveness and precise dose calculation. Promising results have been reported, especially following studies investigating proximal EBDC[51-54] (Table 3).

PALLIATIVE RT

Advanced EBDC patients often experience biliary obstruction, which can lead to jaundice, cholangitis, hepatic failure, biliary sepsis, and even death. Biliary stent insertion is commonly used to escape the vicious cycle of malignant biliary obstruction. Traditionally, endoscopic polyethylene stent insertion was preferred due to hemorrhage and bile leaks associated with liver puncture secondary to percutaneous stent insertion[55]. After stent insertion, recurrent obstruction related to tumor progression is a critical event compromising the quality of life and survival of patients with advanced EBDC. Practically, ILBT can help maintain biliary stent patency, which can significantly prolong stent patency and survival[56]. However, ILBT is invasive and requires longer hospitalization[57], and it is uncommonly performed despite positive results[58], although high-dose ILBT could be an alternative to traditional low-dose ILBT[59]. As mentioned earlier, advanced EBRT techniques, such as IMRT and SBRT, are expected to meet the need of dose escalation

Table 2 Contemporary series of definitive radiotherapy for unresectable extrahepatic bile duct cancer

Ref.	Study period	Study design	No. of pts	EBRT (median)	Brachytherapy	Chemotherapy	Median OS (mo)	
Deodata *et al*[44]	1991-1997	Retrospective	22	50.4 Gy	30-50 Gy (n = 12)	5-FU (95.5%)	23.0[1]	
Brunner *et al*[45]	1994-2001	Retrospective	25	45 Gy	10 Gy (n = 4)	FM (40%), GP (56%)	11.8[2]	
Schleicher *et al*[46]	1991-1999	Retrospective	30	30 Gy	24-40 Gy (n = 18)	5-FU (80%)	5.7[2]	
Takamura *et al*[48]	1988-1998	Retrospective	93	50 Gy	39.2 Gy[3]	-	12[2]	
Shin *et al*[49]	1986-1995	Retrospective	31	50.4 Gy	15 Gy (n = 14)	-	21%[4]	P = 0.015
					- (n = 17)		0%[4]	
Yoshioka *et al*[50]	2000-2011	Retrospective	209	50 Gy	8-30 Gy (n = 56)	Various (57%)	31%[4]	P = 0.862
					- (n = 153)		40%[4]	
Torgeson *et al*[42]	2004-2014	NCBD	1070	54-89 Gy	-	Various (100%)	14.5	P < 0.001
			1871	-	-		12.6	
Autorino *et al*[47]	2002-2009	Phase 2	27	50 Gy	15-20 Gy (n = 6)	Gemcitabine (100%)	14	

[1]From the date of cancer diagnosis;
[2]From the time of radiotherapy initiation;
[3]mean;
[4]2-yr overall survival rate. ERRT: External beam radiotherapy; OS: Overall survival; 5-FU: 5-fluorouracil; FM: 5-FU plus mitomycin-C; GP: Gemcitabine plus cisplatin; NCDB: National Cancer Database.

Currently, metallic biliary stent insertion and EBRT are widely used to maintain stent patency and delay fatal biliary obstruction for advanced EBDC patients. Several studies have reported on the safety and effectiveness of EBRT combined with metallic stents in terms of prolonging stent patency (Table 4). Lee *et al*[60] compared 18 patients who received EBRT (RT group) and 32 patients who did not (no-RT group) after undergoing uncovered metallic stent insertion. Although stent patency (median, 4.7 mo *vs* 4.5 mo, P = 0.94) and OS (median, 14 mo *vs* 9 mo, P = 0.11) were not significantly different between the RT and no-RT groups, there was no serious adverse reaction in either group.

Meanwhile, Isayama *et al*[59] reported that RT enhanced OS and stent patency after comparing survival and stent patency among 39 patients with advanced EBDC (RT group, n = 28; no-RT group, n = 11). The RT group showed improved OS (median, 22.1 mo *vs* 5.7 mo; P = 0.0031) and stent patency (at 1 year, 50% *vs* 0%; P = 0.0165) relative to the no-RT group. Regarding complications, five patients (18%) in the RT group experienced hemorrhagic gastroduodenal ulcers but recovered after starting on anti-ulcer agents. Shinchi *et al*[61] also demonstrated that EBRT can provide a definite benefit for advanced EBDC patients (RT group, n = 30; no-RT group, n = 20) with metallic stents. Chemotherapy was given in 23% of the RT group and 40% of the no-RT group. The RT group had a mean OS of 10.6 mo, which was significantly longer than that of the no-RT group (6.4 mo, P < 0.05). RT administration was associated with prolonged stent patency (mean, 9.8 mo *vs* 3.7 mo; P < 0.001). Within the RT group, one patient experienced grade 4 hematologic toxicity, one patient experienced grade 3 anorexia and nausea, and one patient presented with grade 3 gastroduodenal bleeding necessitating transfusion.

For most studies, the dose of EBRT for palliation has been 45-50 Gy[59-61], which is similar to the RT dose used in the definitive treatment setting (Table 2). Five weeks of RT is a relatively long time considering the aim of palliation. Tan *et al*[62] used a shorter course of palliative RT, with a total dose of 37.0 to 40.7 Gy in 10 to 11 fractions for unresectable EBDC patients (25 patients in the RT group and 13 patients in the no-RT group). Early complications were noted in three patients (12%) and three patients (23%) in the RT and no-RT groups, respectively. There was only one procedure-associated death, which was of a patient who did not undergo RT. RT also prolonged survival (median, 12.2 mo *vs* 8.9 mo; P = 0.025) and stent patency (median, 10.9 mo *vs* 6.5 mo; P = 0.022).

In summary, biliary stenting offers opportunities to relief obstruction-related symptoms and delay death for advanced EBDC patients. EBRT could prolong stent patency and survival, and it is less invasive than ILBT. For patient convenience, a shorter course of palliative RT with a larger daily fraction size could be considered.

FUTURE PERSPECTIVES

Although RT may have a positive effect on LRC for EBDC patients, clear evidence

Table 3 Stereotactic body radiotherapy for hilar cholangiocarcinoma

Ref.	Study period	Study design	No. of pts	RT dose	RT modality	Late toxicity ≥ Gr 3	Median OS (mo)
Kopek *et al*[51]1	1999-2006	Retrospective	27	45 Gy/3fx	linear accelerator	22.2% (duodenal ulcer)	10.6[2]
Momm *et al*[52]	1998-2008	Retrospective	13	32-56 Gy/8-16fx	linear accelerator	None	33.5[3]
Polistina *et al*[53]	2004-2009	Retrospective	10	30 Gy/3fx	Cyber Knife	None	35.5[3]

[1]Includes intrahepatic cholangiocarcinoma as well (3.7%);
[2]from the date of radiotherapy initiation;
[3]From the date of cancer diagnosis.

from phase III trials is required. Limited numbers of phase III clinical trials are being conducted for unresectable or resected EBDC patients. For unresectable EBDC, an important topic is whether CRT is superior to chemotherapy alone. The agents used for single chemotherapy are gemcitabine and cisplatin, and gemcitabine is used for CRT. The doses for definitive RT are 45 Gy in 25 fractions for microscopic disease and a higher dose of 52.5 to 60 Gy in 25 fractions for gross disease (NCT02773485). After resection, adjuvant CRT *vs* chemotherapy alone is also being tested. For adjuvant CRT, induction chemotherapy with gemcitabine plus capecitabine followed by CRT with capecitabine is given; and for adjuvant chemotherapy alone, gemcitabine plus capecitabine is used. The total dose for adjuvant RT is 50.4 Gy in 28 fractions (NCT02798510).

One of the most important barriers to administering RT for EBDC patients is the lack of guidelines for clinical target volume (CTV) delineation. Insufficient CTVs cannot accomplish efficient LRC, while extensive CTVs may lead to unnecessary adverse effects. Recently, visualization of LN recurrence has been used for determining appropriate CTV boundaries[10,63]; however, discordance among studies is inevitable owing to the rareness of EBDC and its associated complex anatomical classification. To investigate solutions to these limitations, Socha *et al*[64] comprehensively searched the literature for articles reporting pathological data on the LN involvement patterns and LRF locations of biliary tract cancers. The authors also searched for articles about adjuvant RT and extracted information about CTV. The literature review revealed that the areas of potential geographic misses were the paraaortic LNs (entire EBDC), superior mesenteric artery LNs (middle and distal EBDCs), and anterior pancreaticoduodenal LNs (distal EBDC). Conversely, celiac LNs were considered to be unnecessarily irradiated for middle and distal EBDCs. Based on these results, an atlas was proposed for CTV delineation[65]. The innovation of RT techniques makes the delivery of higher RT doses within a sub-millimeter scale. To catch up to the technical progress, a sophisticated and standardized guideline for CTV delineation is essential.

CONCLUSION

LRF is the major pattern of initial failure after surgical resection for EBDC patients. The addition of RT has been considered to have the potential to improve LRC. A phase II trial of adjuvant CRT for resected EBDC and GBCA showed a high level of local control even in R1-resected patients. Although there are no phase III trials comparing resection alone *vs* adjuvant treatments, retrospective studies have reported that adjuvant CRT is associated with improved LRC after curative-intent resection of EBDC. For patients with unresectable EBDC, a combination of EBRT and ILBT was traditionally administered. With the progression of modern RT techniques, less invasive and more intensive IMRT or SBRT have been tried as substitutes for ILBT. In patients unamenable to curative treatment, biliary stents are commonly inserted to relieve obstruction-related symptoms and delay death. Additional RT— either ILBT or EBRT—has been reported to be associated with prolonged stent patency and survival. At this time, several phase III clinical trials are being conducted to establish clear evidence. Additionally, a standard guideline for CTV delineation is needed.

Table 4 Palliative radiotherapy for stent patency in hilar cholangiocarcinoma

Ref.	Study period	Study design	No. of pts	EBRT	Brachytherapy	Median OS (mo)		Median stent patency (mo)	
Lee *et al*[60][1]	2005-2008	Retrospective	18	≥ 50 Gy	-	14.0	P = 0.11	4.7	P = 0.94
			32	-	-	9.0		4.5	
Isayama *et al*[59]	1986-2008	Retrospective	28	Median 50 Gy	24 Gy (n = 11)	22.1	P = 0.0031	50%[2]	P = 0.0165
			11	-	-	5.7		0%[2]	
Shinchi *et al*[61]	1992-1998	Retrospective	30	Median 46 Gy[3]	-	10.6[3]	P < 0.05	9.8[3]	P = 0.0002
			10	-	-	6.4[3]		3.7[3]	
Tan *et al*[62]	2007-2013	Retrospective	25	37.0-40.7 Gy	-	12.2	P = 0.025	10.9	P = 0.022
			13	-	-	8.9		6.5	

[1]Location not specified;
[2]Crude stent patency rate at 1-yr;
[3]mean. ERRT: External beam radiotherapy; OS: Overall survival.

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