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Original Research Article

Patterns of locoregional recurrences and suggestion of the clinical target volume in resected perihilar extrahepatic cholangiocarcinoma

Younghee Park [a,1], Wonguen Jung [a,1], Kyubo Kim [a,*], Ah Ram Chang [b], Hae Jin Park [c], Hyeon Kang Koh [d], Byoung Hyuck Kim [e]

[a] Department of Radiation Oncology, Ewha Womans University College of Medicine, Seoul, South Korea
[b] Department of Radiation Oncology, Soonchunhyang University College of Medicine, Seoul, South Korea
[c] Department of Radiation Oncology, Hanyang University College of Medicine, Seoul, South Korea
[d] Department of Radiation Oncology, Konkuk University School of Medicine, Seoul, South Korea
[e] Department of Radiation Oncology, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, South Korea

A R T I C L E I N F O

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A B S T R A C T

Purpose: To evaluate the patterns of locoregional recurrence (LRR) in patients with perihilar extrahepatic cholangiocarcinoma (PEHC) treated with radical resection and to suggest the optimal target volume for elective nodal irradiation.

Methods: Medical records of PEHC patients who underwent radical resection between January 2000 and September 2021 at five institutions were reviewed. Patients who were confirmed with LRR in the follow-up imaging study were included. The LRR sites were mapped onto the corresponding sites in template computed tomography images. The margin around the vascular structure was investigated to generate the clinical target volume (CTV) covering the common sites of regional recurrences.

Results: A total of 87 LRRs in 46 patients were identified, 29 (33.3%) of which were local recurrences and 58 (66.7%) were regional recurrences. The most common site of local recurrence was the liver resection margin ($n = 16$), followed by the anastomosis site ($n = 8$). Regional recurrences were observed most commonly in the *para*-aortic area ($n = 13$), followed by in the aortocaval space ($n = 11$), portal vein area ($n = 11$), and portocaval area ($n = 9$). Nodal CTV was generated by adding an individualized margin around the portal vein, aorta, common hepatic artery, celiac artery, and left gastric artery.

Conclusions: The LRR patterns in the resected PEHC were evaluated and specific guidelines for nodal CTV delineation were provided, which may help physicians delineating the target volume in postoperative radiotherapy for PEHC. These findings need further validation in a lager cohort.

Introduction

Extrahepatic cholangiocarcinoma (EHC) is a rare malignancy that originates from the extrahepatic part of the biliary epithelium. The EHC can be subdivided into perihilar and distal types, based on the tumor location. Although complete surgical resection is regarded as the only potentially curative treatment for the EHC, the prognosis remains poor even after curative resection because of frequent recurrences. The locoregional recurrence (LRR) is the most common pattern of recurrence in the EHC, which implied the potential benefit of adjuvant radiotherapy (RT) [1,2]. Previous retrospective studies have reported improved locoregional control and survival outcomes with adjuvant RT [3–5]. However, no consensus has yet been reached on the role of adjuvant RT, the patient groups who could benefit from it, and suitable RT target volumes.

In our previous study, we had compared the clinical target volumes (CTVs) of adjuvant RT for biliary tract cancer, as delineated by nine radiation oncologists [6]. We noted large variations in CTV volumes and suggested the necessity of developing guidelines for delineating the target volume. Many physicians refer to the Radiation Therapy

* Corresponding author at: Department of Radiation Oncology, Ewha Womans University College of Medicine, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 07985, South Korea.

E-mail address: kyubokim.ro@gmail.com (K. Kim).

[1] Younghee Park and Wonguen Jung contributed equally to this study.

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Oncology Group (RTOG) guidelines for pancreatic head cancer for extrapolating the target volume in case of distal EHC (DEHC), because of spatial proximity of the two cancers [7]. However, CTV by the RTOG guidelines did not adequately cover the nodal recurrences in DEHC after surgical resection [8]. In a previous study, we had evaluated the patterns of LRR in resected DEHC and suggested the optimal target volume for elective nodal irradiation [9]. Very few studies have investigated the optimal target volume in perihilar EHC (PEHC). In addition, extrapolation of the target volume in PEHC from that of pancreatic head cancer could result in inappropriate target coverage. Therefore, it is essential to reach a consensus for the target volume in PEHC.

This study retrospectively investigated the data of patients who underwent curative surgical resections for PEHC and developed LRR. The detailed patterns of LRR were evaluated and the CTV with adequate coverage of the high-risk area was investigated.

Material and methods

Patients

The medical records of PEHC patients from five institutions who underwent curative radical resection between January 2000 and September 2021 were retrospectively reviewed. Patients with LRR confirmed on follow-up abdominal computed tomography (CT) after surgery were included. The exclusion criteria were as follows: 1) neoadjuvant chemotherapy before surgery, 2) LRR detected before RT, 3) previous history of abdominal RT, and 4) history of other malignancy. The clinical, pathological, and radiological data were collected using the protocol approved by the Institutional Review Board of each participating institution and informed consent was waived. Types of surgery, tumor histology, differentiation, pathologic stage (based on the seventh edition of the American Joint Committee on Cancer system) [10], resection margin status, lymphovascular invasion, perineural invasion, and adjuvant treatment were recorded.

Contouring and mapping of LRR

The contouring and mapping of recurrence sites were carried out using a method similar to that described in our previous studies [8,9]. The specific site of each recurrence was obtained from the radiology report of the CT scan. The LRR was defined based on the radiologic evidence of recurrence in the tumor bed (liver resection margin, bile duct remnant, anastomosis site, or liver hilum) or in the regional lymph nodes. The LRR sites were contoured on individual CT images using the MIM software (Cleveland, OH). For display purposes, the CT image of a standard patient with no recurrence was selected as a template. According to the RTOG consensus guidelines [7], the portal vein (PV), common hepatic artery (CHA), celiac artery (CA), superior mesenteric artery (SMA), and aorta were delineated on the template CT and the left gastric artery (LGA) was contoured proximally 20 mm from the take-off of the CA. Each LRR site was manually mapped onto the corresponding position of the template CT by referring to the relevant vascular structure and a 3-dimensional map was generated using the MIM software. The contouring and mapping were performed by a single radiation oncologist for consistency.

Results

A total of 46 patients with confirmed LRR were evaluated. The baseline patient and tumor characteristics are summarized in Table 1. The median age was 68.5 years (range, 43.0–81.0) and 35 patients (76.1 %) were male. Hepatectomy with bile duct resection was performed in 33 patients (71.7%), bile duct resection in 7 (15.2%), hepatectomy with pancreaticoduodenectomy in 3 (6.5%), and pancreaticoduodenectomy in 3 (6.5%). Most of the patients ($n = 39$, 84.8%) had T2 disease, while lymph node metastasis was found in 20 patients (43.5%). Twelve patients (26.1%) had a negative resection margin. Lymphovascular invasion and perineural invasion were present in 21 (45.7%) and 39 patients (84.8%), respectively. Adjuvant treatment was administered to 30 patients (65.1%); 16 received chemotherapy alone, one received RT alone, and 16 received both chemotherapy and RT. Chemotherapy was mostly fluoropyrimidine-based (26 of 32, 81.3%) and the median RT dose was 50.4 Gy (range, 32–54 Gy). Primary tumor bed and regional lymphatics were included in the RT field.

The median time interval between surgery and LRR was 12.1 months (range, 1.4–133.0 months). A total of 87 LRRs were identified, 29 (33.3%) of which were local recurrences and 58 (66.7%) were regional recurrences. The anatomic distribution of LRR is summarized in Table 2. For local recurrences, the most common site was liver resection margin ($n = 16$), followed by the anastomosis site ($n = 8$). Para-aortic area ($n =$

Table 1
Baseline patient and tumor characteristics (n = 46).

Variable	No. (%)
Age, median (range, year)	68.5 (43.0, 81.0)
Gender	
Male	35 (76.1)
Female	11 (23.9)
Surgical procedure	
Hepatectomy with bile duct resection	33 (71.7)
Bile duct resection	7 (15.2)
Pancreaticoduodenectomy*	3 (6.5)
Hepatectomy with pancreaticoduodenectomy	3 (6.5)
Tumor diameter, median (range, cm)	2.5 (1.0, 5.0)
Pathologic T stage	
T1	3 (6.5)
T2	39 (84.8)
T3	3 (6.5)
T4	1 (2.2)
Pathologic N stage	
N0	23 (50.0)
N1	19 (41.3)
N2	1 (2.2)
Unknown	3 (6.5)
Margins	
Negative	12 (26.1)
Positive/close	34 (73.9)
Differentiation	
Well	10 (21.7)
Moderately	25 (54.3)
Poorly	6 (13.0)
Unknown	5 (10.9)
Lymphovascular invasion	
No	19 (41.3)
Yes	21 (45.7)
Unknown	6 (13.0)
Perineural invasion	
No	3 (6.5)
Yes	39 (84.8)
Unknown	4 (8.7)
Adjuvant treatment	
No adjuvant therapy	16 (34.8)
Chemotherapy alone	13 (34.8)
Concurrent or sequential chemoradiotherapy	17 (37.0)

* Whipple's operation or pylorus-preserving pancreaticoduodenectomy.

Table 2
The anatomic distribution of local recurrence (n = 87).

Sites of recurrence	No. (%)
Local	29 (33.3)
Liver resection margin	16 (18.4)
Liver hilum	1 (1.1)
Distal bile duct remnant	2 (2.3)
Proximal bile duct remnant	1 (1.1)
Intrahepatic duct	1 (1.1)
Biliary or pancreatic anastomosis	8 (9.4)
Regional	58 (66.7)
Aortocaval space	11 (12.6)
Celiac axis area	1 (1.1)
Common hepatic artery area	3 (3.4)
Left perigastric space	5 (5.7)
Para-aortic area	13 (14.9)
Peripancreatic area	1 (1.1)
Portal vein area	11 (12.6)
Portocaval area	9 (10.3)
Retrocaval space	4 (4.6)

13), PV area (*n* = 11), aortocaval space (*n* = 11), and portocaval area (*n* = 9) were the common areas of regional recurrences.

Because the local recurrence site was largely dependent on the location of the primary tumor and the type of surgery, a standardized target volume could not be created, which gives rise to the need of using an individualized approach. Therefore, we evaluated regional recurrences only and investigated the optimal CTV for elective nodal irradiation by expanding the vascular structures, including the PV, CHA, CA, LGA, and aorta, which cover most of the common recurrence sites. We created the nodal CTV (CTVn) by adding the suggested vascular margin as follows: 1) 10 mm around the PV, CHA, and CA in all directions; 2) 15 mm around the LGA in all directions; and 3) 15 mm anteriorly, 5 mm posteriorly, and 15 mm laterally from the aorta without the superior/inferior margin. The regional recurrences and the suggested CTVn were displayed onto a maximum intensity projection image (Fig. 1). With this CTVn, 50 of 58 regional recurrences (86.2%) were covered, and those in the aortocaval space, CA area, CHA area, peripancreatic area, and portocaval area were fully covered. However, some of the recurrences in the left perigastric space (2 of 5), *para*-aortic area (1 of 13), PV area (2 of 11), and retrocaval space (3 of 4) were not included in the CTVn (Table 3). The relative location of the recurrences not covered by CTVn was displayed on axial images of the template CT (Fig. 2).

Discussion

Because of the rare incidence, the benefit and optimal modality of the adjuvant therapy for PEHC have not yet been determined. Previous studies investigated various biliary tract cancers together and showed the benefit of adjuvant RT [4,5,11–13]. Only a few studies evaluated the

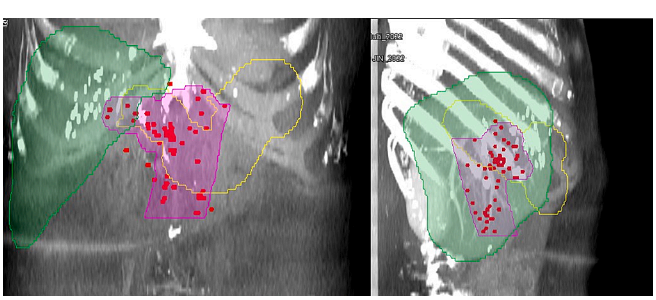

Fig. 1. Sites of regional recurrences (red dot) and suggested CTV (pink line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
The distribution of regional recurrences inside and outside the suggested CTVn.

Regional recurrences	All (n = 58)	Inside CTVn (n = 50)	Outside CTVn (n = 8)
Aortocaval space	11	11 (22.0)	0 (0.0)
Celiac axis area	1	1 (2.0)	0 (0.0)
Common hepatic artery area	3	3 (6.0)	0 (0.0)
Left perigastric space	5	3 (6.0)	2 (25.0)
Para-aortic area	13	12 (24.0)	1 (12.5)
Peripancreatic area	1	1 (2.0)	0 (0.0)
Portal vein area	11	9 (18.0)	2 (25.0)
Portocaval area	9	9 (18.0)	0 (0.0)
Retrocaval space	4	1 (2.0)	3 (37.5)

role of adjuvant treatment in PEHC. Nassour et al. compared the adjuvant therapy and observation after surgical resection in patients with PEHC obtained from the National Cancer Database [14]. After propensity score matching, they showed an improved overall survival rate with the adjuvant treatment in patients with a positive resection margin. Subgroup analysis comparing adjuvant chemoradiotherapy and adjuvant chemotherapy alone showed a marginal survival benefit with chemoradiotherapy. A similar result was reported by Im et al [15]. They conducted a retrospective study involving 196 patients with resected PEHC and investigated the benefits of adjuvant RT and chemotherapy. They showed that adjuvant chemoradiotherapy improved the survival rate of patients with a positive resection margin or stage III–IV disease. Therefore, benefits of adjuvant RT are suggested and need to be further validated in future studies.

It is important that RT target volume adequately covers the high-risk area for recurrences; however, no consensus for the optimal treatment volume of PEHC has yet been reached. Therefore, recurrence patterns should be evaluated for identifying high-risk areas. In the present study, we evaluated the specific sites of LRRs that developed after curative surgical resection. We noted that 33.3% (29 of 87) of the LRR sites were local, with the most prevalent site being the liver resection margin (16 of 29, 55.2%), followed by the anastomosis site (8 of 29, 30.8%). Jarnagin et al. reported similar results to that of ours [16]. They investigated the initial recurrences after resection for gallbladder and hilar cholangiocarcinoma. The LRRs were more prevalent as initial recurrences in hilar cholangiocarcinoma, while distant metastases were predominant in gallbladder cancer. When the specific site was investigated, the liver resection margin was the most frequent site of recurrence (12 of 24, 50.0%), followed by the hilum (7 of 24, 29.1%) and the bilioenteric anastomosis site (5 of 24, 20.8%). Our work showed that local recurrence sites were largely heterogeneous and we could not generate a standardized target volume for local recurrence. However, it is suggested that liver resection margin and anastomosis site should be sufficiently included with individualization based on the primary tumor site and the type of surgery.

Of the 87 LRRs in our study, 58 (66.7%) were regional recurrences. The most frequent recurrent sites were the para-aortic area (n = 13, 22.4%), aortocaval space (n = 11, 19.0%), PV area (n = 11, 19.0%), and portocaval area (n = 9, 15.5%). A few studies have reported on the high-risk nodal area for biliary tract cancer. Marinelli et al. performed a systemic review of the studies on the pathologic evaluation of lymph node metastasis in resected bile duct cancer [17]. They evaluated the rate of lymph node involvement based on the site of the primary tumor which was categorized into intrahepatic cholangiocarcinoma, EHC, and gallbladder cancer. They suggested that the lymph nodes with an involvement rate of ≥5% should be included in the CTV. Hence, they recommended that pericholedochal, hepatoduodenal ligament, retroportal, peripancreatic, common hepatic, para-aortic, and left gastric lymph nodes should be included in the CTV for EHC. However, they did not consider the EHC subsites, although they provided specific guidelines for determining the CTV of the primary sites. Socha et al. also

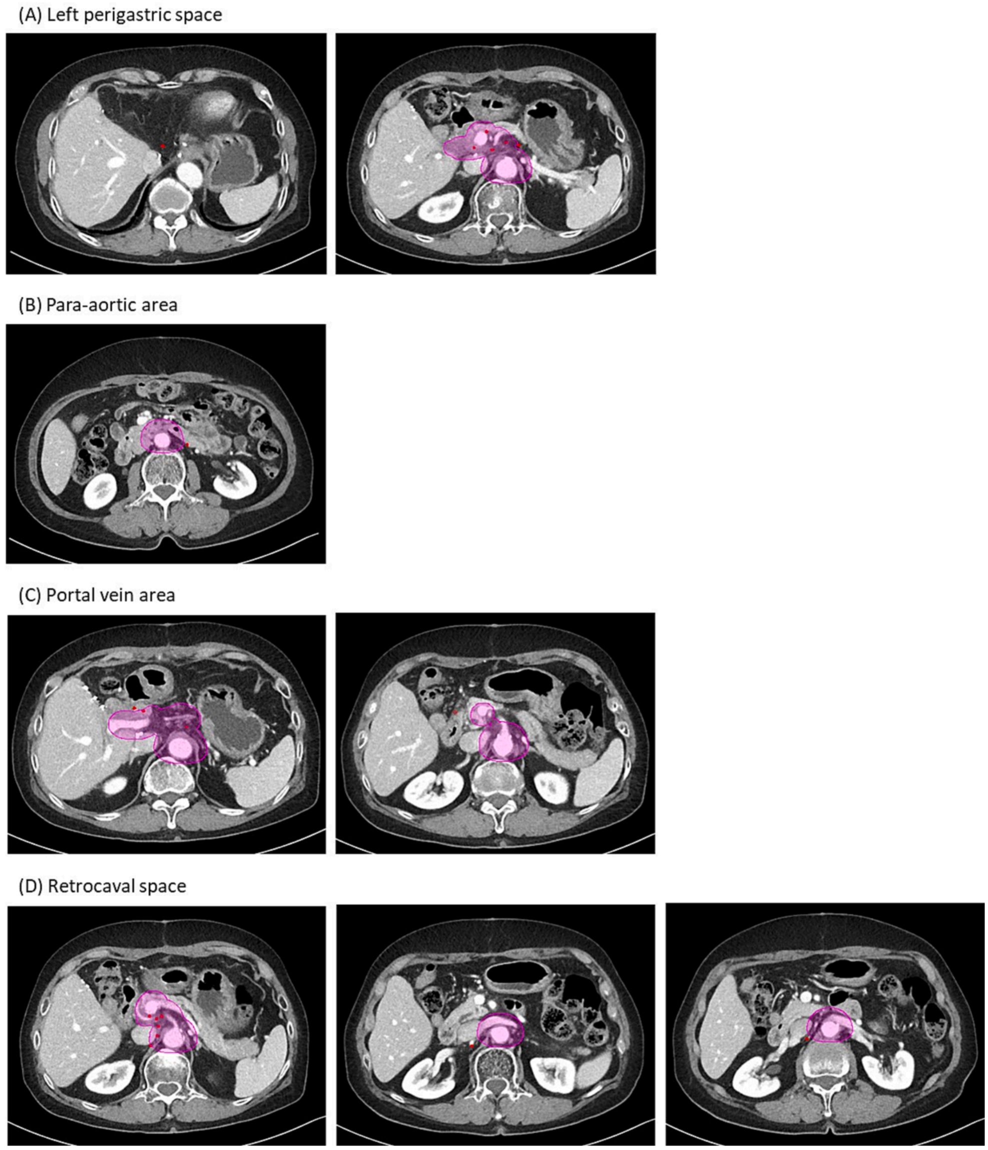

Fig. 2. Relative location of regional recurrences (red dot) and suggested CTV (pink line) on axial images of the templatec CT. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

conducted a systematic review and investigated the pathologic/surgical data on the patterns of lymph node involvement or nodal recurrence in bile duct cancer and estimated the risk of lymph node involvement [18]. Additionally, they reviewed the literatures on adjuvant RT and estimated the frequency of inclusion of each lymph node in the CTV. They compared the risk of lymph node involvement/recurrence and its frequency of inclusion in the CTV, demonstrated the discrepancy between them, and suggested the need for consensus guidelines. They conducted another systematic review and meta-analysis of pathologic data and provided the risk of involvement of each nodal station, and suggested nodal CTV specific to the primary tumor site and tumor stage [19]. They identified the following lymph node areas with $\geq$5% risk of involvement: CHA, hepatoduodenal ligament, CA, posterior pancreaticoduodenal, para-aortic, and left gastric lymph node stations, and suggested that they should be included in the nodal CTV. Although the classification of the nodal station is not uniform and the risks of involvement are slightly different, both previous studies and our study reported similar high-risk nodal areas for recurrences.

We investigated the optimal vascular margins to encompass regional recurrences as much as possible and determined individualized margins for each vascular structure such as PV, CHA, CA, LGA, and aorta. To the best of our knowledge, this is the first study that provides specific guidelines for nodal CTV delineation in PEHC. Although Bisello et al. did provide a guideline for CTV delineation of biliary tract cancer [20], they included all subsites in EHC and derived the data based on a review of the previous literatures. They did not validate it using patient data. In addition, they suggested a uniform 10-mm margin around the vasculatures, which would be insufficient for the LGA and para-aortic areas in our study.

We reported the highest recurrence rate for the para-aortic area (13 of 58, 22.4% of regional recurrences). Socha et al. also demonstrated that the para-aortic area was at a high risk for geographic miss in the CTV for PEHC and suggested that adequate coverage of this area was needed [18]. Long et al. retrospectively reviewed patient data with bile duct cancer and mapped the involved para-aortic lymph nodes into a standard CT [21]. By expanding 18 mm anteriorly, 12 mm to the left, and 24 mm from the aorta, they were able to cover 96% of recurrences. In our study, the expansion with the margins of 15 mm to the anterior, 5 mm to the posterior, and 15 mm to the lateral from the aorta covered 92.3% (12 of 13) of the para-aortic lymph nodes. Because Long et al. evaluated the margin around the aorta only, larger margins than those in our study might be needed. Expanding the PV, CHA, and CA could provide more generous margins around the aorta.

Some of the recurrences were not covered with our CTVn. In the left perigastric space, five recurrences (8.6%) developed, two of which were not included in the CTVn. Previous studies did not include the left perigastric space as a high-risk area for PEHC [18,22]. On the contrary, Socha et al. recommended the inclusion of the left gastric lymph nodes in the CTV for PEHC [19]. Additionally, they reported different patterns of lymph node involvement between the right and left intrahepatic cholangiocarcinoma and suggested that left gastric lymph nodes should be included for left intrahepatic cholangiocarcinoma. However, because increasing the coverage of the left perigastric space would increase the gastrointestinal toxicity rate, a larger margin for all patients is not feasible. Instead, more extensive inclusion of this area could be considered for patients with high risk such as tumors extending to the left biliary tree, although validation through further studies is needed. For the retrocaval area, four recurrences were noted, most of which (n = 3, 75%) were not covered with our CTVn. However, the retrocaval recurrences account for only 4.6% of regional recurrences, which is regarded as a low risk for recurrence. Therefore, CTVn was not expanded to include this area.

Our study has several limitations. Because the location of specific tumors is diverse within the perihilar lesion, the surgical procedure was highly heterogeneous. Therefore, there could be unknown geometric errors during the mapping. Additionally, because of the rarity of this disease, the sample size was small. Hence, validation with a sufficient number of patients is needed.

Despite these limitations, our study is valuable because it provides detailed patterns of LRR after the surgical resection focusing on PEHC and specific guidelines for nodal CTV delineation for adjuvant RT. We suggest individualized margins around each major vasculature, which would help physicians in creating a nodal CTV encompassing the high-risk area in resected PEHC.

Conclusion

This study investigated patients with LRR after radical resection for PEHC. The recurrence patterns were investigated and the optimal target volume covering the common sites of recurrences was explored. We identified specific margins around the PV, CHA, CA, LGA, and aorta to create a CTV for elective nodal irradiation. These findings provide a useful guideline for physicians delineating the target volume, although validation is needed.

Declaration of Competing Interest

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