The clinical target volume delineation of para aortic lymph node region for adjuvant radiotherapy based on the regularity of lymph node metastasis in biliary tract cancer

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Abstract

Background: To determine the high-risk lymphatic drainage area and the precise delineation of para aortic clinical target volume(CTV) for biliary tract cancer(BTC) according to the regularity of lymph node metastasis(LNM).

Methods: The imaging records of patients with BTC from 2015 to 2020 were analyzed retrospectively. The metastasis risk for different lymph node regions was assessed. The impact of different recurrence sites on survival was evaluated by Kaplan–Meier method. The diagnosed para aortic lymph nodes(PALNs) were manually mapped to standard axial CT images. Referring to the distance from the volume center of lymph nodes to the edge of aorta, the asymmetric CTV expansion from para aortic were defined.

Results: A total of 251 LNMs were identified in study cohort. These lymph nodes mainly concentrated in group 16a2 (13%) and 16b1 (17%). In validation cohort, a total of 93 LNMs were diagnosed and the highest involvement region was 16b1(33%), followed by 16a2. The upper boundary of 16a2 and the lower boundary of 16b1 were defined as the superior border and the inferior border of para aortic CTV respectively. 18 mm in the front, 12 mm on the left and 24 mm on the right for para aortic CTV were considered as the optimal expansion range. The CTV expansion included 96% (73/76) of PALNs in 16a2 and 16b1 in study cohort and 96% (47/49) of PALNs in validation cohort. Besides, the prognosis in patients with PALN recurrence was significantly better than that in patients with distant organ recurrence(Hazard Ratio(HR)=0.219; 95% confidence interval 0.067-0.711; P=0.006) and was not significantly worse than that of patients without PALN (HR=3.271; 95%CI 0.704-15.185; P=0.111).

Conclusions: The lymph metastasis risk of PALN 16a2 and 16b1 was the highest and Based on the distribution of PALNs, a new para aortic CTV was defined to construct a more accurate target volume.

Introduction

Biliary tract cancer(BTC) refers to a spectrum of invasive adenocarcinomas, including cholangiocarcinoma and gallbladder carcinoma(GBC)^[1]. The prognosis is poor with a 5-year survival of around 5–15% (all stages jointly analysed)^[2-3]. Complete surgical resection is the cornerstone of treatment^[4], but after surgical resection, relapse rates are high, with around 60–70% of patients expected to have disease recurrence^[5]. And local recurrence rate usually range from 39% to 69%^[6]. The trend of local recurrence of BTC provides a rationale for additional adjuvant therapy after definitive surgery. Adjuvant strategies have been explored for many years, in the form of radiotherapy, chemo-radiotherapy and chemotherapy. Phase II clinical study SWOGs 0809^[6] proved that postoperative adjuvant radiotherapy for extrahepatic cholangiocarcinoma (eCCA) and GBC can benefit in local control and survival.

According to the NCCN guidelines for BTC, patients with positive resection margins or positive lymph nodes are recommended for postoperative adjuvant radiotherapy. Usually, the delineation of clinical target volume(CTV) of adjuvant radiotherapy is based on the pattern of regional lymph node metastasis(LNM). According to the AJCC cancer staging manual, diseases that spread to the celiac, periaortic, or caval lymph nodes were usually corresponds to distant metastasis (M1) in the TNM classification of BTCs. Even so, clinical radiation fields generally encompassed periaortic or caval lymph nodes. A meta-analysis^[7] showed that the common lymph node recurrence areas of intrahepatic cholangiocarcinoma(iCCA), eCCA and GBC included para aortic, with the involvement rates of 7%, 15.2% and 6% respectively. And a review article by Socha et al^[8]assessed the risk of lymph node involvement based on histopathological surgical data and the areas of inclusion in the target volume of adjuvant radiotherapy in BTC and found that the para aortic region was a high-risk and a potential missing area for any tumor sites of biliary tract. Because of the high rate of retroperitoneal lymph node metastasis and rare surgical dissection of lymph nodes in this region^[9-11], adjuvant radiotherapy is preferred to eliminate potential microscopic diseases within a clinical irradiation field. However, there is still a lack of an accurate and reproducible para-aortic CTV delineating recommendations for adjuvant radiotherapy of biliary malignant tumors. Inconsistent delineation standards of adjuvant radiotherapy between different treatment institutions may lead to poor local control in small para-aortic CTV setting or serious adverse reactions in large para-aortic treatment fields.

Therefore, the purpose of this study was to identify high-risk lymphatic drainage regions according to the regularity of LNM, and construct a more accurate para aortic CTV according to the distribution pattern of para aortic lymph nodes (PALNs) to provide a reference for the CTV delineation of adjuvant radiotherapy in biliary malignant tumors.

Methods

Patients

The study was approved by the internal institutional review board of our hospital (IRB number 2021007K). We reviewed medical charts of patients with BTC treated in our institution between January 2015 and July 2020 to screen eligible patients for the study cohort and validation cohort. Patients with LNM diagnosed at the first examination were selected as the study cohort. Patients with postoperative recurrence were selected and the patients among them with lymph node recurrence diagnosed by imaging were identified as the validation cohort. The patient selection criteria and the study design flow chart are shown in Additional file 1.

The imaging diagnostic methods of LNM include computed tomography(CT), magnetic resonance imaging (MRI) or positron emission tomography-computed tomography (PET-CT). The positive lymph nodes on imaging images are identified by the following features: (1) the lymph nodes are round shape with the short axis length ≥ 1 cm or the ratio of length to diameter < 2 ; (2) there is an infiltrating margin; (3) increase in quantity or volume compared with previous images; (4) presence of

central necrosis or non-uniform enhancement; and (5) respond to therapy. LNM need to be evaluated by two experienced radiologists. No histological confirmation of LNM was obtained.

Metastatic lymph node classification and mapping

The classification of lymph nodes is based on the anatomical definition of lymph node stations in Japanese Gastric Cancer Association (JGCA)^[12]. The para-aortic region was divided into 16a1, 16a2, 16b1 and 16b2.

A patient without LNM who received total marrow irradiation in our center was selected as the standard patient. This patient underwent a planned CT scan in the supine position. The scan margins was from the top of the skull to the L5 vertebral body, and the slice thickness was 3 mm. Two radiation oncologists and one radiologist transferred the diagnosed lymph nodes to the corresponding position in the axial CT image of the standard patient with reference to the anatomical site. All nodes are replaced by points with a diameter of 6 mm. The lymph nodes were plotted in the Varian planning system (version 13.5; Varian Medical Systems, Palo Alto, CA, USA)

Design and validation of para-aortic CTV

According to the lymph node involvement rate of para aortic region, the inferior border and superior border of para-aortic CTV were determined first. Then, all PALNs were classified as left-lateral para-aortic (LPA) and right-lateral para-aortic (RPA) according to their relation to the aorta. After that, a parallel line was drawn through the center of the aorta, and these lymph nodes were divided into anterior-lateral para-aortic(APA) and posterior-lateral para-aortic(PPA). Finally, the extent of CTV expansion were determined by measuring the distance from the volumetric center of all lymph nodes in the range of the head and tail to the proximal edge of the aorta. We expand the blood vessels with average distance from the edge of the aorta to the center of the lymph nodes, and then calculate the 90th percentile and 95th percentile of the distance. Combining these extended distances separately to find the most suitable combination that could obtain more than 95% lymph node to create CTV^[13]. The CTV was avoided at bowel, muscle and bone. Total coverage $\geq 95\%$ is considered reasonable and acceptable. The PALN in validation cohort was also projected on the axial CT images of the standard patient, and the para aortic CTV was drawn using the expanded margins calculated from the study cohort, and the coverage of CTV was evaluated.

Statistical analysis

All data are presented as medians with interquartile ranges (IQRs) for continuous variables and numbers with percentages for categorical variables. Overall survival (OS) was calculated from the time of surgery until the date of death or latest follow-up. Survival analysis was estimated by Kaplan-Meier method and the impact of different recurrence sites on survival was tested with the log-rank test. All statistical analyses were performed using SPSS version 26.0. Image post-processing was carried out using a commercially available photo editing software: Adobe Photoshop CC 2019.

Results

Patient characteristics

A total of 218 patients diagnosed with BTCs during January 2015 to July 2020 in our hospital were collected. Sixty-one patients with LNM diagnosed at the first examination were identified as the study cohort, including 15 patients with GBC, 35 patients with iCCA and 11 patients with eCCA. There are 31 patients with PALN in study cohort (Table1). 45 patients with postoperative recurrence were collected, including 12 GBC, 18 iCCA and 15 eCCA. Among them, 21 patients with intrahepatic recurrence only, 7 patients with distant organ recurrence (peritoneum, bone, muscle) and 19 patients with lymph node recurrence (Table2). 19 patients with postoperative lymph node recurrence were selected as validation cohort (Table1). There were 14 patients with PALN recurrence in the validation cohort.

Distribution of positive lymph nodes in study cohort and validation cohort

A total of 251 lymph nodes were identified in study cohort. These lymph nodes mainly concentrated in region 16a2 (13%) and 16b1 (17%), followed by region 12 (12%) and 8 (9%). Instead, regions 9, 10, 11, 13, 14, 16a1, 16b2, 17 and 112 showed only slight risk of lymph node involvement. And other regions, including 7, 111, mediastinal region and left supraclavicular region, showed moderate risk of lymph node invasion. According to different tumor locations, subgroup analysis showed that region 16b1 was the most common area of LNM in both iCCA and GBC, with the metastasis rates of 17% and 18%, respectively, followed by 16a2 (11%), 111 (11%) and mediastinal region (11%) in iCCA, left supraclavicular region (17%) and 12 (15%) in GBC. In eCCA, the highest involvement region is 16a2 (28%), followed by region 12 (24%) and 16b1 (17%). However, the high metastasis rate of region 16b1 was similar among tumors at different sites, and the metastasis rate of region 16a2 was higher in eCCA than iCCA and GBC. As shown in figure1A. In study cohort, there were 92 PALNs, the specific distribution is shown in Additional file2. Over half (60%) of PALNs located in the LPA, 40% are located in RPA and 60% are located in APA.

A total of 93 positive lymph nodes were diagnosed in validation cohort. As shown in figure1B. Among them, the highest involvement region was 16b1 (33%), followed by 16a2 (18%). And the involvement rates of regions 111 and 7 were 13% and 11%, respectively. The involvement rates of region 16b1 in GBC, iCCA and eCCA were 29%, 37% and 32%, respectively, while the involvement rates of region 16a2 were 7%, 26%, and 8% respectively. There were 56 PALNs recurrence in validation cohort, the distribution of PALNs is similar to that in the study cohort, about 70% of the lymph nodes are located in LPA, 30% in RPA and 59% in APA (see Additional file2).

Prognostic impact of PALN recurrence in BTC

The median OS of all relapsed patients was 18.9 months (IQR 9.8-32.95). Patients with distant recurrence after surgery were divided into three subgroups: with PALN recurrence, with intrahepatic recurrence and with other distant organ recurrence. Survival analysis was carried out for any two groups. Patients with

PALN recurrence had a better prognosis (Hazard Ratio(HR)=0.219, 95% confidence interval(CI) 0.067-0.711, P=0.006) when compared with patients with distant organ recurrence(Figure2A). And there was no significant difference in survival between the patients with PALN recurrence and patients with intrahepatic recurrence only(HR=1.183, 95% CI 0.539-2.594, P = 0.675)(see Additional file3). However, the OS in patients with intrahepatic recurrence only was significantly better than that in patients with distant organ recurrence(HR=0.367, 95% CI0.142-0.948, P = 0.031)(see Additional file3). In addition, we divided all postoperative patients with lymph node recurrence into two groups. In all patients with lymph node recurrence, the prognosis in patients with PALN was not significantly worse than that of patients without PALN(HR=3.271; 95%CI 0.704-15.185; P=0.111)(Figure2B).

Delineation of para-aortic CTV

A total of 92 PALNs in study cohort were projected onto axial CT images of the standard patient. As shown in Additional file4. In the para aortic region, 16a2 and 16b1 have extremely high involvement rates in both cohorts. Therefore, we define the upper boundary of 16a2, that is, the upper edge of celiac trunk, as the superior border of para aortic CTV, and the lower boundary of 16b1, that is, the upper edge of inferior mesenteric artery, as the inferior border of para aortic CTV, which is equivalent to from the middle of T12 vascular body to the upper edge of L3 vascular body. In the horizontal direction, the mean distances of all lymph nodes in 16a2 and 16b1 from the volumetric centre of the nodes to the proximal edge of the aorta were 9 mm(range 4-24) for APA, 7mm(range 3–14) for LPA and 12mm (range 5–29) for RPA. The 90th percentile distances from the center of lymph nodes to the aorta were 14mm for APA, 11mm for LPA and 22mm for RPA. The 95th percentile distances were 18mm, 12mm and 24mm (Table3). The expansion margins of the aorta at 9 mm in the front, 7 mm on the left and 12 mm on the right got 67%(n = 51/76) coverage of the lymph node centre. The expansion margins of the aorta at 14mm in the front, 11 mm on the left and 22 mm on the right got 93% (n = 71/76) coverage. The expansion margins of the aorta at 18mm in the front, 12 mm on the left and 24 mm on the right got 96% (n = 73/76) coverage. Margins were cropped at bowel, muscle, and bone(Figure3).

Validation of para-aortic CTV coverage

In validation cohort, a total of 56 PALNs were projected onto the standardized axial CT images (Figure4A, 4B). Within the range from the upper edge of celiac trunk to the upper edge of inferior mesenteric artery, the average distance from the volume center of lymph nodes on the left side of the aorta to the edge of the aorta is 10mm(range 5–20). Similarly, the average distance on the right side also is 10mm(range 6–23). The average distance in front of the aorta was 9 mm(range5–23)(Table3). The CTV expansion margins calculated from the study cohort was applied to the validation cohort and 96% (n = 47 / 49) coverage of lymph nodes was obtained(Figure 4C).

Discussion

Lymphatic metastasis is a common metastasis form in biliary malignant tumors. In this study, we summarized and compared the regularity of LNMs in different cohorts, and found that the involvement

rate of para-aortic region was the highest. and the PALNs were mainly concentrated in the 16a2 and 16b1 regions. Meanwhile, we evaluated the impact of PALN recurrence on survival. The prognosis in patients with PALN recurrence was better than that in patients with other distant organ recurrence. In order to better prevent the recurrence of the para-aortic region, we mapped the location of PALNs to help to define para aortic CTV accurately.

The patients in study cohort were those who found LNM in the first imaging examination. The abdominal structure of these patients was not affected by surgical anatomy and can truly reflect the lymphatic metastasis regularity. In addition, the initially diagnosed patients have not received anti-tumor treatment such as radiotherapy and chemotherapy, and the lymph node metastasis will not be affected by the curative effect. We collected all positive lymph nodes and found that the involvement rates of LNM in the 16b1 and 16a2 areas were significantly higher than that in the 16a1 or other regional lymphatic drainage areas according to the regularity of LNMs. While regional lymph node areas, including 7, 8 and 12, showed a moderate risk of involvement. The involvement rates of other lymphatic drainage areas in the abdomen were less than 5%. The results of subgroup analysis showed that the rate of LNM in each region was slightly different in different tumor sites. In fact, many previous studies have summarized the law of recurrence of BTCs after surgery^[14]. Wonguen Jung et al^[15] analyzed the local recurrence patterns of 36 cases of distal eCCA after pancreatoduodenectomy. They found that the involvement rate of para aortic region was 16.1%, the superior mesenteric artery area was 16.1%, and the portal vein area was 14.5%. Another study^[16] summarized the recurrence rate of 145 patients with CCA and found that the recurrence rates of portal vein and retroperitoneal lymph nodes were 16.3% and 17.4%, respectively. However, in this study, the distribution frequency of LNM were summarized rather than the recurrence rate. The distribution trend of PALN in the validation cohort was similar to that in the study cohort. The proportion of PALNs was still higher than that of the first station regional lymphatic drainage area, and it was mainly concentrated in 16b1 and 16a2. It further confirmed that the para aortic region was a high-risk area for LNM. The involvement rate of 16b1 was greater than that of 16a2 in each cohort, while the involvement rates of 16a1 and 16b2 were both lower. But the involvement rate of 16b1 in patients with postoperative metastasis was much higher than that in patients with first diagnosis, and 16a2 and 16b2 were also slightly higher, which may be related to the changes of anatomical structure caused by operation. Besides, due to the intraoperative dissection of group 8, 12, and 13, postoperative LNM was lower than that of newly diagnosed patients. However, the involvement rates of lymph node in the mediastinal region and left supraclavicular region were much greater in the study cohort than in patients with postoperative recurrence. Group7 and 111 showed medium involvement rate in each cohort, and the validation cohort was slightly larger than the study cohort. There was no significant distribution difference of LNM of other lymph node areas between the two groups and both showed low involvement rates.

At present, PALN dissection in surgery is not recommended. And the guidelines do not recommend the resection of the primary site if the patients have PALN metastasis. PALN, as the final lymph node of the abdominal lymphatic system from the bile duct, is related to the poor prognosis of biliary

malignancies^[17-18] and corresponds to distant metastasis (M1) in the TNM classification. Many previous retrospective studies^[14,19,20] suggested adjuvant radiotherapy for the para aortic region based on the postoperative recurrence pattern of biliary malignancies. However, these studies did not evaluate the necessity of radiotherapy of para aortic region from the perspective of improving survival. Our research further evaluated the effect of PALN recurrence on survival except summarizing the regularity of LNM. In this study, the patients with postoperative PALN recurrence had a better prognosis than patients with distant organ recurrence, and patients with PALN had a slightly increased risk of death compared with patients without PALN, although the difference was not statistically significant. Unfortunately, there were few patients with regional lymph node recurrence only after surgery, so we were unable to compare them with patients with PALN recurrence. We believe that the prognosis of patients with PALN recurrence was different from that of patients with other recurrence. The para-aortic area may be regarded as a sub-regional lymphatic drainage area. Besides, studies have founded that the incidences of postoperative lymph node recurrence and microscopic venous infiltration were extremely high in patients with PALNs metastasis^[21]. In order to eliminate the possible micrometastasis in the paraaortic region and avoid recurrence and metastasis, postoperative adjuvant therapy is necessary. Undoubtedly, radiotherapy is the most effective means to control regional recurrence^[19,22]. However, there is still a lack of accurate recommendations for para aortic CTV delineation. Here, we have tried to define the delineation of para aortic CTV by referring the distribution of PALNs.

The term "paraaortic" is not really defined in the radiotherapy of BTC. Early studies lacked a specific description of the boundary of para aortic CTV, which may lead to major inconsistencies in the boundary of the target area. Choi HS et al^[20] summarized the postoperative failure pattern of eCCA and found that most local recurrences occurred between the T10/11 interspace and the L1/2 interspace. They believed that 16a2 (11.3%) should be included in the treatment volume and 16a1 (1.4%), 16b1 (1.4%) and 16b2 (0%) should be omitted for reduced RT-related toxicity. Michael Hughes et al^[19] believed that the para-aortic CTV range of adjuvant radiotherapy for distal CCA should from the bottom of T10 to the bottom of L2. Similarly, Mallick S et al^[14] also suggested that the para aortic CTV should extend from at least 1 cm of the cranial or portal lymph node station to the L2 level. Compared to their results, the CTV that calculated in this study had a slightly lower inferior border because of the low involvement rate of LNM in 16a1. There is almost no metastasis in 16a1 region in eCCA. As for the inferior border, the CTV continued to the upper edge of the L3 vertebral body was recommended. This seems to be lower than the results of previous studies. The difference maybe related to the patients cohort with a tendency of PALNs to distribute downward. With regard to the expansion edge of CTV, Mallick S et al^[14] believed that para aortic CTV should be constructed by increasing the edge of 3-3.5 cm on the right, 2-2.5 cm in the front, 1-1.5 cm on the left and 0.2 cm in the back. Compared to the data gathered in this study, the CTV created according to Mallick S may be considered too generous. Their proposed margin may lead to unnecessary irradiation and higher renal dose, especially in the right area of the aorta. We obtained a relatively small para aortic CTV expansion range, which still can provided 96% coverage of the PALNs. The CTV expansion margins were applied to the validation cohort and also achieved a satisfactory coverage of PALNs. Based on the asymmetric distribution of PALN, an asymmetric para aortic CTV was formed to

ensure that the high-risk lymph node regions were not omitted and the surrounding normal tissue can be better protected.

This study has some potential limitations. First of all, the metastatic lymph nodes were only confirmed on imaging and not confirmed by pathology. Indeed, CT, MRI, and PET-CT have high sensitivity and specificity in identifying LNM based on different sequences. Secondly, due to the limitation of the number of cases, no recommendations are offered for the para aortic CTV according to different tumor location. However, according to the results of enrolled patients, regardless of subgroups, the involvement rates of 16b1 and 16a2 were greater than those of 16a1 and 16b2. Finally, fixed points were used to represent metastatic lymph nodes, basing on the assumption that the metastatic lymph nodes expand symmetrically. If the purpose is to cover micrometastasis, the lymph node center will represent the area to be covered. This method has been used in previously published literature^[13,23-24].

Conclusions

In this study, the distributions of LNM in patients with initially diagnosed and in patients with postoperative recurrence were summarized and the involvement rate of LNM in para-aorta region 16a2 and 16b1 was highest. Based on the distribution of PALNs, a new para aortic CTV delineation was defined to help construct an accurate target volume for adjuvant radiotherapy in BTC.

Abbreviations

BTC: Biliary tract cancer

GBC: Gallbladder carcinoma

eCCA: extrahepatic cholangiocarcinoma

iCCA: intrahepatic cholangiocarcinoma

NCCN: National Comprehensive Cancer Network

AJCC: American Joint Committee on Cancer

LNM: Lymph node metastasis

CTV: Clinical target volume

PALN: Para aortic lymph node

CT: Computed tomography

MRI: Magnetic resonance imaging

PET-CT: Positron emission tomography-computed tomography

LPA: Left-lateral para-aortic

RPA: Right-lateral para-aortic

APA: Anterior-lateral para-aortic

PPA: Posterior-lateral para-aortic

OS: Overall survival

IQR: Interquartile ranges

HR: Hazard Ratio

CI: Confidence interval

Declarations

Ethics approval and consent to participate: The study was approved by the ethics committee (EC) of the Zhongnan Hospital of Wuhan University (IRB number 2021007K)

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Author Contributions: FZ and XL designed the study. XL and HW drafted the manuscript. JP and LY and HX participated in data collection. JD and WW and LX coordinated, edited, and finalized the drafting of the manuscript. All authors read and approved the final manuscript.

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Tables

Table1. Characteristics of patients in study cohort and validation cohorts

Variable	Value	
	Study cohort N=61	Validation cohort N=19
Age(y),median(IQR)	60(52-66)	57(48-64)
Gender		
Male	33(54%)	12[63%]
Female	28(46%)	7[37%]
Tumor Location		
Gallbladder	15(25%)	4[21%]
Intrahepatic bile duct	35(57%)	9[47%]
Extrahepatic bile duct	11(18%)	6[32%]
Approach of operation		
Radical resection of hilar cholangiocarcinoma	-	2[11%]
Radical pancreaticoduodenectomy	-	4[21%]
Radical cholecystectomy	-	4[21%]
Resection of iCCA	-	9[47%]
Postoperative adjuvant therapy		
Chemotherapy	-	1(5%)
Radiotherapy	-	1(5%)
Concurrent chemoradiotherapy	-	3(16%)
No adjuvant therapy	-	14(74%)
Histology		
Adenocarcinoma	57(93%)	19[100%]
Other types	4(7%)	0[0%]
PALN		
With PALN	31(51%)	14[74%]
Without PALN	30(49%)	5[26%]
Number of PALNs	92	56

IQR, interquartile range; iCCA, intrahepatic cholangiocarcinoma; -, not applicable; PALN, para-aortic lymph node

Table2. Characteristics of patients with postoperative recurrence

Variable	Value
Age(y), median(IQR)	58(51.5-65)
Gender	
Male	22(49%)
Female	23(51%)
Tumor Location	
Gallbladder	12(26%)
Intrahepatic bile duct	18(40%)
Extrahepatic bile duct	15(34%)
Tumor size (cm), median(IQR)	3.5(2.0-5.75)
Pathologic T stage	
T1-2	23(51%)
T3-4	22(49%)
Pathologic N stage	
N-	20(45%)
N+	11(24%)
Nx	14(31%)
Pathological type	
Adenocarcinoma	43(95%)
Other types	2(5%)
Recurrence location	
Lymph node ^a	19(42%)*
Intrahepatic ^b	21(47%)
Distant organ ^c	7(16%)*

IQR, interquartile range; a, refers to including lymph node recurrence, regardless of whether it is combined with other sites recurrence; b, only intrahepatic metastasis occurred, not accompanied by other sites recurrence; c, refers to distant organ recurrence, regardless of whether it is combined with other sites recurrence; *, two patients had both PALN and distant organ recurrence.

Table3. Distance from volumetric centre of PALN in LN16a2 and LN16b1 to aorta in two cohorts

Location of PALNs	Study (n = 76 nodes)			Validation (n =49 nodes)		
	Mean distance from aorta (mm) (range)	The 90th percentile of the distances (mm)	The 95th percentile of the distances (mm)	Mean distance from aorta (mm) (range)	The 90th percentile of the distances (mm)	The 95th percentile of the distances (mm)
LPA	7(3-14)	11	12	10(5-20)	12	13
RPA	12(5-29)	22	24	10(6-23)	15	20
APA	9(4-24)	14	18	9 (5–23)	12	18

PALN, para-aortic lymph node; LPA, left-lateral para-aortic; RPA, right -lateral para-aortic; APA, anterior-lateral para-aortic

Figures

A

B

Figure 1

Frequency map of positive lymph nodes

A. Frequency map for study cohort

B. Frequency map for validation cohort

BTCs, biliary tract cancer; iCCA, intrahepatic cholangiocarcinoma; GBC, gallbladder carcinoma; eCCA, extrahepatic cholangiocarcinoma; LN, lymph node; LNMR, mediastinal lymph node; LNRS, right supraclavicular lymph node; LNLS, left supraclavicular lymph node

A

B

Figure 2

Kaplan-Meier curves for overall survival according to different recurrence sites

A. The Kaplan-Meier curves for patients with distant organ recurrence or PALN recurrence (HR=0.219; 95%CI 0.067-0.711; P=0.006)

B. The Kaplan-Meier curves for patients with PALN or without PALN recurrence (HR=3.271; 95%CI 0.704-15.185; P=0.111)

PALN, para-aortic lymph node; HR, hazard ratio; CI, confidence interval

Figure 3

Proposed atlas of para aortic CTV

A. The upper delineation of para aortic CTV

B. The lower delineation of para aortic CTV

C. Para aortic CTV(Sagittal plane)

A and B, aorta expansion with 18mm in the front, 12 mm on the left and 24 mm on the right; CTV, clinical target volume

Figure 4

Validation of the para aortic CTV coverage

A. PALN map in validation cohort

B. Lymph node map of region 16a2 and 16b1 in validation cohort

C. Coverage of the para aortic CTV in the validation cohort

CTV, clinical target volume; PALN, para-aortic lymph node

Supplementary Files

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