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Nodal recurrence mapping and clinical target volumes after resection of intrahepatic cholangiocarcinoma or combined hepatocellular-cholangiocarcinoma

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ABSTRACT

Background: Scarce evidence exists for clinical target volume (CTV) definitions of regional lymph nodes (LNs) in intrahepatic cholangiocarcinoma (iCCA) or combined hepatocellular-cholangiocarcinoma (cHCC-CCA). We investigated the mapping pattern of nodal recurrence after surgery for iCCA and cHCC-CCA and provided evidence for the nodal CTV definition.

Methods: We retrospectively reviewed the medical records of patients with iCCA or cHCC-CCA who underwent surgery between 2010 and 2020. Eligibility criteria included patients pathologically diagnosed with iCCA or cHCC-CCA after surgery and a first recurrent event in regional LNs during follow-up. All recurrent LNs were registered onto reference computed tomography images based on the vascular structures to reconstruct the node mapping. Fifty-three patients were eligible. LN regions were classified into four risk groups.

Results: Hepatic hilar and portal vein-vena cava were the most common recurrent regions, with recurrence rates of 62.3 % and 39.6 % (high-risk regions), respectively. Recurrence rates in the left gastric, diaphragmatic, common hepatic, superior mesenteric vessels, celiac trunk, and paracardial regions ranged from 15.1 % to 30.2 % (intermediate-risk regions). There were fewer recurrences in the para-aortic (16a1, a2, b1) and splenic artery and hilum regions, with rates <10 % (low-risk regions). No LN recurrence was observed in the para-oesophageal or para-aortic region (16b2) (very low-risk regions). Based on node mapping, the CTV should include high- and intermediate-risk regions for pathologically negative LN patients during postoperative radiotherapy. Low-risk regions should be included for pathologically positive LN patients.

Conclusion: We provide evidence for CTV delineation in patients with iCCA and cHCC-CCA based on recurrent LN mapping.

Abbreviations: cHCC-CCA, combined hepatocellular-cholangiocarcinoma; CT, computed tomography; CTV, clinical target volume; iCCA, intrahepatic cholangiocarcinoma; LN, lymph node; RT, radiotherapy.

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1. Introduction

Intrahepatic cholangiocarcinoma (iCCA) constitutes a diverse group of malignancies arising from the epithelial cells of the intrahepatic bile ducts. iCCA is the second most common primary hepatic malignancy, accounting for 10 %–15 % of all primary liver tumours [1,2]. iCCA is highly aggressive, and most patients present with advanced-stage disease [3,4], rendering a dismal prognosis with high recurrence rates after dissection and 5-year survival rates of 7 %–20 % [5–8]. Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is an independent entity that shares the characteristics of iCCA and HCC [9]. It is a rare type of liver malignancy accounting for 0.4 %–14.2 % of primary liver carcinomas [10–13], with an aggressive disease course and a poor prognosis similar to that of iCCA [9,14,15].

Surgical resection remains the mainstay of potentially curative therapy for iCCA or cHCC-CCA; however, only approximately 35 % of patients with early stage disease are amenable to curative surgical resection [16]. The reported median disease-free survival after surgery is 12–36 months [17,18]. Adjuvant radiotherapy (RT) and chemotherapy for iCCA after resection remain controversial according to an early meta-analysis [19]; however, an increasing number of retrospective studies have shown a survival benefit of postoperative RT for high-risk patients with iCCA [20–24]. Lymph node (LN) metastasis is more frequent in iCCA and cHCC-CCA (20 % to 40 % of patients) than in HCC (<5% of patients) [19,25]. Furthermore, regional LN involvement is an important predictor of short disease-free survival [18,26]. Remnant liver and regional LN recurrence is the prominent pattern of treatment failure in iCCA after curative surgery [20]. Therefore, the adjuvant RT clinical target volume (CTV) should be defined as the primary tumour bed, resection margins, and regional LNs.

Currently, there is little evidence regarding the CTV definitions of regional LNs in iCCA or cHCC-CCA. Our previous retrospective study demonstrated the survival benefit of adjuvant RT following narrow-margin hepatectomy for iCCA, but no unified CTV of regional LNs was established [24]. Hence, the present study aimed to investigate the patterns of regional LN recurrence after curative surgery for iCCA and cHCC-CCA to provide insights into CTV delineation in adjuvant RT.

2. Materials and methods

2.1. Patients

The medical records of patients with iCCA and cHCC-CCA who underwent surgery at the Cancer Hospital of the Chinese Academy of Medical Sciences between January 2010 and January 2020 were retrospectively reviewed. Eligibility criteria included patients (a) who were pathologically diagnosed with iCCA or cHCC-CCA after curative surgical resection; (b) with a recurrent event in regional LNs during follow-up after surgery; and (c) who had qualified diagnostic chest-abdomen-pelvis computed tomography (CT) images acquired during LN recurrence. Exclusion criteria involved patients who underwent adjuvant RT. The Ethics Committee of National Cancer Centre/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College approved this study (No. 22/0882-3283), which was conducted in accordance with both the Declarations of Helsinki and Istanbul. The requirement of informed consent was waived owing to the retrospective nature of the study.

2.2. Data collection in initial diagnosis and surgery

Collected data included the following variables: (a) clinical characteristics for the first diagnosis before surgery, including sex, age, Eastern Cooperative Oncology Group performance status, history of hepatitis, alpha-foetoprotein and carbohydrate antigen 199, and Child–Pugh score; (b) operative details, including anatomical or non-anatomical resection and LN or non-LN dissection; (c) pathological data after surgical resection, including tumour size and location, number of primary tumours, surgical margin, pathological grade, presence of lymphovascular invasion, and the number of positive and negative LNs; and (d) adjuvant chemotherapy after surgery.

2.3. Follow-up and first recurrence with LNs

Patients were followed up every 3 months during the first 2 years and every 6 months during the next 3 years after primary treatment. During each follow-up, a complete medical history was obtained and a physical examination was performed. Additionally, patients underwent CT of the chest and abdomen, magnetic resonance imaging of the upper abdomen, or positron emission tomography-CT for evaluation. All available images were reviewed thoroughly. Recurrence patterns were categorised as local (intrahepatic), regional LNs, or distant failure. LNs with one or more of the following characteristics were considered malignant: short axis >10 mm, necrosis, LN fusion, fluorodeoxyglucose avid, and responsive to anticancer treatment. Regional failure as the first site of recurrence, with or without failure elsewhere, was further evaluated.

2.4. Node mapping

Simulation CT images of one female patient (166 cm, 65 kg) treated in our department after surgery for pathological T1N0M0 stage iCCA were selected as a reference. Recurrent LNs for all patients were registered using hand drawings from diagnostic CT/magnetic resonance imaging scans onto reference images based on vascular structures. The epicentre of every node was contoured by dotting the geometric centre with a pen diameter of 10 mm. Anatomical definitions of LN regions were based on the classification of nodal stations in gastric cancer [27].

2.5. Statistical analysis

Univariate analysis was performed using Pearson's chi-square or Fisher's exact test for categorical variables. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using SPSS for Windows (version 24.0; IBM Corp., Armonk, NY, USA, released in 2016).

3. Results

3.1. Clinicopathological characteristics at initial diagnosis and surgery

A total of 53 patients were eligible; of these, 42 patients had iCCA and 11 patients had cHCC-CCA. The median age of the patients was 59 (35–70) years. Table 1 shows the clinical characteristics of the patients at initial diagnosis and surgery. The cHCC-CCA group had a higher proportion of patients with a history of hepatitis B and elevated alpha-foetoprotein levels than the iCCA group. There was no significant difference in the number of patients with elevated carbohydrate antigen 19–9 levels between the groups. The tumour burden represented by tumour size as well as pathological T and N stage was similar between the groups. Approximately one-third of the patients in both groups received perioperative chemotherapy. LN dissection was performed in 85.7 % (36/42) and 54.5 % (6/11) of patients with iCCA and cHCC-CCA, respectively; however, the median number of dissected LNs was only 6 (1–31). LN metastasis was observed in 38.1 % (16/42) and 45.5 % (5/11) of patients with iCCA and cHCC-CCA, respectively. Approximately 70 % of all patients underwent R0 resection.

3.2. First recurrence patterns of LNs

The median follow-up time was 13.15 (3.74–52.38) months. Among the 53 patients, 14 (26.4 %) experienced regional LN recurrence alone, and 39 (73.6 %) had simultaneous recurrence elsewhere at the first recurrence. The median time to progression was 7.69 (1.02–43.96) months. Forty (75.5 %) patients experienced recurrence within 18

Table 1
Clinicopathological characteristics of all patients at initial surgery.

Characteristics	All patients		iCCA		cHCC-CCA		*p*
	n = 53		n = 42		n = 11		
	No.	%	No.	%	No.	%	
Age							0.138
≥60	25	47.2	22	52.4	3	27.3	
<60	28	52.8	20	47.6	8	72.7	
Sex							0.602
Male	33	62.3	26	61.9	7	63.6	
Female	20	37.7	16	38.1	4	36.4	
ECOG							0.792
1	52	98.1	41	97.6	11	100.0	
2	1	1.9	1	2.4	0	0.0	
HBV							0.010
Negative	28	52.8	26	61.9	2	18.2	
Positive	25	47.2	16	38.1	9	81.8	
Elevated AFP							0.007
Yes	8	15.1	3	7.1	5	45.5	
No	37	69.8	32	76.2	5	45.5	
Unknown	8	15.1	7	16.7	1	9.1	
Elevated CA19-9							0.561
Yes	34	64.2	26	61.9	8	72.7	
No	11	20.8	10	23.8	1	9.1	
Unknown	8	15.1	6	14.3	2	18.2	
Child–Pugh score							0.095
5	47	88.7	38	90.5	9	81.8	
≥6	3	5.7	3	7.1	0	0	
Unknown	3	5.7	1	2.4	2	18.2	
Anatomical resection							0.070
Yes	32	60.4	28	66.7	4	36.4	
No	21	39.6	14	33.3	7	63.6	
No. of primary tumours							0.340
1	45	84.9	37	88.1	8	72.7	
≥2	8	15.1	5	11.9	3	27.3	
Tumour size							0.277
≤5 cm	26	49.1	19	45.2	7	63.6	
>5 cm	27	50.9	23	54.8	4	36.4	
Pathological grade							0.017
2	11	20.8	10	23.8	1	9.1	
3	38	71.7	31	73.8	7	63.6	
Unknown	4	7.5	1	2.4	3	27.3	
Surgical margin							0.097
R0	36	67.9	27	64.3	9	81.8	
R1	12	22.6	12	28.6	0	0	
Unknown	5	9.4	3	7.1	2	18.2	
LN dissection							0.037
Yes	42	79.2	36	85.7	6	54.5	
No	11	20.8	6	14.3	5	45.5	
LN metastasis							0.089
Yes	23	43.4	21	50.0	2	18.2	
No	30*	56.6	21	50.0	9	81.8	
Lymphovascular invasion							0.736
Yes	21	39.6	16	38.1	5	45.5	
No	32	60.4	26	61.9	6	54.5	
pT stage							0.059
T1a	24	45.3	17	40.5	7	63.6	
T1b	21	39.6	20	47.6	1	9.1	
T2	8	15.1	5	11.9	3	27.3	
pN stage							0.057
N0	30	56.6	21	50.0	9	81.8	
N1	23	43.4	21	50.0	2	18.2	
Perioperative chemotherapy							0.503
Yes	17	32.0	14	33.3	3	27.3	
No	36	67.9	2	18.2	8	72.7	

Abbreviations: iCCA, intrahepatic cholangiocarcinoma; cHCC-CCA, combined hepatocellular-cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; AFP, alpha-foetoprotein; CA19-9, carbohydrate antigen 19–9; LN, lymph node.

* Including 11 patients without LN dissection.

months. Intrahepatic recurrence occurred in 54.7 % of patients, while distant failure accounted for 35.9 %. Simultaneous intrahepatic recurrence and distant metastasis occurred more often in patients with cHCC-CCA than in patients with iCCA, with proportions of 81.9 % vs. 47.6 % and 45.5 % vs. 33.3 %, respectively.

3.3. Distribution of positive dissected and recurrent LNs

Fig. 1 depicts the distribution of pathologically positive LNs at initial surgery and the first recurrent regional LNs identified in the follow-up images of the 53 patients. The hepatic hilar (37.7 %), common hepatic (24.5 %), and portal vein-vena cava (15.1 %) were the most common regions for pathologically positive dissected LNs, accounting for 77.3 % of all positive LNs. Metastases to other regions were observed in less than 10 % patients. Most metastatic LNs were in dissected fields, similar to the patterns of metastatic LN regions at initial surgery, indicating the importance of local adjuvant therapy despite regional nodal dissection.

3.4. Risk classification of LN regions

Based on the recurrence rates in different LN regions, we categorised these regions into high-risk, intermediate-risk, low-risk, and very low-risk. We defined LN regions with recurrence rates >30 %, 10 %–30 %, 1 %–10 %, and <1 % as high-, intermediate-, low-, and very low-risk regions (Table 2), respectively. The hepatic hilar was the most common recurrent region, followed by the portal vein-vena cava, with a recurrence rate of 40 %–60 %. Recurrence rates in the left gastric, diaphragmatic, common hepatic, superior mesenteric, celiac trunk, and paracardial vessels were similar and moderate, ranging from 15 % to 30 %. Recurrence was less common in the para-aortic (16a2, b1, a2) and splenic artery and hilum regions, with rates of <10 %. No LN recurrence in the para-oesophageal or para-aortic region (16b2) was observed in the study cohort. iCCA and cHCC-CCA had similar LN recurrence distributions, but the intermediate-risk regions of cHCC-CCA had a relatively high relapse rate (Table 2). Univariate analyses were performed to find out the relation between different clinical characteristics and recurrent LNs distribution. The results were listed in Table 3. No characteristic was identified to have significant influence on LN recurrence pattern,

3.5. Validation of risk classification and low skip LN region recurrence

To validate our risk classification of LN regions, we defined skip recurrence as LN relapse in intermediate-risk or low-risk regions without relapse in high-risk regions or relapse in low-risk regions without relapse in intermediate-risk regions. Table 4 lists the skip recurrences of all patients. Skip recurrence to intermediate-risk regions without high-risk region involvement occurred in 13.2 % (7/53) of patients. In contrast, skip recurrence to low-risk regions without high-risk and intermediate-risk region involvement only occurred in 3.8 % (2/53) of patients. This result confirmed the rationality of our risk classification; however, if postoperative RT is performed for patients without postoperative pathological LN involvement, we recommend that CTV include the high-risk and intermediate-risk regions because the skip recurrence in the intermediate-risk regions without the high-risk region was higher than 10 %.

3.6. Node mapping and CTV recommendation based on risk classification

Node mapping was reconstructed to show the vessel-based distribution of recurrent LNs for the 53 included patients on digitally reconstructed radiographic images (Fig. 2A) and typical slices of CT axial images (Fig. 2B–F). High-risk, intermediate-risk, and low-risk regions were delineated according to the frequency of recurrent LN distribution and adjacent anatomical structures (Fig. 2B–F, Table 4). The para-aortic (16a2) region with a recurrence rate of 7.5 % was classified as a low-risk region; however, it was included in the intermediate-risk region in Fig. 2B–E because it was located at the same slices and was completely attached to high-risk LN regions. In clinical practice, we recommend CTV delineation of the high-risk and intermediate-risk regions for all

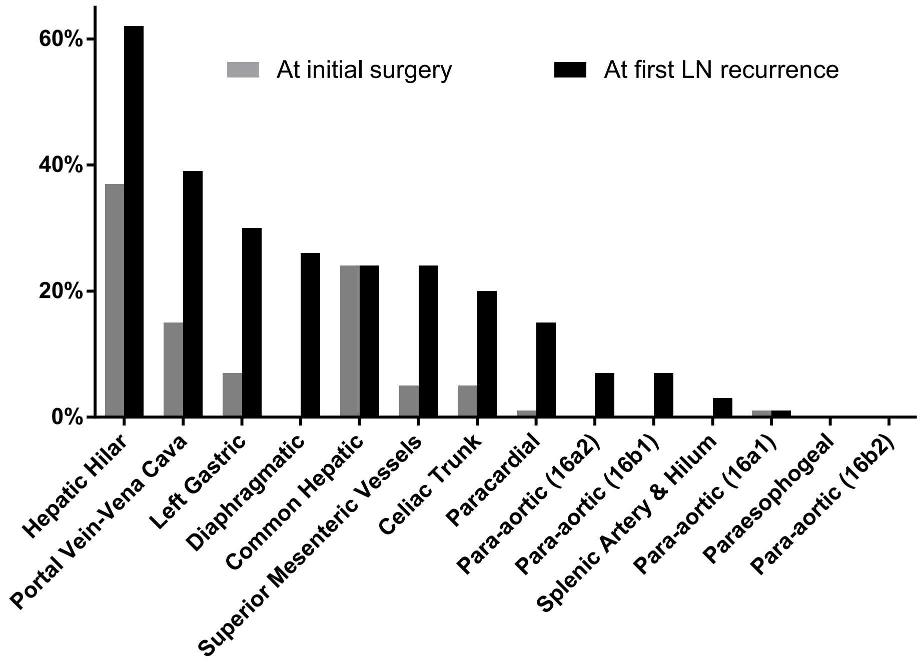

Fig. 1. The frequency of positive lymph nodes (LNs) at initial surgery and first recurrence.

Table 2
Risk classification of lymph node regions according to recurrence rate.

Risk classification	All patients n = 53		iCCA n = 42		cHCC-CCA n = 11		*p*
	No.	%	No.	%	No.	%	
High-risk regions							
Hepatic hilar	33	62.3	25	59.5	8	72.7	0.331
Portal vein-vena cava	21	39.6	17	40.5	4	36.4	0.545
Intermediate-risk regions							
Left gastric	16	30.2	12	28.6	4	36.4	0.436
Diaphragmatic	14	26.4	11	26.2	3	27.3	0.608
Common hepatic	13	24.5	8	19.0	5	45.5	0.082
Superior mesenteric vessels	13	24.5	9	21.4	4	36.4	0.257
Celiac trunk	11	20.8	8	19.0	3	27.3	0.410
Paracardial	8	15.1	5	11.9	3	27.3	0.206
Low-risk regions							
Para-aortic (16a2)	4	7.5	4	9.5	0	0	0.382
Para-aortic (16b1)	4	7.5	4	9.5	0	0	0.382
Splenic artery & hilum	2	3.8	2	4.8	0	0	0.625
Para-aortic (16a1)	1	1.9	0	0	1	9.1	0.208
Very low-risk region							
Para-oesophageal	0	0	0	0	0	0	NA
Para-aortic (16b2)	0	0	0	0	0	0	NA

Abbreviations: iCCA, cholangiocarcinoma; cHCC-CCA, combined hepatocellular-cholangiocarcinoma.

patients. Low-risk regions should also be included in the CTV for patients with dissected positive LNs, especially those with LNs in intermediate-risk regions.

4. Discussion

This study proposed risk classifications of LN regions and recurrent LN maps for postoperative patients with iCCA or cHCC-CCA based on the follow-up images from a large cohort. The main finding of this study—the categorisation of LN regions into four risk groups based on recurrence rates—may provide insight into CTV contouring for radiation oncologists to deliver adjuvant RT to patients with iCCA or cHCC-CCA. Furthermore, surgeons may use these findings to determine the extent of LN dissection in patients with iCCA or cHCC-CCA.

The role of routine lymphadenectomy in patients with iCCA remains controversial [28]. The incidence of nodal involvement is high, and LN metastasis has been observed in approximately 40 % of patients [18,29,30]. However, data from the National Cancer Institute's Surveillance, Epidemiology, and End Results showed that only 55 % of patients with iCCA underwent pathologic evaluation of at least one regional LN [18,30]. LN metastasis is a widely accepted negative prognostic factor [18,29,30]. Therefore, lymphadenectomy has potential therapeutic benefits for improving staging and decreasing locoregional recurrence [31,32]. In our cohort, 79.2 % of patients underwent LN dissection; nevertheless, the median number of dissected LNs was merely 6 (1–31), and LN metastasis was observed in 43.4 % of patients. Moreover, the distribution of dissected positive and recurrent LNs showed that lymphadenectomy did not decrease LN recurrence in the same LN region, possibly due to the limited number of LN regions and dissected LNs. Hence, locoregional adjuvant therapy may improve the prognosis of patients without lymphadenectomy or inadequate LN dissection.

The literature on adjuvant RT is sparse because of the low incidence of iCCA and cHCC-CCA. Surgical resection is the most important treatment and is the only potential cure. However, the complete resection rate remains poor, and R0 resection is achievable in only approximately 30 % of patients [33,34]. Patients who undergo R1 resection have survival rates similar to those who are treated without surgery, and local recurrence is the most common failure pattern [34,35]. Local failure rates exceeded 50 % in many studies even after R0 resection, indicating that surgery may be insufficient for most patients [17,18,36–40]. The tendency of iCCA and cHCC-CCA to recur locally provides a rationale for additional local therapy after surgery. An analysis of 3,839 patients from the National Cancer Institute's Surveillance, Epidemiology, and End Results database showed that the median overall survival after surgery and RT was 11 months compared with 6 months after surgery alone [41]. The role of adjuvant RT remains controversial and calls for future phase III trials [41–45]; that said, patients with risk factors, including microscopically positive margins or multiple LN metastases, might

Table 3
Univariate analysis on recurrent LNs distribution according to different primary clinical characteristics at initial surgery.

Clinical characteristic	Total No.	High-risk regions		p	Intermediate-risk regions		p	Low-risk regions		p
		No.	%		No.	%		No.	%	
No. of primary tumours				0.611			0.999			0.665
1	45	38	84.4		37	82.2		9	20.0	
≥2	8	6	75.0		7	87.5		2	25.0	
Tumour location				0.219			0.281			0.916
Left upper liver	12	9	75.0		12	100.0		3	25.0	
Left lower liver	13	12	92.3		10	76.9		3	23.1	
Right upper liver	8	5	62.5		7	87.5		1	12.5	
Right lower liver	20	18	90.0		15	75.0		4	20.0	
Tumour size				0.142			0.999			0.788
≤5 cm	26	24	92.3		22	84.6		5	19.2	
>5 cm	27	20	74.1		22	81.5		6	22.2	
Surgical margin*				0.394			0.394			0.113
R0	36	31	86.1		31	86.1		6	16.7	
R1	12	9	75.0		9	75.0		5	41.7	
LN metastasis				0.999			0.715			0.999
Yes	23	19	82.6		20	87.0		5	21.7	
No	30	25	83.3		24	80.0		6	20.0	
Perioperative chemotherapy				0.999			0.126			0.301
Yes	17	14	82.4		12	70.6		5	29.4	
No	36	30	83.3		32	88.9		6	16.7	

* Four of all 53 patients couldn't provide status of surgical margin

Table 4
Validation of risk classification and potential skip lymph node region recurrence.

Metastasis to high-risk regions	No. of patients (%)	Metastasis to intermediate-risk regions	No. of patients (%)	Metastasis to low-risk regions	No. of patients (%)
Yes	44 (83.0)	Yes	37 (69.8)	Yes	5 (9.4)
				No	32 (60.4)
		No	7 (13.2)	Yes	2 (3.8)
				No	5 (9.4)
No	9 (17.0)	Yes	7 (13.2)	Yes	2 (3.8)
				No	5 (9.4)
		No	2 (3.8)	Yes	2 (3.8)
				No	0 (0)

benefit. The National Comprehensive Cancer Network guidelines recommend that patients with iCCA and positive resection margins or regional LN metastasis receive adjuvant RT. Our previous retrospective study showed that postoperative RT following narrow-margin hepatectomy is efficacious and well tolerated in patients with iCCA adjacent to major vessels [24]. However, no consensus has been reached regarding the failure pattern of regional LNs or CTV delineation.

Few reports on CTV delineation of regional LNs for iCCA or cHCC-CCA have been published, and existing studies have demonstrated a lack of clear and detailed clinical practice. Gil et al. [20] explored the recurrence patterns of iCCA after surgery and observed that 45.2 % of patients with iCCA had regional LN recurrence. Notably though, this report did not demonstrate the detailed location and frequency of LN recurrence. Yu et al. [23] investigated the failure patterns for post-operative patients with iCCA and discovered that LN regions 16a2, 9, 8, 12, 13, and 14 were common sites of recurrence. However, the study did not investigate recurrence mapping and risk classification. Thus, our study provides LN recurrence mapping with detailed data and proposes four risk classifications of LN regions and CTV suggestions based on mapping for clinical practice.

Recurrence patterns might be different for different primary tumour locations due to lymphatic drainage characteristics. Accordingly, we compared the recurrence rates of high-risk and intermediate-risk LN regions between the four locations of primary tumours in the liver, and the results were presented in Table 5. The recurrence rates of diaphragmatic and left gastric or paracardial LN regions were considerably higher when the primary tumour was in the left upper liver than when it was in other locations. Specifically, 58.3 % (7/12) of tumours located in the left upper liver had diaphragmatic LN recurrence, compared to 37.5 %, 20.0 %, and no recurrence of tumours in the right upper, right lower, and left lower liver, respectively. In total, 50 % (10/20) of tumours in the upper liver had diaphragmatic LN metastasis, compared to approximately 12.1 % (4/33) of tumours in the lower liver. Therefore, a broader treatment volume, including the diaphragmatic region, is indicated for patients with upper lobe cancer. Conversely, the diaphragmatic region should be spared to reduce the radiation dose to normal tissues, including the liver.

LN metastasis is more frequent in patients with iCCA than in patients with cHCC-CCA [19,25]; however, to our knowledge, no study has compared the differences between the two entities. As such, we investigated the frequencies of LN metastasis in each LN region according to different pathological diagnoses. The metastatic rates between the two groups were similar in each region, although only 11 patients with cHCC-CCA were included in this analysis. Thus, CTV delineation in patients with iCCA and cHCC-CCA was similar in this study.

This study had some limitations. Although to our knowledge this study included the largest cohort and number of characteristics to date, it was a retrospective investigation, and only 53 patients were eligible for inclusion. The predictors of LN recurrence in each region were not analysed because of the sample size. In addition, recurrence rates might be underestimated in retrospective analyses because of incomplete evaluation during each follow-up and difficulty in LN recurrence diagnosis via radiographic detection only. Despite these limitations, the CTV may be contoured based on our recommendations in future trials, and the treatment results may be used to validate our findings.

5. Conclusion

In conclusion, this study provides evidence for CTV delineation in patients with iCCA and cHCC-CCA based on recurrent LN mapping, offering insights into the design of the range of LN dissection and target volumes of postoperative RT in future clinical trials of iCCA and cHCC-CCA.

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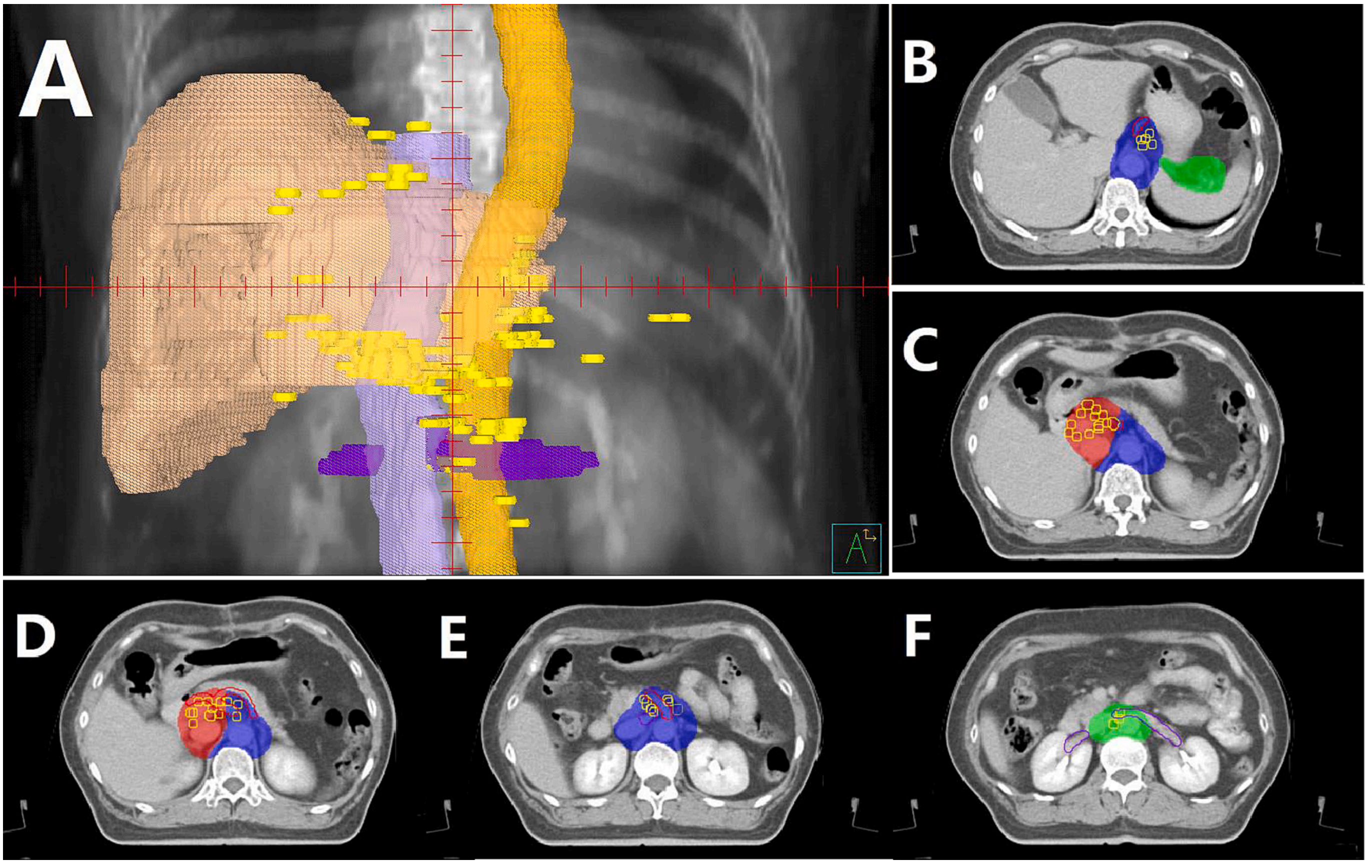

Fig. 2. The recurrent nodal gross tumour volume (yellow) for the 53 included patients on (A) a digitally reconstructed radiograph image (light orange: liver; orange: aorta; lavender: vena cava; purple: kidney vein); and clinical target volume recommendations according to risk classification (high risk: red; medium risk: blue; low risk: green) on typical slices of computed tomography axial images at the (B) left gastric artery; (C) hepatic hilar; (D) portal vein-vena cava; (E) celiac trunk; and (F) kidney vein. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 5
Lymph node recurrence rates according to tumour location.

Lymph node regions/location	Left upper liver n = 12		Left lower liver n = 13		Right upper liver n = 8		Right lower liver n = 20		*p*
	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	
High-risk regions									
Hepatic hilar	8	66.7	8	61.5	4	50.0	13	65.0	0.878
Portal vein-vena cava	3	25.0	5	38.5	1	12.5	12	60.0	0.072
Intermediate-risk regions									
Left gastric/paracardial	9	75.0	5	38.5	3	37.5	5	25.0	0.048
Diaphragmatic	7	58.3	0	0	3	37.5	4	20.0	0.008
Celiac trunk/common hepatic	2	16.7	8	61.5	2	25.0	8	40.0	0.112
Superior mesenteric vessels	3	25.0	2	15.4	2	25.0	6	30.0	0.822

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Author contribution

B.C, H.Z and Y.X.L designed the research; Z.B.Y, L.M.W, Y.R.Z, J.J.Z, F.Y, H.Z, Y.X.L and B.C contributed to the study concept and study co-ordination. Z.B.Y, L.M.W, Y.R.Z, H.Z and B.C reviewed the CT and MRI image of patients. Z.B.Y, L.M.W, Y.R.Z, Y.X.L and B.C wrote the paper. Z.B.Y, L.M.W, Y.R.Z and B.C analyzed data; All authors provided study materials or patients' data and approved the final version of the manuscript.

CRediT authorship contribution statement

Zhuanbo Yang: Data curation, Writing – original draft, Visualization, Investigation, Formal analysis. **Liming Wang:** Data curation, Investigation, Formal analysis, Methodology. **Yirui Zhai:** Writing – original draft, Validation, Formal analysis, Methodology, Software. **Jianjun Zhao:** Data curation, Writing – original draft, Validation, Software. **Feng Ye:** Data curation, Investigation, Formal analysis, Methodology, Software. **Shulian Wang:** Writing – review & editing. **Liming Jiang:** Validation, Resources. **Yan Song:** Resources. **Yongkun Sun:** Resources. **Ji Zhu:** Visualization, Resources, Software. **Yuan Tang:** Resources. **Yueping Liu:** Resources. **Yongwen Song:** Resources. **Hui Fang:** Resources. **Ning Li:** Resources. **Shunan Qi:** Resources. **Ningning**

Lu: Resources. **Ye-Xiong Li:** Conceptualization, Writing – review & editing, Methodology, Supervision. **Hong Zhao:** Conceptualization, Writing – review & editing, Methodology, Supervision. **Bo Chen:** Conceptualization, Funding acquisition, Writing – review & editing, Methodology, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] El-Diwany R, Pawlik TM, Ejaz A. Intrahepatic cholangiocarcinoma. Surg Oncol Clin N Am 2019;28:587–99. https://doi.org/10.1016/j.soc.2019.06.002.

[2] Mejia JC, Pasko J. Primary liver cancers: intrahepatic cholangiocarcinoma and hepatocellular carcinoma. Surg Clin North Am 2020;100:535–49. https://doi.org/10.1016/j.suc.2020.02.013.

[3] Banales JM, Cardinale V, Carpino G, Marzioni M, Andersen JB, Invernizzi P, et al. Expert consensus document: cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). Nat Rev Gastroenterol Hepatol 2016;13:261–80. https://doi.org/10.1038/nrgastro.2016.51.

[4] Andersen JB, Spee B, Blechacz BR, Avital I, Komuta M, Barbour A, et al. Genomic and genetic characterization of cholangiocarcinoma identifies therapeutic targets for tyrosine kinase inhibitors. Gastroenterology 2012;142:1021–31.e15. https://doi.org/10.1053/j.gastro.2011.12.005.

[5] Kamsa-Ard S, Luvira V, Suwanrungruang K, Kamsa-Ard S, Luvira V, Santong C, et al. Cholangiocarcinoma trends, incidence, and relative survival in Khon Kaen, Thailand from 1989 through 2013: a population-based cancer registry study. J Epidemiol 2019;29:197–204. https://doi.org/10.2188/jea.JE20180007.

[6] Strijker M, Belkouz A, van der Geest LG, van Gulik TM, van Hooft JE, de Meijer VE, et al. Treatment and survival of resected and unresected distal cholangiocarcinoma: a nationwide study. Acta Oncol 2019;58:1048–55. https://doi.org/10.1080/0284186X.2019.1590634.

[7] Groot Koerkamp B, Wiggers JK, Allen PJ, Besselink MG, Blumgart LH, Busch OR, et al. Recurrence rate and pattern of perihilar cholangiocarcinoma after curative intent resection. J Am Coll Surg 2015;221:1041–9. https://doi.org/10.1016/j.jamcollsurg.2015.09.005.

[8] Spolverato G, Kim Y, Alexandrescu S, Marques HP, Lamelas J, Aldrighetti L, et al. Management and outcomes of patients with recurrent intrahepatic cholangiocarcinoma following previous curative-intent surgical resection. Ann Surg Oncol 2016;23:235–43. https://doi.org/10.1245/s10434-015-4642-9.

[9] Beaufrère A, Calderaro J, Paradis V. Combined hepatocellular-cholangiocarcinoma: an update. J Hepatol 2021;74:1212–24. https://doi.org/10.1016/j.jhep.2021.01.035.

[10] Wang J, Wang F, Kessinger A. Outcome of combined hepatocellular and cholangiocarcinoma of the liver. J Oncol 2010;2010:917356. https://doi.org/10.1155/2010/917356.

[11] Zhang H, Yu X, Xu J, Li J, Zhou Y. Combined hepatocellular-cholangiocarcinoma: an analysis of clinicopathological characteristics after surgery. Medicine (Baltimore) 2019;98:e17102.

[12] Jarnagin WR, Weber S, Tickoo SK, Koea JB, Obiekwe S, Fong Y, et al. Combined hepatocellular and cholangiocarcinoma: demographic, clinical, and prognostic factors. Cancer 2002;94:2040–6. https://doi.org/10.1002/cncr.10392.

[13] Yin X, Zhang BH, Qiu SJ, Ren ZG, Zhou J, Chen XH, et al. Combined hepatocellular carcinoma and cholangiocarcinoma: clinical features, treatment modalities, and prognosis. Ann Surg Oncol 2012;19:2869–76. https://doi.org/10.1245/s10434-012-2328-0.

[14] Munoz-Garrido P, Rodrigues PM. The jigsaw of dual hepatocellular-intrahepatic cholangiocarcinoma tumours. Nat Rev Gastroenterol Hepatol 2019;16:653–5. https://doi.org/10.1038/s41575-019-0185-z.

[15] Brunt E, Aishima S, Clavien PA, Fowler K, Goodman Z, Gores G, et al. cHCC-CCA: consensus terminology for primary liver carcinomas with both hepatocytic and cholangiocytic differentation. Hepatology 2018;68:113–26. https://doi.org/10.1002/hep.29789.

[16] Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BS J, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001;234:507–17; discussion 517–9. https://doi.org/10.1097/00000658-200110000-00010.

[17] Choi SB, Kim KS, Choi JY, Park SW, Choi JS, Lee WJ, et al. The prognosis and survival outcome of intrahepatic cholangiocarcinoma following surgical resection: association of lymph node metastasis and lymph node dissection with survival. Ann Surg Oncol 2009;16:3048–56. https://doi.org/10.1245/s10434-009-0631-1.

[18] Endo I, Gonen M, Yopp AC, Dalal KM, Zhou Q, Klimstra D, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. Ann Surg 2008;248:84–96. https://doi.org/10.1097/SLA.0b013e318176c4d3.

[19] Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. JAMA Surg 2014;149:565–74. https://doi.org/10.1001/jamasurg.2013.5137.

[20] Gil E, Joh JW, Park HC, Yu JI, Jung SH, Kim JM. Predictors and patterns of recurrence after curative liver resection in intrahepatic cholangiocarcinoma, for application of postoperative radiotherapy: a retrospective study. World J Surg Oncol 2015;13:227. https://doi.org/10.1186/s12957-015-0637-z.

[21] Jia AY, Wu JX, Zhao YT, Li YX, Wang Z, Rong WQ, et al. Intensity-modulated radiotherapy following null-margin resection is associated with improved survival in the treatment of intrahepatic cholangiocarcinoma. J Gastrointest Oncol 2015;6:126–33. https://doi.org/10.3978/j.issn.2078-6891.2014.102.

[22] Wang L, Deng M, Ke Q, Lou J, Zheng S, Bi X, et al. Postoperative adjuvant therapy following radical resection for intrahepatic cholangiocarcinoma: a multicenter retrospective study. Cancer Med 2020;9:2674–85. https://doi.org/10.1002/cam4.2925.

[23] Yu W, Hu C, Shui Y, Wu K, Zhang L, Chen Y, et al. Failure patterns after curative resection for intrahepatic cholangiocarcinoma: possible implications for postoperative radiotherapy. BMC Cancer 2019;19:1108. https://doi.org/10.1186/s12885-019-6328-3.

[24] Zheng X, Chen B, Wu JX, Jia AY, Rong WQ, Wang LM, et al. Benefit of adjuvant radiotherapy following narrow-margin hepatectomy in patients with intrahepatic cholangiocarcinoma that adhere to major vessels. Cancer Manag Res 2018;10:3973–81. https://doi.org/10.2147/CMAR.S172940.

[25] Wakizaka K, Yokoo H, Kamiyama T, Ohira M, Kato K, Fujii Y, et al. Clinical and pathological features of combined hepatocellular-cholangiocarcinoma compared with other liver cancers. J Gastroenterol Hepatol 2019;34:1074–80. https://doi.org/10.1111/jgh.14547.

[26] Wang Y, Li J, Xia Y, Gong R, Wang K, Yan Z, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol 2013;31:1188–95. https://doi.org/10.1200/JCO.2012.41.5984.

[27] Rosa F, Costamagna G, Doglietto GB, Alfieri S. Classification of nodal stations in gastric cancer. Transl Gastroenterol Hepatol 2017;2:2. https://doi.org/10.21037/tgh.2016.12.03.

[28] Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. Intrahepatic Cholangiocarcinoma: Expert Consensus Statement. HPB (Oxford) 2015;17:669–80. https://doi.org/10.1111/hpb.12441.

[29] Ribero D, Pinna AD, Guglielmi A, Ponti A, Nuzzo G, Giulini SM, et al. Surgical approach for long-term survival of patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis of 434 patients. Arch Surg 2012;147:1107–13. https://doi.org/10.1001/archsurg.2012.1962.

[30] de Jong MC, Nathan H, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. J Clin Oncol 2011;29:3140–5. https://doi.org/10.1200/JCO.2011.35.6519.

[31] Weber SM, Jarnagin WR, Klimstra D, DeMatteo RP, Fong Y, Blumgart LH. Intrahepatic cholangiocarcinoma: resectability, recurrence pattern, and outcomes. J Am Coll Surg 2001;193:384–91. https://doi.org/10.1016/s1072-7515(01)01016-x.

[32] Shimada K, Sano T, Nara S, Esaki M, Sakamoto Y, Kosuge T, et al. Therapeutic value of lymph node dissection during hepatectomy in patients with intrahepatic cholangiocellular carcinoma with negative lymph node involvement. Surgery 2009;145:411–6. https://doi.org/10.1016/j.surg.2008.11.010.

[33] Nakeeb A, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996;224:463–73; discussion 473–5. .

[34] Lang H, Sotiropoulos GC, Frühauf NR, Dömland M, Paul A, Kind EM, et al. Extended hepatectomy for intrahepatic cholangiocellular carcinoma (ICC): when is it worthwhile? Single center experience with 27 resections in 50 patients over a 5-year period. Ann Surg 2005;241:134–43. https://doi.org/10.1097/01.sla.0000149426.08580.a1.

[35] Miwa S, Miyagawa S, Kobayashi A, Akahane Y, Nakata T, Mihara M, et al. Predictive factors for intrahepatic cholangiocarcinoma recurrence in the liver following surgery. J Gastroenterol 2006;41:893–900. https://doi.org/10.1007/s00535-006-1877-z.

[36] Anderson CD, Pinson CW, Berlin J, Chari RS. Diagnosis and treatment of cholangiocarcinoma. Oncologist 2004;9:43–57. https://doi.org/10.1634/theoncologist.9-1-43.

[37] Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. Semin Liver Dis 2004;24:115–25. https://doi.org/10.1055/s-2004-828889.

[38] Puhalla H, Schuell B, Pokorny H, Kornek GV, Scheithauer W, Gruenberger T. Treatment and outcome of intrahepatic cholangiocellular carcinoma. Am J Surg 2005;189:173–7. https://doi.org/10.1016/j.amjsurg.2004.11.009.

[39] Yedibela S, Demir R, Zhang W, Meyer T, Hohenberger W, Schönleben F. Surgical treatment of mass-forming intrahepatic cholangiocarcinoma: an 11-year Western single-center experience in 107 patients. Ann Surg Oncol 2009;16:404–12. https://doi.org/10.1245/s10434-008-0227-1.

[40] Taylor-Robinson SD, Toledano MB, Arora S, Keegan TJ, Hargreaves S, Beck A, et al. Increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales 1968–1998. Gut 2001;48:816–20. https://doi.org/10.1136/gut.48.6.816.

[41] Shinohara ET, Mitra N, Guo M, Metz JM. Radiation therapy is associated with improved survival in the adjuvant and definitive treatment of intrahepatic cholangiocarcinoma. Int J Radiat Oncol Biol Phys 2008;72:1495–501. https://doi.org/10.1016/j.ijrobp.2008.03.018.

[42] Pitt HA, Nakeeb A, Abrams RA, Coleman J, Piantadosi S, Yeo CJ, et al. Perihilar cholangiocarcinoma. Postoperative radiotherapy does not improve survival. Ann Surg 1995;221:788–802. https://doi.org/10.1097/00000658-199506000-00017.

[43] Miyazaki M, Ito H, Nakagawa K, Ambiru S, Shimizu H, Shimizu Y, et al. Aggressive surgical approaches to hilar cholangiocarcinoma: hepatic or local resection? Surgery 1998;123:131–6. https://doi.org/10.1016/S0039-6060(98)70249-1.

[44] Stein DE, Heron DE, Rosato EL, Anné PR, Topham AK. Positive microscopic margins alter outcome in lymph node-negative cholangiocarcinoma when resection is combined with adjuvant radiotherapy. Am J Clin Oncol 2005;28:21–3. https://doi.org/10.1097/01.coc.0000139017.90599.f5.

[45] Cameron JL, Pitt HA, Zinner MJ, Kaufman SL, Coleman J. Management of proximal cholangiocarcinomas by surgical resection and radiotherapy. Am J Surg 1990;159: 91–7; discussion 97–8. https://doi.org/10.1016/s0002-9610(05)80612-9.