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Vascular resection and reconstruction in surgery for advanced intrahepatic cholangiocarcinoma – single center experience with 59 vascular resections

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ABSTRACT

Major vascular involvement in intrahepatic cholangiocarcinoma (iCCA) is often considered a relative contraindication to resection, resulting in limited data on hepatectomy with vascular resection and reconstruction. This study aimed to assess perioperative and long-term outcomes of hepatectomy combined with vascular resection and reconstruction in a high volume single center.

We retrospectively analyzed all patients undergoing surgical exploration for iCCA between 2008 and 2023, with follow-up through January 2025. Data were evaluated for vascular resections involving the portal vein, major hepatic veins, or inferior vena cava, and their impact on outcomes.

Among 345 explored patients, 265 (77 %) underwent resection with curative intent; 41 (16 %) required 59 vascular resections with reconstruction. Factors significantly associated with vascular resection included extent of hepatectomy, nodal status, tumor grading, and UICC stage. Vascular invasion was confirmed histologically in 37 % of resected vessels.

Ninety-day mortality was higher in the vascular resection group (15 % vs. 6 %), with biliary reconstruction identified as a key mortality risk factor. Median overall survival was 17 months for vascular resection patients versus 25 months without. Recurrence-free survival was similar between groups. Within the vascular resection group, macrovascular invasion was associated with worse survival (11 vs. 25 months).

The 5-year survival rate was 20 %, exceeding outcomes of palliative treatment. As only one-third of vascular resections showed confirmed macrovascular invasion, suspected vascular involvement should not be an absolute contraindication to resection. Nonetheless, caution is adviced when hepaticojejunostomy is required. Further studies are needed to assess outcomes following neoadjuvant therapy.

1. Introduction

Intrahepatic cholangiocarcinoma (iCCA) accounts for approximately 10 % of all primary malignant liver tumors, with a rising incidence in western countries [1]. Due to the late onset of symptoms, ICCAs are often diagnosed in locally advanced stages or even with extrahepatic spread [2,3]. Hence, prognosis of patients is poor with 5-year survival rates between 15 and 25 % in tumors confined to the liver, and below 5 % in cases with initial extrahepatic metastases [4,5].

Curative intent-resection is the current standard of care in the treatment of iCCA but these procedures can be highly demanding. Traditionally, major vascular involvement has been considered at least a relative contraindication to resection. With ongoing improvement in hepatobiliary surgery and, in particular, in vascular management due to

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the influence of transplantation surgery, the limits of surgical hepatectomy were progressively pushed and the indications for resection expanded [6]. The feasibility of combined hepatic and vascular resection for intrahepatic cholangiocarcinoma (iCCA) has been demonstrated (referring to Table 1); however, its impact on outcomes remains uncertain. This is particularly due to the limited availability of data on hepatectomy involving resection and reconstruction of major venous structures, such as the vena cava, portal vein, or major hepatic veins. Existing studies are largely based on small cohorts or multi-center analyses, where differences in surgical approaches and patient selection often limit the comparability of data and hinder the ability to draw definitive conclusions [7,8].

Furthermore, data on the frequency of true invasion of major hepatic vessels by iCCA is sparse. Notably, only one multicenter analysis has reported a histologically confirmed macrovascular invasion rate of 13.7 % in resected iCCA cases (Table 1) [9–11].

This study therefore aims to evaluate the impact of hepatectomy in combination with major vascular resection and reconstruction on the postoperative outcome and the oncological survival in patients with iCCA.

2. Materials and methods

This manuscript is written following STROCSS guidelines.

Data of patients who underwent surgical exploration for iCCA were prospectively collected in our institutional liver resection database. The observation period started in January 2008 and ended at the end of December 2023. Follow-up was conducted until January 2025 to allow at least one year of follow-up. The analysis was conducted in a retrospective fashion. Other malignancies such as perihilar or distal cholangiocarcinoma, hepatocellular carcinoma or gallbladder carcinoma were excluded from this analysis. iCCA any size were included. To distinguish centrally located iCCA from perihilar cholangiocarcinoma, tumor with contact/compression/or invasion of the liver hilum exceeding a diameter of 3 cm and with obvious origin from secondary or tertiary bile ducts (in preoperative imaging and/or histologically) were included as iCCA. Further histological differentiation in small duct or large duct type iCCA was omitted for this study [12]. Data analysis focused on vascular resections due to suspected tumor invasion. Only those cases involving both vascular resection and subsequent vessel reconstruction were included. Vascular resections due to anatomic reasons were excluded from the analysis.

All patients had signed informed consent that perioperative and follow-up data may be collected anonymously and used for scientific analyses. According to the regulations of the federal state law (state hospital law §36 & §37) and the independent ethics committee of Rheinland-Palatinate, no ethical approval is necessary for this study.

2.1. Preoperative work-up

For staging and resection planning, we preferred contrast enhanced multiphasic computed tomography (CT) of the abdomen and thorax. A majority of patients presented with the initial diagnosis made and imaging obtained at the referring center. We accepted externally produced CT scans or magnetic resonance imaging (MRI) whenever the imaging quality was considered sufficient by our radiologists. We did not seek preoperative histological confirmation through biopsy if resection seemed technically possible.

In some selected cases showing complex tumor growth or when extended vascular reconstruction seemed necessary, a 3-dimensional liver reconstruction model based on three-phase CT scans was produced prior to surgery for more accurate resection planning (Picture 1) [13].

2.2. Surgical procedures and definitions

Vascular reconstruction resection (VRR) was performed when invasion of the major hepatic vessels was suspected either by preoperative imaging (CT/MRI) criteria or upon intraoperative evaluation. All surgical explorations and resections were performed by a team of experienced surgeons with special expertise in hepatobiliary surgery. The type of vascular reconstruction was chosen depending on the pertinent intraoperative findings.

VRR was defined as surgical repair of a vascular defect >25 % of the lumen of the vessel. The surgical methods used were direct sutures (either longitudinal or transverse suture), patch plasty, end-end-anastomosis or inposition of a prothesis (Picture 2).

The approach to vascular reconstruction was selected according to the specific characteristics, type, and size of the vascular defect encountered. The reconstruction techniques varied based on the defect. Smaller defects were managed using direct suture (plasty), either alone or accompanied by flap graft coverage when additional reinforcement was necessary. For defects of moderate size or when the direct suture would constrict the vessel, a direct end-to-end anastomosis was preferred. Larger or more complex defects required the placement of an interposition graft to repair the vascular defect. Initially, synthetic grafts were frequently used due to their availability and ease of application. With increasing clinical experience our preference shifted. The risk of bacterial adherence to the synthetic surfaces and incidence of thrombosis under anticoagulation, potentially leading to graft occlusion led to favour biological derived materials. These preferred alternatives include peritoneum, autologous veins harvested from the patient, and bovine pericardium. These biological grafts provide enhanced biocompatibility and reduced thrombogenicity, contributing significantly to improved patient outcomes and graft longevity (Table 2) [14–16].

Table 1
Results of vascular resection in patients with intrahepatic cholangiocarcinoma – overview of literature.

Authors	Year	Center	Patients	Time period	Vascular resection n (%)	Histological proven infiltration	Post-OP mortality (90 days)[a]	OS
Ali SM	2013	Single center	121	1997–2011	14 (12 %)	not stated	1 (7 %)	32 months
Reames BN	2017	Multi center	1087	1990–2016	128 (12 %)	not stated	15 (12 %)	33.4 months
Hu LS	2018	Multi center	1089	1990–2015	Not stated	149 (macrovascular invasion)	not stated	118 patients >18 months
Conci S	2020	Multi center	270	1995–2015	31 (11.5 %)	24	9 (3.3 %)	30.1 % 5-year (CVR) 22.2 % 5-year (PVR)
Alikhanov R	2021	Single center	10	2016–2020	10 (100 %)	8 (80 %)	Not stated	4 > 12 months
Palen A	2021	Two centers	78	2010–2018	20 ICV only	not stated	2 (10 %)	78 % 1-year, 45 % 3-year, 32 % 5-year
Present	**2025**	**Single center**	**345**	**2008–2023**	**59 (17 %)**	**22 (37 %)**	**6 (15 %)**	**22.2 months 73 % 1-year, 37 % 3-year, 23 % 5-year**

[a] of patients with vascular resection; CVR = Vena cava resection; PVR = vena porta resection.

Table 2
The vascular resections and subsequent vessel reconstructions due to suspected tumor infiltration. Smaller defects were reconstructed using direct suture. For defects of moderate size or when the direct suture would constrict the vessel, a direct end-to-end anastomosis was preferred. Larger or more complex defects sometimes required the placement of an interposition graft if a direct end-to-end anastomosis was not possible (* autologous patch from resected portal vein; ** Interpositioning vein; ***graft from donor).

vessel	Number of resections	Type of resection		Type of reconstruction				
		tangential	tubular	end-end	Gore-tex	Direct suture	Pericardial patch	other
Vena cava	21	13				6	7	
			8	4	4			
major hepatic vein	17	12				9	2	1*
			5	4				1**
portal vein	21	3				2	1	
			18	17				1***

Liver resections were classified into minor, major and extended resections according to Reddy et al.: minor hepatectomies included resection of up to two liver segments, major hepatectomies resection of three to four liver segments and extended hepatectomies as any liver resection including more than four liver segments [17]. Pathology data were obtained from the official pathology report and reconfirmed by a senior pathologist in all cases. UICC stage was attributed according to the standard nomenclature of the AJCC/UICC 8th edition [18]. Overall survival was defined as the time from date of surgery to date of death or the last follow-up. Patients who were alive at the time of the last follow-up were censored. Recurrence-free survival was defined according to the definition of Punt's relapse-free survival: from the time of surgery to any event (recurrence, death from the same cancer, treatment-related deaths); second primary were ignored, and loss to follow-up was censored [19]. The postoperative morbidity and mortality was documented and analyzed according to the standardized classification of surgical complications by Clavien-Dindo [20].

Follow-up of all patients was continued until April 2024 or time of decease, respectively. Our routine follow-up features cross-sectional imaging every three months for at least two years after surgery.

2.3. Statistical analyses

Statistical analyses were performed with SPSS 29 (SPSS Inc., released 2020, IBM SPSS Statistics for Windows, Version 29.0, IBM Armonk, NY, USA: IBM Corp). The analysis of the morbidity and mortality and comparing features for the vascular resections were conducted with crosstabulation, Pearson chi-square test and exact fisher test. Overall survival and recurrence-free survival analysis was conducted with the Kaplan-Meier method and log-rank test. A p-value of <0.05 was considered significant.

3. Results

Within the study period, 345 patients underwent surgical exploration for iCCA. Curative intent-resections were possible in 264/345 patients (77 %). In 81 patients, iCCA were found to be irresectable due to peritoneal carcinomatosis or advanced intrahepatic tumor growth with a risk of a too small liver remnant. Fig. 1 shows a flow diagram of our cohort.

Regarding type of hepatectomy, 55 minor, 101 major, and 108 extended liver resections were performed. One patient underwent antesitum resection. In 53 patients, hepatectomy was combined with the resection of the hilar bifurcation requiring hepaticojejunostomy (Table 3).

3.1. Vascular resections

Single or multiple vascular resections (n = 59) were performed in 41 patients (16 % of 264 patients) due to suspected invasion as described above. In 30 cases, one major vessel was resected and reconstructed, in six cases two and in five cases three vessels.

VRR was significantly associated with the extend of resections as well as with nodal status and UICCA stage (Table 1). VRR were performed significantly more often in extended resections (30/108; 28 %) compared to major (7/101; 7 %) or minor resections (4/55; 8 %; P =

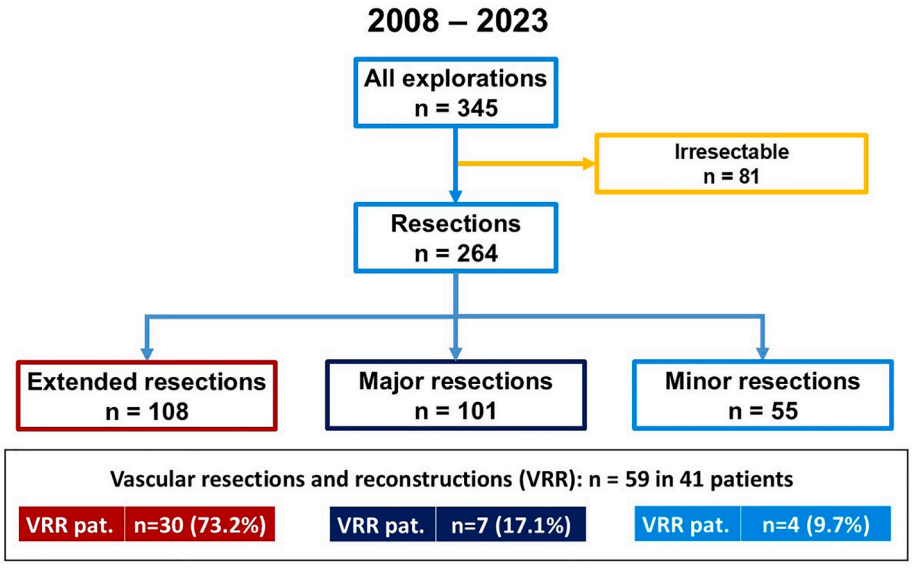


Fig. 1. A flow diagramm of our cohort of 345 patients and 264 curativ intent-resections.

Table 3
Patient characteristics of the resection group.

	Resection group	Vascular ext.	No vascular ext.	p-value
	n = 264	n = 41	n = 223	
Age (y), median [IQR]	64,8	68,9	64,3	p = 0.436
Gender (women/men)	132/132	24/20	110/110	p = 0.491
ASA classification (1/2/3/4)	1/117/136/7	1/14/23/3	2/103/112/4	P = 0.097
BMI (Body-Mass-Index)	26	26	26	P = 0.530
Neoadjuvant treatment yes/no	27/237	4/37	23/200	p = 0.666
Resections				
Extended resections	**108**	**30**	**78**	**p = 0.001** extended vs. major vs. minor
Right trisectionectomy	37	14	23	
Left trisectionectomy	47	14	33	
ALPPS	9	–	9	
Mesohepatectomy (ante-situm resection 1)	15	2	13	
Major resections	**101**	**7**	**94**	
Right hepatectomy	32	3	29	
Left hepatectomy	40	4	36	
Trisegmentectomy	29	1	28	
Minor resections	**55**	**4**	**51**	
Bisegmentectomy	39	3	36	
Monosegmentectomy	11	1	10	
Atypic/wedge resection	5	–	5	
Histology				
Solitary/Multifocal	193/66 (+5)	30/11	163/55 (+5)	p = 0.841
Number of nodules (median, [range])	1 (1–10)	1,0 (1–10)	1 (1- 10)	
Tumor size[a] (median, [range])	6,5 mm [0,4–20,0]	6,5 mm (0,4–18,0)	6,5 mm (0,4–20,0)	p = 0.801 <5 vs. ≥5 cm
Lymph nodes harvested (median, [range])	5 [0−31]	5 (0- 30)	5 (0–31)	
R-stage				p = 0.095
R0	207	27	180	R0 vs. R1
R1	54	14[b1]	40[b2]	
Rx	3	–	3	
T-stage				**p = 0.037**
T1a	47	4	43	T1/2 vs. 3/4
T1b	72	13	59	
T2	92	15	77	
T3	20	–	20	
T4	30	9	21	
Tx	3	–	3	
N-stage				**p = 0.014**
N0	162	21	141	N0 vs. N1
N1	73	19	54	
Nx	29	1	28	
Grading				**p = 0.026**
G1	4	–	4	G1/2 vs 3/4
G2	174	31	143	
G3	59	6	53	
G4	2	–	2	
no grading[c]	25	4	21	
UICC-stage				**p = 0.019**
Ia	33	2	31	I vs. II/ IIIa vs. IIIb/IV
Ib	49	8	41	
II	57	8	49	
IIIa	12	–	12	
IIIb	76	22	54	
IV	14	1	13	
Ux[d]	22	–	22	

[a]of largest nodule (if multifocal).
[b1]R1 parenchymal 13 cases, 1x R1 vascular.
[b2]R1 parenchymal 38 cases, 6x R1 vascular, 6x R1 ductus hepaticus.
[c]because of neoadjuvant treatment.
[d]Patients with Nx were not UICC classified; significant p-values are bold (≤0.05).

0.001). In minor hepatectomies, VRR was performed in repeated hepatectomy (after major hepatectomy as first resection) in two cases or when iCCA was located in the caudate lobe. A positive lymph node status (N1) was histologically present in 19/41 (46 %) of patients with VRR compared to 54/223 (24 %) in the NVRR group (p = 0.004), and 23/41 (56 %) of patients of VRR were grouped in UICCA-Stage IIIb or IV versus 67/223 (30 %) in the NVRR group (P = 0.004).

Biliary resection and reconstruction were performed in 12/41 (29 %) of patients with and in 41/223 (18 %) of cases without VRR (P = 0.166).

Histological examination confirmed vascular invasion in 22 of 59 (37 %) resected vessels. This included 10/21 inferior vena cava, 5/17 major hepatic veins and 7/21 portal veins. (Table 3).

3.2. Morbidity and mortality after vascular extended resections

Major complications (Dindo III-IV) occurred in 10/41 (24 %) of cases with VRR compared to 23/223 (10 %) in the NVRR group (P = 0.002; mortality excluded). Postoperative bleeding occurred significantly more often after VRR than after NVRR with 9 % versus 2 % (P = 0.016), while portal vein thrombosis, sepsis and multi organ failure (MOF) did not. 90-day mortality occurred in 22 (8 %) of all cases, 6 (15 %) in the VRR cohort and 16 (6 %) in the NVRR cohort. The difference in mortality between VR and NVRR was statistically significant. In 6 fatalities in the VRR group, 5 patients died from MOF/sepsis and one patient (ante-situm resection) from intraoperative cardiac decompensation (Table 4). The need for additional hepaticojejunostomy (HJ) was a significant risk factor for mortality (P < 0.001) in both groups, with (mortality VRR with HJ 3/12 (25 %) vs. without HJ 3/29 10.3 %)) and without VRR (mortality NVRR with HJ 8/41 (19.5 %) vs. without HJ 8/182 (4.4 %)).

3.3. Overall survival (OS) and recurrence-free survival (RFS)

The median overall survival (OS) was 24 months in all patients (95 % CI: 19.1579 to 27,895), 17 months in the VRR group (95 % CI: 5.923 to 33.648) and 25 months in the NVRR group (95 % CI: 19.389 to 30.320) (P = 0.208; Fig. 2). 1-, 3-, and 5-year OS survival was 73 %, 37 % and 23 % in all, 60 %, 35 % and 20 % in VRR and 76 % 38 % and 23 % in NVRR. Patients with VRR and histologically confirmed vascular invasion had a

Table 4
Overview of the cases of postoperative death in VRR.

Year of surgery	Resection	New world	BDA	PV	MHV	IVC	Infiltration	Reason POD
2009	Extended Right	H145678-PV-B	yes	e-e	⦰	⦰	Yes, PV	liver failure
2014	Mesohepatectomy (ante situm)	H48-IVC	⦰	⦰	Gore tex	Gore tex	Yes, IVC + MHV	cardiac failure
2015	Extended right	H45678-PV-IVC	⦰	e-e	⦰	patch	Yes, IVC	liver failure
2017	Extended Right	H45678-PV-MHV-B	yes	e-e	patch	⦰	No	liver failure
2018	Right hepatectomy	H5678-PV	⦰	recon	⦰	⦰	Yes, PV	PVT, liver failure
2022	Extended Left	H12345′8′-PV-B	yes	e-e	⦰	⦰	No	MOF

MOF = multi organ failure; PVT = portal vein thrombosis; e-e = end to end anastomosis.

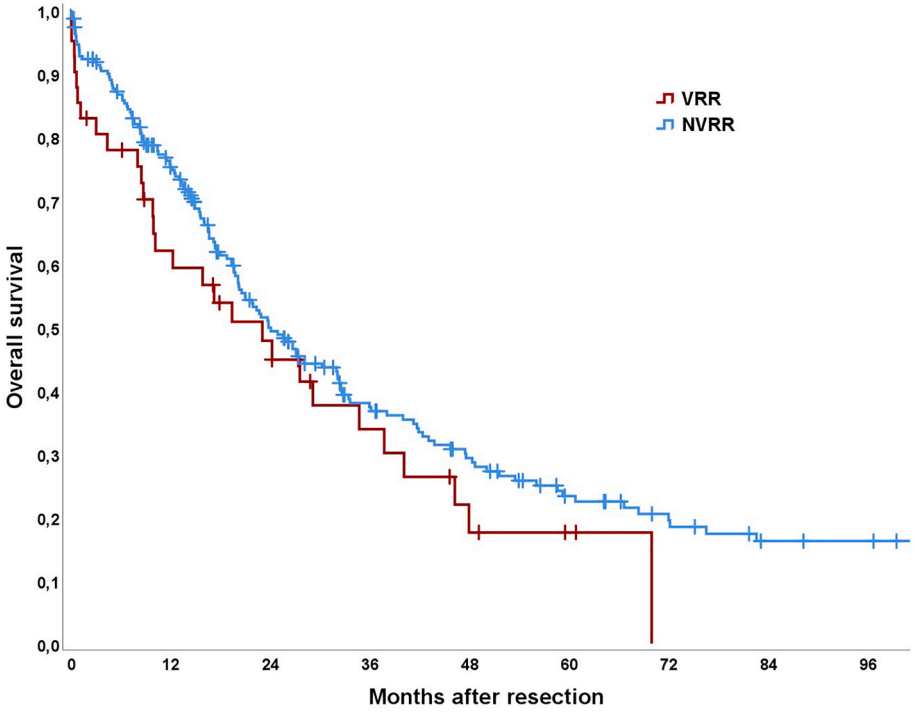


Fig. 2. Overal survival of VRR versus NVRR after curativ intent-resection, in months.

median OS of 9 months (95 % CI: 6.428 to 12.443) compared to 24 months in VRR patients without infiltration (95 % CI: 8.394 to 39.935; P = 0.040). Comparing OS for patients without vascular infiltration, the median OS for VRR without infiltration was 24 months (95 % CI: 8.394 to 39.935) to NVRR without infiltration with a median OS of 26 months (95 % CI: 19.294 to 31.731; P = 0.136; Fig. 4 in Appendix).

Median OS in node negative patients was significantly better than in lymph node positive (31 months; (95 % CI: 25.086 to 39.089) versus 18 months (95 % CI: 13.683 to 20.903; P = 0.003). The best median OS was in node negative tumors without vascular invasion (33 months; 95 % CI: 27.786 to 37.113), the worst in nodal positive tumors and macrovascular invasion (12 months, 95 % CI: 7.645 to 16.815; n = 10; P = 0.025). In patients having a R1 resection and nodal positive iCCA the median OS was 15 months (95 % CI: 9.432 to 20.35; n = 16).

Within the observation period tumor recurrence occurred in 156/264 (59 %) of patients. The median recurrence-free survival (RFS) was 10 months (95 % CI: 7.989 to 11.934) in all patients, 11.5 months (95 % CI: 3.134 to 19.814) in the VRR group and 9.8 months in the NVRR group (95 % CI: 8.073 to 11.587; P = 0.791; Fig. 3). 1-, 3-, and 5-year RFS survival was 32 %, 13 % and 6 % in all, 30 %, 7 % and 0 % in VRR, 32 %, 14 % and 8 % in NVRR. Patients with VRR and histologically confirmed vascular invasion had a median RFS of 8.3 months (95 % CI: 3.795 to 26.386) compared to 10 months in VRR patients without infiltration (95 % CI: 1.317 to 18.080; P = 0.255). Patients with proven vascular invasion showed no significant difference for RFS compared to all patients without (10.3 months; 95 % CI: 7.055 to 13.460; vs. 9.8 months, 95 % CI: 7.556 to 12.104; P = 0.846). Comparing RFS for patients without vascular infiltration, the median RFS did not differ (VRR without infiltration 10 months; 95 % CI: 7.553 to 12.108; NVRR without infiltration 10 months 95 % CI: 0.000 to 32.231; P = 0.903; Fig. 5 in Appendix).

4. Discussion

Of all patients receiving resection with curative intent, in 16 % (41 patients) 59 vascular resections were required because of suspected tumor infiltration. Only in 37 % of the suspected cases with vascular tumor infiltration macrovascular invasion was histologically confirmed. Factors associated with VRR included extent of hepatectomy, N-status, tumor grading, and UICC stage. The 90-day mortality was higher in VRR patients (15 % vs. 6 %), with biliary reconstruction being a significant mortality risk factor. Median OS was 17 months for VRR patients versus 25 months for non-VRR. While median RFS did not differ, macrovascular invasion in VRR-patients correlated with poorer OS (9 vs. 24 months) and RFS (8.3 vs. 10 months).

This study presents a large single center experience with 59 vascular resections in 41 out of 264 (16 %) patients undergoing surgical resection for iCCA. The higher proportion of vascular resections in our series is likely attributable to the inclusion of resections and reconstructions involving a major hepatic vein. It should be noted that reconstruction of

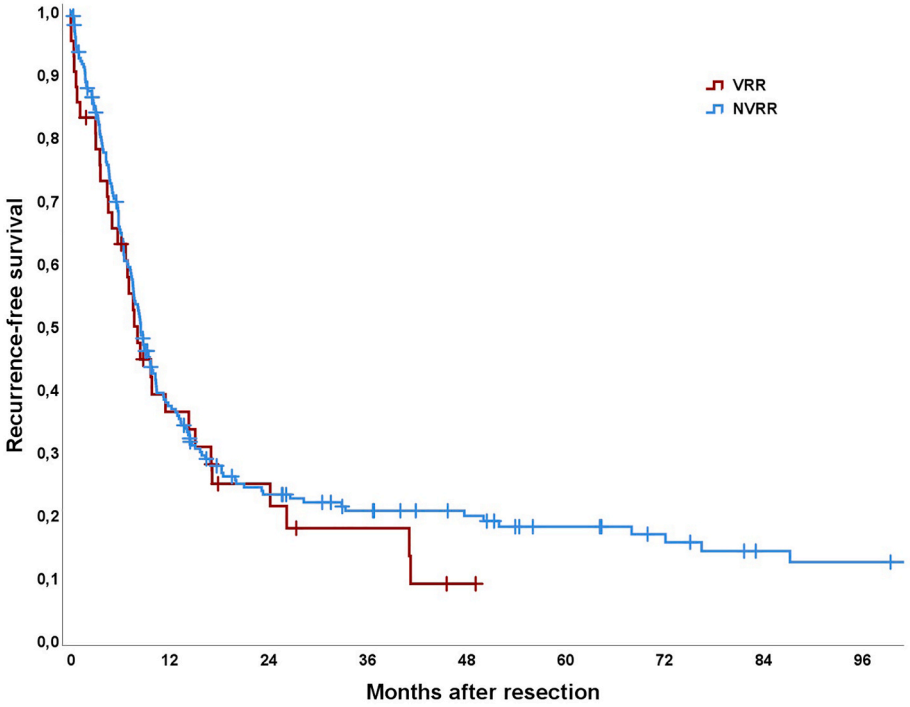
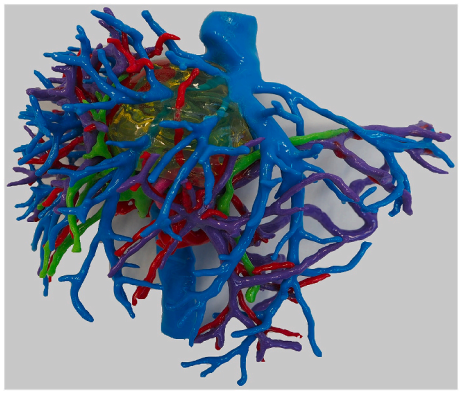


Fig. 3. Recurrence-free survival of VRR versus NVRR after curativ intent-resection, in months.



Picture 1. Printed 3D reconstruction of a patient with a central cholangiocellular carcinoma that received extended right hemihepatectomy with resection of the bile duct and bilioenteric diversion, resection and reconstruction of the portal vein and reconstruction of the remaining left hepatic vein.

Picture 2. Reconstruction of the vena cava inferior with patch plasty.

a major hepatic vein was performed only in cases where preserving the vein was deemed essential for patient survival (quo ad vitam). Even when limiting the analysis to resections of the vena cava and the portal vein, 33 out of 264 patients (12.5 %) required reconstruction of these vessels, which is still higher than reported in other studies. This, along with the greater number of additional biliary reconstructions performed in conjunction with vascular resections, may reflect a more aggressive surgical approach at our center.

The primary limitation of our study is its retrospective design. While it represents the largest single-center analysis conducted to date, the sample size remains relatively small, and the study cohort is too heterogeneous to draw definitive treatment recommendations.

Surgical radicality is a major prognostic determinant after resection for iCCA amongst other well know non-surgical factors such as nodal status, multifocality, and number and intrahepatic distribution of tumor nodules. Especially in locally advanced tumors, however, radicality can only be achieved by extending hepatic resection to the major bile ducts or major blood vessels which comes at the expense of an increased perioperative morbidity and mortality of an otherwise fairly low-risk hepatectomy-only procedure. With regard to a questionable oncological benefit and an undoubtedly increased perioperative risk, the role of extended resections is controversial and considered as contraindicated by many. Data on whether such procedures should be performed at all, and under which circumstances they are indicated, are scarce [6,8,14,15,21–23].

Resections and reconstructions of a major vessel was performed only when invasion of the vessel was suspected, and if considered necessary to achieve tumor-free margins whilst preserving sufficient functional liver parenchyma. Factors such as surgical extent, positive lymph node status, and advanced UICC stage significantly influenced the need for VRR. The 16 % rate of vascular resections and reconstructions is higher than in previous reports where it ranged from 7.7 % to 11.8 % [7,8,24,25]. The higher proportion of vascular resections in our series is likely attributable to the inclusion of resections and reconstructions involving

a major hepatic vein.

In this present series, the postoperative morbidity and mortality of resections with vascular extensions was higher than in most reported data. Considering that 68 % of the vascular resections/reconstructions were carried out in extended resections, many of them in combination with biliary reconstruction, our findings are in a similar range with those of a multicenter study reported by di Benedetto et al. who found a 90-day-mortality of 13.8 % after hepatic resection combined with resection and reconstruction of the IVC [26]. It is noteworthy that in di Benedetto's multicenter analysis, only 44 % of patients had iCCA. Our analysis identified the combination of extended hepatectomy with both vascular and biliary reconstruction as the most significant risk factor for postoperative morbidity and mortality. In such cases, postoperative mortality exceeded the 10 % threshold, which aligns with surgical outcomes observed following complex hepatectomy for perihilar cholangiocarcinoma. In light of these findings, we have adopted a more conservative approach. Hepatectomy combined with vascular and biliary reconstruction is now reserved for highly selected patients.

Most published studies on hepatectomy with vascular resection/reconstruction on iCCA did not report the rate of true i.e. histology-proven invasion [25]. Performing vascular resection upon suspicion of vascular invasion by either preoperative radiologic or intraoperative criteria, the actual rate of histology-proven vascular invasion was 37 % in our series. We conclude that patients with suspected vascular invasion should not be excluded from resection a priori, as nearly two-thirds of these patients ultimately do not exhibit vascular invasion. Given the challenges in reliably predicting vascular invasion, vascular resection and reconstruction appear to be justified in all cases where involvement of major vascular structures is suspected. This is particularly relevant since surgical detachment of the tumor from major vascular structures, resulting in an R1 vascular margin, is - unlike in cases of CRLM - associated with a higher risk of local recurrence and reduced OS [27].

Patients undergoing hepatectomy combined with vascular resection/reconstruction had a tendency towards a shorter survival [28]. Our data with a median OS of 9 months for patients with VRR and proven infiltration are worse than multicentric data of Hu et al., who found a median OS 21 months in patients with macrovascular invasion. However, this study cannot be used for comparison due to differences in the study design [9]. While Hu et al. analyzed macrovascular invasion in hepatectomy-only specimens, our VRR data exclusively pertain to cases where invasion of a major vessel necessitated resection and reconstruction. This distinction may serve as a surrogate marker for both a less favorable oncological prognosis and increased surgical complexity in our series.

In this context, our approach can be considered a final surgical option in cases that would otherwise be treated palliatively. For obvious reasons, there is no reliable evidence of macrovascular invasion in patients managed solely with chemotherapy, with or without immunotherapy or targeted therapy. Consequently, defining a suitable reference group for comparison with our surgical outcomes presents a significant challenge.

In our series patients with vascular resection/reconstruction had significantly more advanced tumors. Furthermore, the analysis of our data showed that the prognosis after vascular resection in nodal positive tumors is poor. This corresponds well to results of the Italian multicenter study of Conci et al. who found the worst results with a median survival of 8.5 months in patients having a R1 resection and nodal positive iCCA [7]. In our series, the median OS in these patients was 15 months. As a result, we have adopted the following strategy: If suspicious lymph nodes are identified during surgical exploration, they are harvested and sent for frozen section analysis. In cases of confirmed nodal positivity, combined with the requirement for technically complex vascular reconstruction or additional biliary reconstruction, we typically refrain from proceeding with resection. In rare cases with strong evidence of nodal positivity in the preoperative imaging a diagnostic laparoscopy (or laparotomy if needed) would be planned to harvest the suspicious lymph nodes. This is to avoid futile and potentially harmful up-front surgery precluding necessary systemic treatment which can eventually increase resectability and help to select patients that benefit from secondary resection. Instead, we opt for neoadjuvant therapy as the preferred course of action. Data on the clinical course following neoadjuvant therapy in patients with nodal-positive disease remains limited to date. Emerging evidence supports that neoadjuvant treatment increases the chances oncological resection by potentially downstaging the disease and improving resectability [29,30].

Although data of neoadjuvant and downsizing treatment are limited so far, recent studies have shown that patients with locally advanced iCCA and larger tumor masses may benefit from neoadjuvant therapy [31,32]. Recent advances in systemic treatment, in particular in immunotherapy, i.e. after treatment with Gemcitabin, Cisplatin plus the Anti-PD-L1 antibody Durvalumab, as in the Topaz-1 trial or GemCis plus Anti-PD-1-antibody Pembrolizumab, as in the Keynote-966-study are promising and give reason for improvements in both the palliative as well as the neoadjuvant setting [33–35]. In our group resection of iCCA was performed after pretreatment in 27 patients, mainly with chemotherapy only. Survival data are similar to those after upfront surgery, but it has to be mentioned that pretreatment was not neoadjuvant treatment of a resectable iCCA but downsizing therapy of an initially irresectable tumor, thus indicating more advanced tumors. The need for vascular resection and reconstruction did not differ significantly between patients with and without neoadjuvant treatment. None of the resected vessels initially suspected of invasion following neoadjuvant chemo-/-immunotherapy demonstrated histological evidence of macrovascular invasion. However, the total number of resections performed after tumor downsizing was too limited to draw definitive conclusions.

Similarly, for adjuvant treatment, although not specific for iCCA only, progress in adjuvant therapy may also improve results. Recently, longterm-results of the BILCAP-study with a median survival of 49.6 months in the treatment group (postop. adjuvant treatment with Capecitabin) versus 36.1 months in the control group suggested a further improvement of results after resection [36]. In our study group adjuvant treatment with Capecitabin, although routinely recommended since 2018, has not been administered frequently, thus making it difficult to assess any effect.

In summary, our finding of a 5-year OS of 20 % after complex vascular resection and reconstruction, a result which cannot be achieved by any palliative treatment option, still justifies surgical resection in advanced iCCA with suspected invaded major vascular structures. If there is a need for additional biliary reconstruction, which clearly increases the perioperative morbidity and mortality in our experience, the indication for surgery must be carefully evaluated balancing risk against benefit. If there is confirmed evidence of nodal involvement, we believe the patient is not a candidate for upfront surgery. Our data clearly demonstrate that aggressive surgery alone yields unsatisfactory survival outcomes, highlighting the necessity for adjunctive therapies. Recent advancements in adjuvant and neoadjuvant treatments, particularly with immunotherapy and targeted therapies, offer hope for improving the prognosis of patients with advanced iCCA involving major vascular structures.

5. Conclusion

To our knowledge, this represents the largest series of hepatectomy combined with vascular resection and reconstruction (VRR) reported in the Western world. The 5-year overall survival rate in our cohort was 20 % following complex vascular resection and reconstruction, surpassing the outcomes of current palliative treatment options. Prognosis for histologically confirmed macrovascular invasion and after vascular resection in nodal positive tumors was associated with poorer outcomes. Importantly, as only one-third of patients undergoing VRR had macrovascular invasion, our findings suggest that suspected vascular invasion should not be regarded as an absolute contraindication for resection.

However, the decision to perform vascular resection and reconstruction should be approached cautiously, particularly when additional hepaticojejunostomy is required or nodal involvement confirmed. Further studies are required to assess histological outcomes regarding suspected vascular infiltration, OS and RFS in advanced iCCA, with recent advancements in neoadjuvant treatments, including immunotherapy and targeted therapies.

CRediT authorship contribution statement

Hauke Lang: Conceptualization, Validation, Writing – original draft, Writing – review & editing, Supervision, Project administration. **Lisa-Katharina Gröger:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Beate K. Straub:** Investigation. **Tobias Huber:** Investigation. **Rabea Margies:** Investigation. **Constantin Scholz:** Methodology, Formal analysis, Writing – review & editing. **Friedrich Foerster:** Resources. **Arndt Weinmann:** Resources. **Katja Oberholzer:** Resources. **Janine Baumgart:** Resources. **Jens Mittler:** Resources. **Fabian Bartsch:** Methodology, Software, Investigation, Writing – review & editing, Supervision, Project administration.

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Declaration of competing interest

Prof. Dr. Beate Straub received honoraria from Bayer Healthcare, AstraZeneca, Bistrol Myers Squibb and IMPP.

All other authors declare that there is no conflict of interest regarding the publication of this paper."

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2025.110193.

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