Failure patterns after curative resection for intrahepatic cholangiocarcinoma: Possible implications for postoperative radiotherapy

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Abstract

Objectives: To document the patterns of failure，identify sites at highest risk of recurrence following curative resection of intrahepatic cholangiocarcinoma (IHCC), in order to guide adjuvant postoperative radiotherapy (PORT). Methods: Patients with IHCC who had undergone radical surgery at our institution from July 2010 to August 2017 were retrospectively analyzed. The survival and prognostic factors were evaluated using univariate and multivariate analysis. All sites of recurrence were recorded and classified including the surgical margin, regional lymph nodes, liver remnant and distant metastasis. The sites at highest risk of recurrence form the basis of the target volume of potential adjuvant radiotherapy. Results: The median follow-up time was 23.5 months (2-85 months). The median recurrence free survival (RFS) and overall survival (OS) were 12.1 months and 24.8 months, respectively. Seventy-three (73/127, 57.5%) IHCC patients developed tumor recurrence. The number of initial recurrences occurring in the potential PORT volume, remnant liver and distant sits were 46 (46/73, 63.0%), 36 (36/73, 49.3%) and 22 (22/73, 30.1%) cases, respectively. Of the 46 patients whose initial recurrence were inside the potential PORT volume, 29 (29/73, 39.7%) developed recurrence confined to the potential PORT volume, including 13 tumor bed recurrences, 7 lymph node metastases, and 9 with both tumor bed recurrences and lymph node metastases. The most common lymph node metastases were nodes around the abdominal aorta, followed by lymph nodes along the celiac artery, the common hepatic artery, and in the hepatoduodenal ligament. Conclusions: A high proportion of the recurrences occurred only within the potential PORT volume, implying that adjuvant radiotherapy might improve local-regional control. It seems reasonable to include surgical margins and lymph node stations No.16a2, 9, 8, 12, 13, and 14 in the radiation treatment volume.

Introduction

Intrahepatic cholangiocarcinoma (IHCC) is an uncommon neoplasm, accounting for 5-10% of all cholangiocarcinomas [1, 2]. Prior studies estimated that IHCC made up a minority of cholangiocarcinomas (CCAs) [2]. More recent assessments showed the incidence of IHCC may be rising across the globe [3-5]. Owing to the intrahepatic location of IHCC, early symptoms are rare and most patients present with advanced tumors [6, 7]. IHCC has a dismal survival with limited treatment options. There is a very high rate of both recurrence and metastases [8, 9]. The mainstay of treatment of IHCC is surgical excision. Definitive roles for adjuvant chemotherapy and radiotherapy have not been found, although both are used in daily practice [10, 11].

The literature on adjuvant radiation therapy for IHCC is sparse. In the few retrospective reports found in the English literature through Pubmed, the role of postoperative radiotherapy remains controversial. Shinohara et al. analyzed 3839 patients with IHCC and found improved median OS with adjuvant radiotherapy compared to surgery alone (11 months vs 6 months, p=0.014) [12]. Two other smaller studies also reported benefit of adjuvant radiotherapy for postoperative IHCC [13, 14]. But a meta-analysis found no significant improvement in overall survival using adjuvant treatment (chemotherapy, radiation or both)

compared with surgery alone [15]. Another study conducted by Hammad et al. reported that adjuvant radiotherapy was associated with improved survival for patients with R1/R2 resection, but not for those with R0 resection [16]. To date, there is no prospective randomized study concerning the benefit of adjuvant radiotherapy for IHCC patients. Study on IHCC post-operative failure pattern will help to optimize adjuvant treatment strategies. If the rate of local recurrence is high, adjuvant radiotherapy may be engaged to improve local control. On the contrary, systematic chemotherapy should be considered if distant metastases are the predominant mode of failure.

In the present study, failure patterns of 127 postoperative IHCC patients were retrospectively analyzed, with the aim of providing more reference information for the design of adjuvant treatment.

Methods And Materials

Patients

This study was approved by the Institutional Review Board of the Second Affiliated Hospital, Zhejiang University School of Medicine (SAHZU). From July 2010 to August 2017, 182 patients had undergone surgery for intrahepatic cholangiocarcinoma at SAHZU. Histopathological diagnoses were achieved after surgery. The medical records were retrospectively reviewed. 127 patients who underwent radical resection, with at least 2-month follow-up were included. Data regarding the surgical resection performed and information including sex, age, tumor stage, T classification, N classification, tumor differentiation, resection margins, tumor size, recurrence time, tumor markers, history of hepatitis, hypertension, diabetes, bile duct stone, jaundice, fever and whether postoperative chemotherapy was given were collected. Tumor staging was performed according to the guidelines of the American Joint Committee on Cancer (AJCC) Seventh edition [17] . Follow-up period ended on February 8, 2018. The documentation of recurrence is mainly based on imaging findings and clinical manifestations. RFS was measured from the day of operation to tumor recurrence, and OS from the day of operation to patient's death or last follow-up. Long-term follow-up and patient status were determined by physician follow-up visits. Specific sites of first disease recurrence, time to disease recurrence, OS and RFS were analyzed.

Recurrence patterns

In the present study, the term “local-regional recurrence” was not used, as retroperitoneal lymph nodes recurrences are classified as distant metastases according to the 8th edition of the AJCC staging system. Instead, we use “potential volume of postoperative radiotherapy (PORT)” which emcompass surgical margins, and high-risk lymphatic drainage area including the retroperitoneal nodal sites. The site(s) of initial disease recurrence, determined from cross-sectional imaging studies (CT, MRI or PET-CT) were recorded and classified according to whether they are recurrences inside the potential PORT volume, residual liver, and distant recurrence. Biopsies of recurrent lesions for pathological documentation were encouraged. Radiologic evidence of tumor recurrence (suspicious new findings and progression of

disease documented by serial imaging) was also accepted in patients who did not undergo biopsy. The date of initial disease recurrence was recorded as the time when the first suspicious radiologic finding was initially identified.

Statistical analysis

The correlation of patient characteristics with progression-free survival and overall survival were examined using Kaplan Meier analysis. Patient characteristics include tumor stage, lymph node status, tumor differentiation, nerve invasion, vascular invasion, tumor size, recurrence time, tumor markers, history of hepatitis, schistosomiasis, hypertension, diabetes, gallstones, bile duct stones, jaundice, fever, etc. Significance was evaluated using the log-rank test. Cox proportional hazards models was used for multivariate survival analysis. Statistical significance was defined as a p value<0.05. IBM SPSS Statistics 19.0 was used for statistical analyses.

Results

Patient characteristics

The demographics of the 127 patients are summarized in Table 1. There were 64 men (50.4%) and 63 women (49.6%). The median patient age was 58 years old (range, 26-83 years old). Preoperative tumor markers examination was done in 125 cases, elevated CA-199 and CEA were detected in 82 (67.8%) and 36 (29.8%) cases, respectively. The mean tumor size was 4.5 cm (range 1.0-11.0 cm), of which 43 (33.9%) had a tumor ≥ 5 cm. The differentiation of the IHCC was as follows: poor, 42 cases (33.1%); moderate, 52 cases (40.9%); well, 15 cases (11.8%); unknown, 18 (14.2%). Distribution according to T stage was as follows: T1, 35 cases (27.6%); T2, 56 cases (44.1%); T3, 33 cases (26.0%); and T4, 3 cases (2.4%). Lymph nodes metastasis was found in 41 of the cases (32.3%). According to the TNM staging, patients with stage I, II, III, and IV disease were 28 (22.0%), 34 (26.8%), 21 (16.5%), and 44 (34.6%) cases, respectively. Twenty eight patients received adjuvant chemotherapy.

Initial Disease Recurrence

Seventy-three (73/127, 57.5%) IHCC patients developed tumor recurrence. Disease progression was mainly documented by serial imaging in 65 patients (65/73, 89.0%), while 8 patients (8/73, 11.0%) had biopsy confirmation. Table 2 and Figure 1 show the anatomic locations of all initial tumor progressions.

Initial recurrences occurring in the potential PORT volume, remnant liver and distant sits were 46 (46/73, 63.0%), 36 (36/73, 49.3%) and 22 (22/73, 30.1%) cases, respectively. Among them, 20 cases had multiple sites of initial disease recurrence. Fifty-four patients had no evidence of disease at the last follow-up.

Of the 46 patients whose initial recurrence were inside the potential PORT volume, 29 (29/73, 39.7%) developed recurrence only inside the potential PORT volume, including 13 tumor bed recurrences, 7 lymph node metastases, and 9 with both tumor bed recurrences and lymph node metastases. Three had synchronous recurrences at remnant liver. Another 3 had synchronous recurrences at distant sites, and 11 had synchronous recurrences at remnant liver and distant sites.

Thirty-six patients developed initial recurrence in the remnant liver. Among them, 19 had remnant liver lesions as the only recurrences, 3 had synchronous recurrences in the potential PORT volume, another 3 had synchronous recurrences at distant sites, and 11 had synchronous recurrences at distant sites and the potential PORT volume.

Twenty-two had distant metastases at initial recurrence, 5 of them were distant metastases only (4 lung, 1 peritoneum), 3 had synchronous recurrences in the potential PORT volume, another 3 had synchronous remnant liver recurrences, and 11 had synchronous recurrences in the potential PORT volume and remnant liver.

The common sites of nodal metastases were lymph nodes around the abdominal aorta (station No.16, n=18), lymph nodes along the celiac artery (No.9, n=13), lymph nodes along the common hepatic artery (No.8, n=11), lymph nodes in the hepatoduodenal ligament (No. 12, n=8), lymph nodes on the posterior aspect of the pancreatic head (No.13, n=4) and lymph nodes at the root of the mesentery (No.14, n=2). All patients with station No.16 recurrences had metastatic lesions at other lymph node stations or distant sites. Among them, 11 cases had lesions in No.16a2 with no metastases in No.16b1, 6 had lesions in No.16a2 and No.16b1. Only 1 case had lymph node metastases at station No.16b1 without lesion at No.16a2, but that patient had multiple metastatic nodes on the posterior aspect of the pancreatic head.

Follow-up and Survival

The median follow-up time was 23.5 months (range 2-85 months). At the last follow-up on February 8, 2018, 59 patients were alive. The median recurrence free survival (RFS) and overall survival (OS) were 12.1 months and 24.8 months, respectively. In the univariate analysis of the entire cohort, improved survival was associated with age ≥ 55 years (RFS, 18.5 vs 10.0 months, p=0.046; OS, 34.8 vs 18.6 months, p=0.002) (Fig. 2), tumor size < 5cm (RFS, 19.8 vs 6.7 months, p=0.001; OS, 28.8 vs 21.5 months, p=0.071) (Fig. 3), no lymph node metastasis (RFS, 21.2 vs 6.1 months, p<0.001; OS, 40.2 vs 11.5 months, p<0.001) (Fig. 4), no history of hepatitis (RFS, 17.6 vs 10.4 months, p=0.005; OS, 25.2 vs 19.0 months, p=0.079) (Fig. 5), early tumor stage (stages I and II vs stages III and IV, RFS, 30.2 vs 7.7 months, p<0.001; OS, 45.5 vs 15.7 months, p<0.001) (Fig. 6) and better tumor differentiation (poor vs moderate vs well, RFS, 6.7 vs 15.6 vs 51.7 months, p=0.027; OS, 19.4 vs 28.8 months, not reached for well differentiation patients, p=0.003) (Fig. 7). The results of the univariate analysis are summarized in Table 3. In the multivariate analysis, RFS of tumor size (RR 2.191; 95% confidence interval [CI] 1.257-3.817; p=0.003) and tumor differentiation (RR 0.621; 95% confidence interval [CI] 0.408-0.947; p=0.027) reached statistical

significance. OS of age (RR 0.418; 95% confidence interval [CI] 0.236-0.740; p=0.003) also reached significance.

Discussion

This study analyzed the failure patterns of IHCC patients after they underwent curative resection. Tumor recurrences were found in up to 60% of the patients. Failures inside the potential PORT volume were found to be the most common sites of initial recurrences, followed by metastases in remnant liver and distant sites. Our findings suggest possible targeting of postoperative radiotherapy for IHCC patients.

The frequency of postoperative failures in IHCC, including local-regional recurrence and remnant liver dissemination or distant metastases, has been reported to range from 53.5% to 80.0% [18-22]. Our results, with 57.5% of IHCC patients developing postoperative recurrence, are in line with previous reports. For radiation oncologists, data on the specific patterns of recurrence can help guide postoperative therapeutic targeting. According to the study by Hyder et al, the most common recurrent site after surgery of IHCC was intrahepatic [21]. Doussot et al reported a time dependent recurrence pattern. Recurrence within 24 months most often involved the liver (82.7%), whereas recurrences after 24 months were mostly extrahepatic (61.1%) [22]. Recently, high local-regional recurrent rates, 62.5% and 68% of the total failures have been reported [18, 19]. The proportion of local-regional recurrence varies. Different statistical methods may explain the inconsistent results. For example, marginal recurrences are usually counted as local failures. But sometimes they are included in the intrahepatic failures. Furthermore, results could differ from whether initial recurrences or cumulative events are counted. In our study, recurrences in the potential PORT volume, i.e., surgical margins recurrence, regional and retroperitoneal lymph node metastasis, were found to be the most common relapse sites, accounting for 63% of the initial failures. That is consistent with the results of Song [18] and Luvira [19]. Chen et al. analyzed 320 surgical cases of IHCC with clinically negative lymph node (T1–3N0M0) and observed 76 cases developed lymph node metastasis (LNM) (76/320, 23.8%). They also found histological differentiation, tumor boundary and tumor size significantly correlated with LNM [23]. Postoperative local-regional recurrence for IHCC seems to be common, which suggests a potential role for adjuvant radiotherapy, especially for those with high risk factors.

It is worthwhile pointing out that up to 40% of the recurrences in our patient population occurred only inside the potential PORT volume, without failures in remnant liver nor distant sits. Similar figures could be found in the literature. In the report by Song et al [18], the incidence of local-regional recurrence only as the first site of failure was 33%, which was also the dominant pattern of failure for their patient series. In addition, 18 (18/66, 27.3%) of their patients had non-regional lymph node metastases. The majority of such non-regional nodes could be inside the potential PORT volume. Together with the above mentioned 33% of the cases, the proportion of recurrence confined inside the radiation volume could be around 50%. In another study by Luvira et al [19], recurrences occurring only at surgical margin and regional lymph node account for 27.5% of the total failures. However, 15% of the patients had aortocaval regional lymph

node metastases alone or with surgical margin and regional lymph node metastases. So a total of 42.5% of the patients had recurrences confined to the potential PORT volume. Taken together, about 40% of the IHCC patients recur strictly inside the potential PORT volume as the first site of failure. These findings suggest adjuvant radiotherapy might improve local-regional control.

The target volume of adjuvant radiotherapy was proposed based on the local recurrence pattern, which mainly includes the tumor bed, and the corresponding high-risk lymphatic drainage areas. According to our findings, the most common sites of lymph node metastases were stations No.16, 9, 8, 12, 13, and 14, these lymphatic drainage areas should be included in the radiation volume (Figure 8). Station No.16b1 metastases rarely recurred in isolation. They relapsed as a consequence of lymph flow reflux due to metastases in the above mentioned node stations. We speculate that station No.16b1 metastases might be prevented or reduced if the area inside the proposed radiation volume is under control. Therefore, it might be reasonable not to encompass station No.16b1 in the potential PORT volume. Since lymphatic drainage areas classified as distant metastases were included in the proposed radiation volume, the term “potential volume of PORT” was used instead of one stressing “local-regional recurrence”.

In our study, 44 patients developed recurrences outside the potential volume of PORT. For these patients, chemotherapy may be helpful. Until now, the role of chemotherapy in IHCC remains controversial. Miura et al. reported that there was no difference in the median OS between the observation group and the chemotherapy group after resection of intrahepatic cholangiocarcinoma (23 vs 20 months, P = 0.09) [24]. Edeline et al. conducted a phase III multicenter randomized controlled clinical trial using gemcitabine plus oxaliplatin in patients with intrahepatic cholangiocarcinoma after operation. 196 patients with intrahepatic cholangiocarcinoma were randomly divided into gemcitabine plus oxaliplatin group and observation group. They found longer RFS and OS in the gemcitabine plus oxaliplatin group, but there was no statistical difference. In the chemotherapy group, grade III-IV side effects were encounterted more frequently [25]. Schweitzer et al. divided 25 pairs of patients with intrahepatic cholangiocarcinoma after operation into adjuvant chemotherapy group and non-adjuvant chemotherapy group. The results showed that the total survival time of adjuvant chemotherapy group was significantly longer than that of the non-adjuvant chemotherapygroup [26]. Reames retrospectively analyzed 1154 patients with intrahepatic cholangiocarcinoma after radical resection, 347 (30%) received adjuvant chemotherapy, 184 of whom received gemcitabine-based chemotherapy. The results showed that chemotherapy did not change the prognosis of the total group of patients with intrahepatic cholangiocarcinoma, but the subgroup at high risk of recurrence can benefit from chemotherapy [27]. A randomised, controlled, multicentre, phase 3 study (BILCAP) compared capecitabine with observation in resected biliary tract cancer and reported that capecitabine can improve overall survival in patients with resected biliary tract cancer when used as adjuvant chemotherapy [28]. Chemotherapy is not recommended as an adjuvant treatment for intrahepatic cholangiocarcinoma in this year's NCCN guidelines. On the other hand, this year's ASCO clinical practice guidelines recommend capecitabine for 6 months after surgery for intrahepatic cholangiocarcinoma.

In this study, we found patients younger than 55 years old, tumor size larger than 5 cm, high TNM stage, lymph node metastasis, and history of hepatitis were associated with poorer outcome. In previous reports, several prognostic factors were identified for IHCC patients, including tumor size, lymph node metastasis, TNM stage and tumor differentiation [29-33]. Our results are in agreement with previous studies. As regards to the prognostic value of patient age and hepatitis history, reported results were controversial. In a retrospective study by Zhang et al [34], in line with our results, hepatitis was found to be associated with poor prognosis in IHCC, while in the study by Zhou et al., hepatitis was a favorable prognostic factor [35]. The prognositic significance of age was not settled. Most studies reported that age had no prognostic value in cholangiocarcinoma [34, 36-38]. Mavros et al. and Kato et al. found that older age was associated with worse prognosis [39, 40]. However, in our study, we found that patients with age < 55 years old had shorter RFS and OS than those with age ≥ 55 years old, which agreed with the results reported by Yamada et al.[41]. Our data added some information in this respect. But the prognositic value of age is still uncertain.

Conclusions

This study analyzed the failure patterns after curative resection for intrahepatic cholangiocarcinoma. About two thirds of patients with IHCC would recur after operation, with 60% of the recurrences inside the potential volume of PORT. Importantly, up to 40% of the recurrences occurred only inside the potential PORT volume, without lesions in remnant liver and distant sits. Surgical margins and lymph node stations No.16a2, 9, 8, 12, 13, and 14 were the most common sites of recurrence, and should be included in the radiation volume. Our results suggest a possible role for postoperative radiotherapy in the management of patients with intrahepatic cholangiocarcinoma. As IHCC has a relatively low incidence, prospective multicenter single arm clinical trial testing adjuvant radiation might be reasonable.

Abbreviations

IHCC: Intrahepatic cholangiocarcinoma; RFS: Recurrence free survival; OS: Overall survival; PORT: Postoperative radiotherapy; CCAs: Cholangiocarcinomas; SAHZU: Zhejiang University School of Medicine; AJCC: American Joint Committee on Cancer; CI: Confidence interval; RR: Risk ratio; SCI: Science Citation Index; LNM: lymph node metastasis.

Declarations

Ethics, consent and permissions

This study was approved by the Ethics Committee of SAHZU, and was carried out in accordance with the Declaration of Helsinki. All human participants consent to participate in this study.

Consent to publish

Not applicable.

Availability of data and materials

Datasets can be retrieved from authors by formal request from interested readers. Datasets will not be directly shared on public link as the national personal data protection act.

Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

WY participated in the design of the study, carried out the clinical data analysis

and wrote the manuscript; XR collected and interpreted the clinical data, participated in construction of the tables, and wrote part of the manuscript. YS participated in construction of the figures. KW and CL handled with the physics data. LZ polished the article. YC read the CT and MRI image. JX participated in the writing of discussion. QW conceived the study, analyzed the experimental and clinical data and wrote the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Intrahepatic cholangiocarcinoma patient characteristics

Characteristics	No.	%
Gender		
Male	64	50.4
Female	63	49.6
Median age (yrs)	58	
Range (yrs)	26-83	
Node status		
N1	41	32.3
N0	86	67.7
T category		
T1	35	27.6
T2	56	44.1
T3	33	26.0
T4	3	2.4
Type of operative resection		
Less than hemihepatectomy	69	54.3
Hemihepatectomy	42	33.1
Extended hepatectomy	16	12.6
Tumor differentiation		
Well differentiated	15	11.8
Moderate differentiated	52	40.9
Poor differentiated	42	33.1
Unkown	18	14.2
Adjuvant chemotherapy	28	22.0
Tumor size，cm		
Mean	4.5	
Range	1.0-11.0	
Tumor size ≥5cm	43	33.9
AJCC 7th Staging		
I	28	22.0

II	34	26.8
III	21	16.5
IV	44	34.6
CA199, (u/ml) >37U/ml	82	67.8
CEA, (ng/ml) >5ng/ml	36	29.8
Hepatitis	34	26.8
Hypertension	32	25.2
Diabetes mellitus	10	7.9
Bile duct stone	29	22.8
Fever	16	12.6
Jaundice	10	7.9

Table 2 Recurrent patterns of intrahepatic cholangiocarcinoma

	Cases	%
Recurrences inside the potential volume of PORT	**29**	**39.7**
Surgical margin alone	13	17.8
Lymph node alone	7	9.6
Surgical margin and lymph node inside PORT volume	9	12.3
Recurrences outside the potential volume of PORT	**44**	**60.3**
Liver Remnant alone	19	26.0
Lung alone	4	5.5
Surgical margin and liver remnant	3	4.1
Surgical margin, lymph node inside and outside PORT volume	1	1.4
Surgical margin, liver remnant and lung	1	1.4
Surgical margin, lung and abdominal wall	1	1.4
Liver remnant, lymph node inside and outside PORT volume	5	6.8
Liver remnant, lymph node and adrenal	2	2.7
Liver remnant, lung and lymph node	2	2.7
Liver remnant and bone	2	2.7
Liver remnant, adrenal and bone	1	1.4
Liver remnant, lymph node, abdominal wall and peritoneum	1	1.4
Lymph node and bone	1	1.4
Peritoneum alone	1	1.4
Total no. of patients with recurrence	**73**	**100.0**

Table 3. Univariate analyses for PFS and OS among 127 patients who underwent curative surgery for IHCC

Factor	PFS		OS	
	Median survival (month)	P value	Median survival (month)	P value
Age				
< 55 years old	10.0		18.6	
≥ 55 years old	18.5	0.046	34.8	0.002
Sex				
Male	15.6		28.8	
Female	10.5	0.778	21.0	0.599
TMN staging				
I and II	30.2		45.5	
III and IV	7.7	<0.001	15.7	<0.001
T classification				
I	15.4		23.5	
II	10.4		40.2	
III	16.2		24.2	
IV	4.0	0.061	Not reached	0.948
Lymph node metastasis				
N0	21.2		40.2	
N1	6.1	<0.001	11.5	<0.001
Tumor differentiation				
Well	51.7		Not reached	
Moderate	15.6		28.8	
Poor	6.7	0.003	19.4	0.027

Resection Margin				
Positive	4.8		21.0	
Negative	15.6	0.020	25.2	0.304
Tumor size				
< 5cm	19.8		28.8	
≥ 5cm	6.7	0.001	21.5	0.071
Hepatitis				
Positive	10.4		19.0	
Negative	17.6	0.005	25.2	0.079
Hypertension				
Yes	11.7		21.1	
No	15.6	0.856	43.0	0.074
Bile duct stone				
Yes	11.7		18.6	
No	15.6	0.657	30.4	0.063
Jaundice				
Yes	10.2		19.4	
No	15.4	0.406	25.2	0.386
Fever				
Yes	10.5		21.1	
No	15.4	0.737	24.8	0.920
Postoperative chemotherapy				
Yes	11.7		43.0	

No	15.6	0.939	23.5	0.170
CA-199				
Elevated	15.4		26.0	
Not elevated	11.7	0.961	28.8	0.887
CEA				
Elevated	7.7		15.5	
Not elevated	17.6	0.183	40.2	0.016

Figures

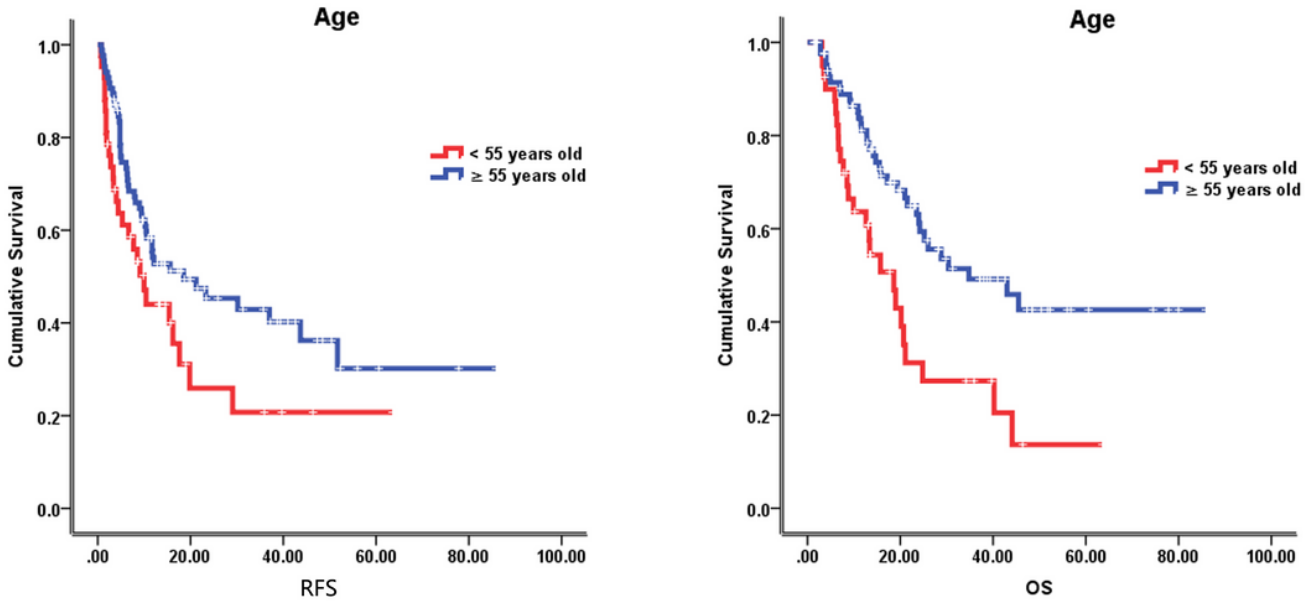

Figure 1

Prognostic value of age in IHCC. Kaplan–Meier curves of RFS and OS in group with age less than 55 years old and equal to or more than 55 years old.

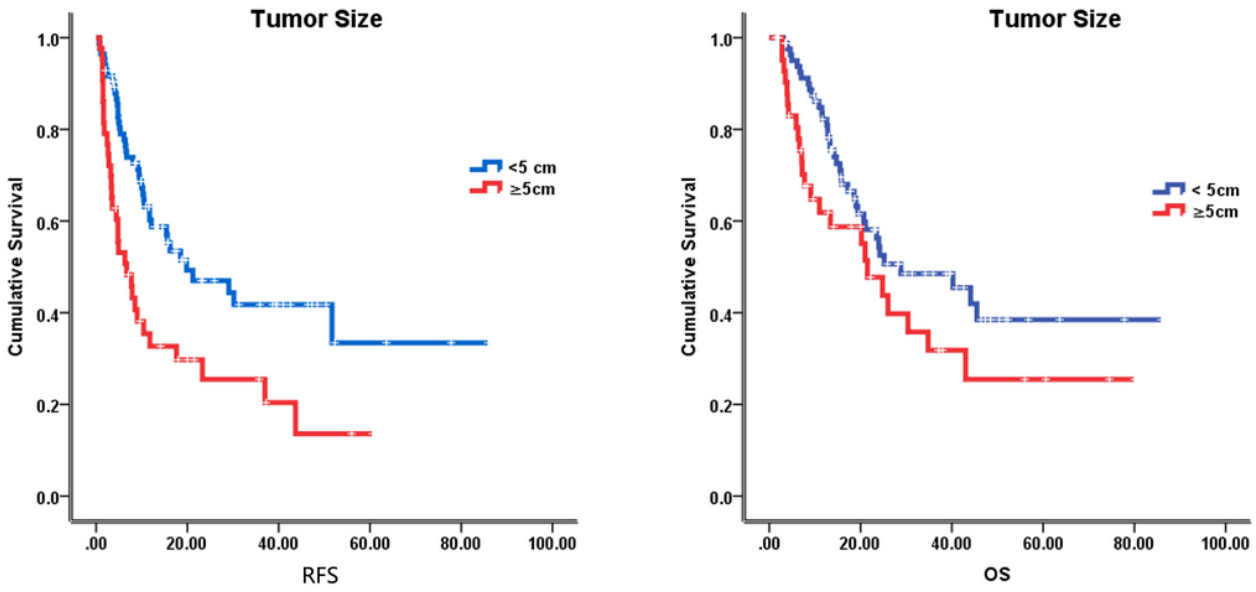

Figure 2

Prognostic value of tumor size in IHCC. Kaplan–Meier curves of RFS and OS in group with tumor size less than 5 cm and equal to or more than 5 cm.

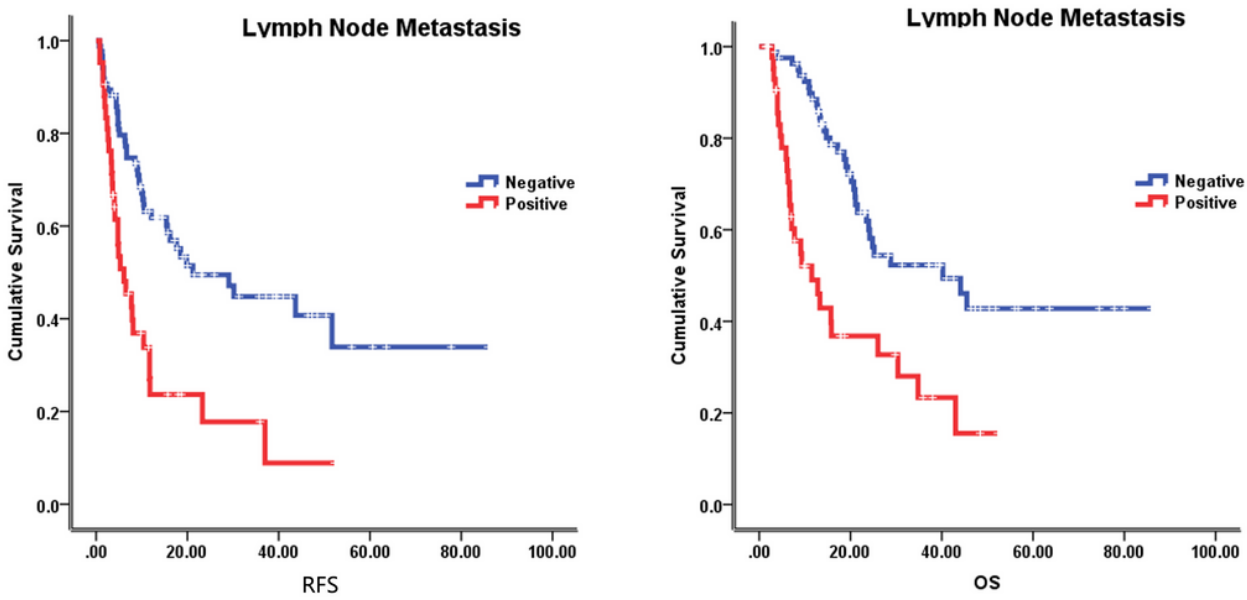

Figure 3

Prognostic value of lymph node metastasis in IHCC. Kaplan–Meier curves of RFS and OS in group with lymph node metastasis and without lymph node metastasis.

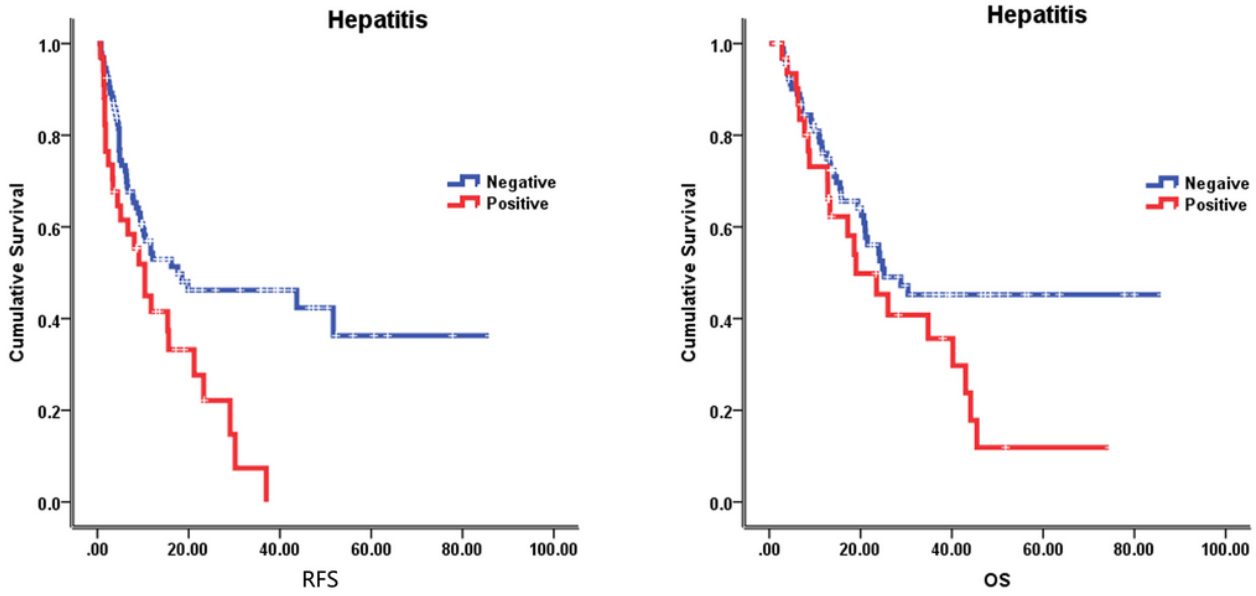

Figure 4

Prognostic value of hepatitis in IHCC. Kaplan–Meier curves of RFS and OS in group with hepatitis and without hepatitis.

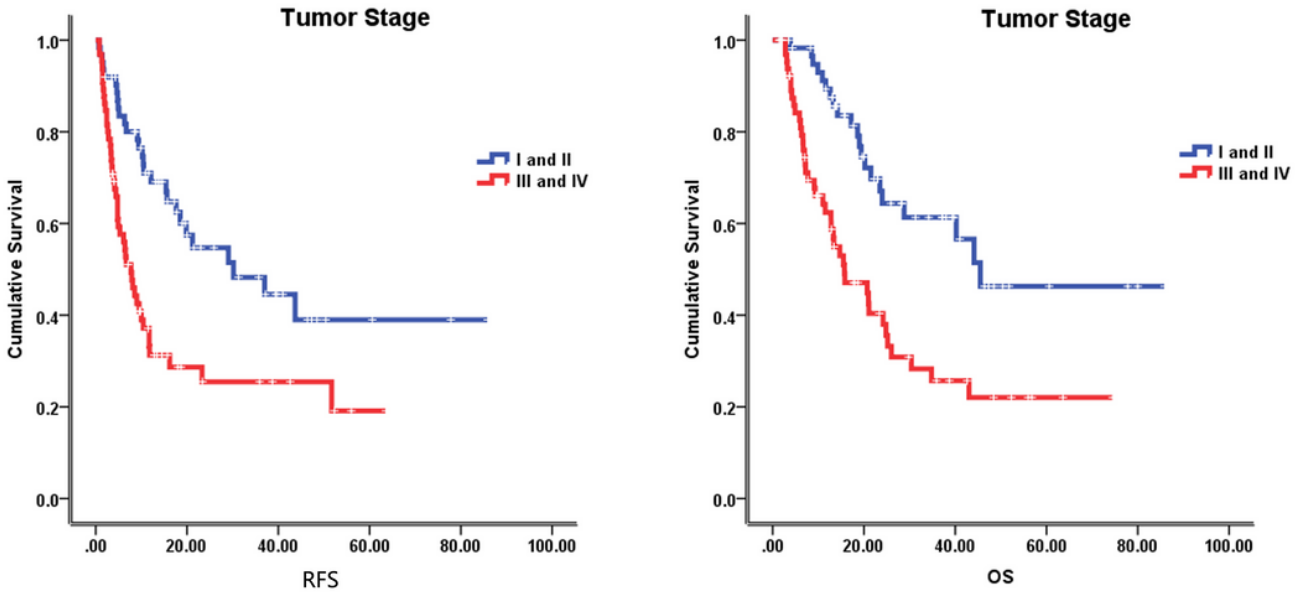

Figure 5

Prognostic value of tumor stage in IHCC. Kaplan–Meier curves of RFS and OS in group with tumor stage I–II and tumor stage III, IV.

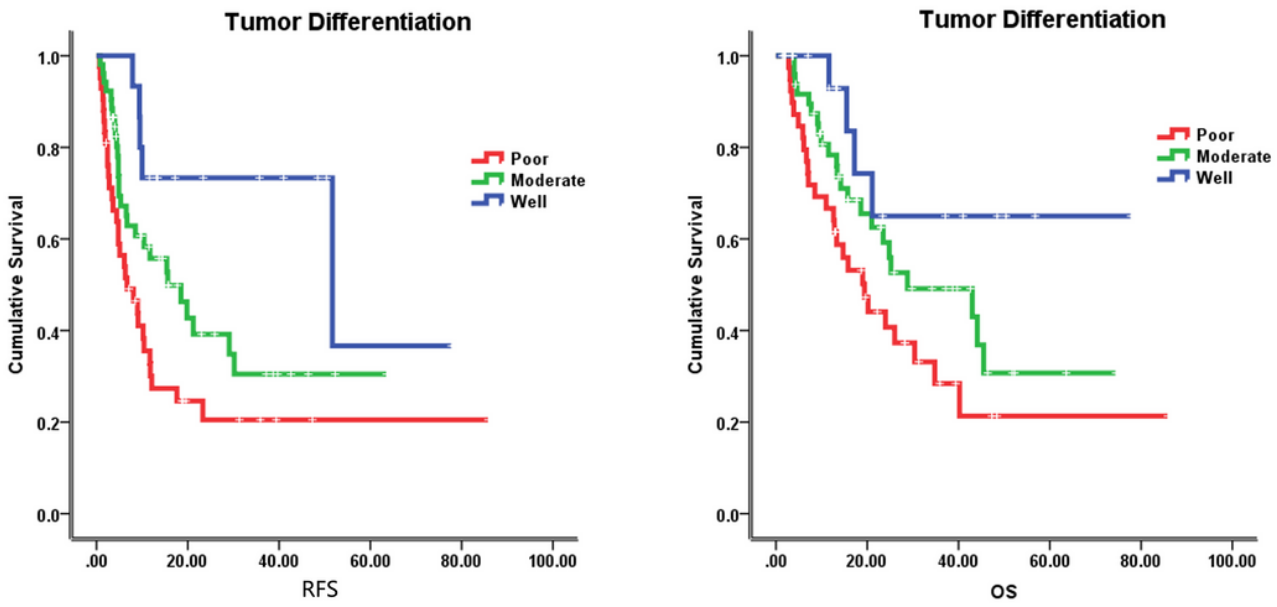

Figure 6

Prognostic value of tumor differntiation in IHCC. Kaplan–Meier curves of RFS and OS in group with well, moderate and poor tumor differentiation.

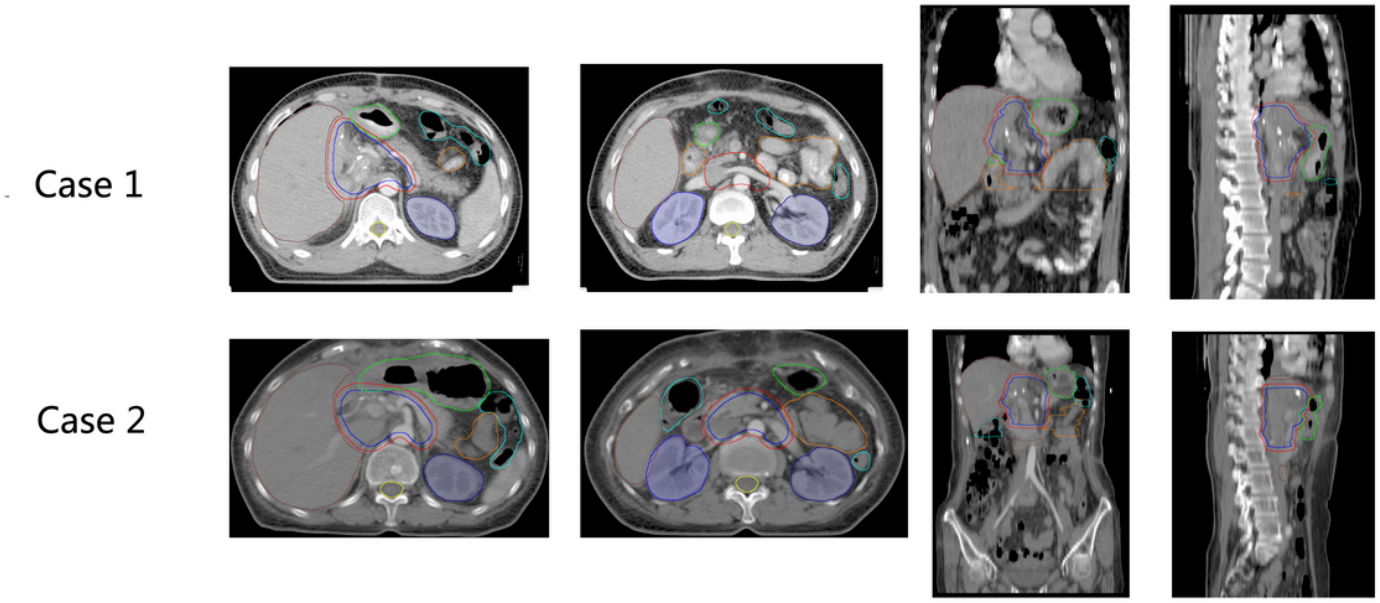

Figure 7

The potential PORT volume in 2 simulated cases. CTV: blue line, PTV: red line, Axial, coronal and sagittal views are shown for case 1 and case 2.