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Outcome of postoperative radiation therapy for cholangiocarcinoma and analysis of dose-volume histogram of remnant liver

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Abstract

The aim of this study was to analyze dose-volume histogram (DVH) of the remnant liver for postoperative cholangiocarcinoma (CCA) patients, to find toxicity rates, and to confirm efficacy of postoperative radiation therapy (RT).

Thirty-two postoperative CCA patients received partial liver resection and postoperative RT with curative intent. The "liver reduction rate" was calculated by contouring liver volume at computed tomography (CT) just before the surgery and at CT for planning the RT. To evaluate late toxicity, the radiation-induced hepatic toxicity (RIHT) was determined by the common terminology criteria for adverse events toxicity grade of bilirubin, aspartate transaminase, alanine transaminase, alkaline phosphatase, and albumin, and was defined from 3 months after RT until liver metastasis was revealed. The radiation-induced liver disease (RILD) was also evaluated.

Tumor stages were distributed as follows: I: 1, II: 8, IIIA: 1, IIIB: 6, IIIC: 14, IVA: 2. Median prescribed total dose was 50 Gy. Median follow-up time was 27 months. Two-year overall survival (OS): 72.4%, disease-free survival: 47.7%, local control: 65.3%, and the median survival time was 40 months. The median "liver reduction rate" was 21%. The OS had statistically significant difference in nodal status ($P = .032$) and "liver reduction rate" >30% ($P = .016$). In the association between the ≥grade 2 RIHT and DVH, there were significantly differences in V30 and V40 ($P = .041$, $P = .034$), respectively. The grade ≥2 RIHT rates differ also significantly by sex ($P = .008$). Two patients (6.2%) were suspected of RILD.

We suggest that RT for remnant liver should be considered the liver V30, V40 to prevent radiation-induced liver dysfunction.

Abbreviations: ALP = alkaline phosphatase, ALT = alanine transaminase, AST = aspartate transaminase, CCA = cholangiocarcinoma, CP = Child–Pugh, CT = computed tomography, CTCAE v 4.0, 2009 = common terminology criteria for adverse events v4.0, CTV = clinical target volume, DVH = dose-volume histogram, HCC = hepatocellular carcinoma, LC = local control, MST = median survival time, OS = overall survival, RIHT = radiation-induced hepatic toxicity, RILD = radiation-induced liver disease, RT = radiation therapy, TS-1 = egafur/gimeracil/oteracil.

Keywords: cholangiocarcinoma, dose-volume histogram, postoperative-radiation therapy, radiation-induced liver disease, remnant liver

1. Introduction

Cholangiocarcinoma (CCA) comprises about 3% of all gastrointestinal (GI) cancers,[1] with only 3000 to 4000 cases per year reported in the US.[2,3] The incidence of extrahepatic CCA is reportedly less than 1.5 in 100,000 people in Western countries,[4,5] but is more common in Asia, including Japan, than in Western countries.[2,6–9] Although CCA is commonly treated with surgery, curative resection may not be possible where the disease has invaded adjacent tissues. Therefore, adjuvant therapies often may be necessary.[10,11]

For microscopic positive margin (R1) or macroscopic positive margin (R2) or regional lymph node metastasis, NCCN guidelines suggest use of adjuvant radiation therapy (RT) with or without chemotherapy. However, this approach is supported by only a few published series, and lack appropriate prospective randomized trials; moreover, some studies have shown no benefit with adjuvant RT. The efficacy of adjuvant RT has been therefore controversial.[2,4,6,12,13] As CCA often invades liver tissues, surgery may include partial liver resection, in case of adjuvant RT, the remnant liver is usually included in radiation field.

There are some criteria of dose-volume histogram (DVH) for whole liver without resection. quantitative analyses of normal tissue effects in the clinic[14] indicates that for conventional fractionation, mean dose to a whole, unresected liver should be <30 to 32 Gy to prevent from classic radiation-induced liver disease (RILD).[15] Also, it is widely used that the volume of liver received 30 Gy was set to keep less than 30% of the whole normal

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liver (V30 < 30%).[16] Although several studies have analyzed normal liver DVH in hepatocellular carcinoma (HCC), no criteria and few reports about tolerance dose of postoperative remnant liver are available.

To our knowledge, this is the first report to analyze the tolerance dose of the remnant liver after surgery for CCA. This study analyzed DVH of the remnant liver after surgery, to find toxicity rates, and to confirm the safety and efficacy of postoperative RT for remnant liver in patients with CCA.

2. Materials and methods

2.1. Patients

Thirty-two patients underwent surgery with partial liver resections for CCA at our institution from July 2004 to November 2016, using external beam radiation therapy with curative intent. We retrospectively reviewed their medical records. Determination of the clinical stage was based on physical examination, chest X-ray, and computed tomography (CT). Almost all of the patients underwent magnetic resonance imaging and some positron emission tomography-CT. All patients were examined before treatment by surgeon and radiation oncologists, and they were classified according to the International Union against cancer staging system. Their disease characteristics are summarized in Table 1. This study was approved by the institutional review board of our institution (IRB number, B18040047), and informed consent was obtained from all patients before treatment.

2.2. Treatment

All 32 patients were received postoperative RT with curative intent. Their types of resection are listed in Table 1. All patients received partial liver resection. The pathological margin status was determined by reviewing the pathology report.

The standard chemotherapy regimen was using gemcitabine, tegafur/gimeracil/oteracil, a combination of these, or cisplatin. The timing of chemotherapy was divided into 4 phases:

(1) neoadjuvant;
(2) postoperative, but before RT;
(3) postoperative, concurrent with RT; and
(4) postoperative, after RT.

Seven patients (21.9%) received no chemotherapy during any of these phases, due to old age, renal disorder or psychopathic disorder.

There was no gross tumor volume because all patients were resected primary tumor, and clinical target volume (CTV) was defined as primary tumor bed. The planning target volume included set-up error, and was defined as a 10 to 15 mm margin from the CTV, with respect to respiratory motion. Photon RT was delivered, using 2 to 4 beams. Patients received external irradiation; the median prescribed total dose was 50 Gy (range: 43.2–56 Gy). Fraction size was 1.8 to 2 Gy and was delivered daily, 5 days per week, using 15 MV X-rays and a shrinking field technique. The radiation field was changed from 0 to 2 times, with regard to liver and kidney tolerance doses.

2.3. Evaluation criteria

Responses were evaluated by means of clinical examination and enhanced CT at approximately 4 to 6 weeks after the completion of treatment. When patients showed no tumor progression within the radiation field and no recurrence after treatment, the disease was considered to be locally controlled and disease free, respectively. Acute and late toxicities associated with treatment were evaluated according to the common terminology criteria for adverse events v4.0 (CTCAE v 4.0, 2009).[17] Acute toxicities were defined as therapy-related adverse events that occurred within 3 months after the beginning of irradiation, and late toxicities as those occurring after 3 months.

The "liver reduction rate" was calculated by contouring liver volume at each phase as follows;

(1) the volume at CT just before the surgery and
(2) the volume at CT for planning the RT.

Hepatic function was assessed by examining serum levels of bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and albumin. In this study, radiation-induced hepatic toxicity (RIHT) was determined by CTCAE toxicity grade of bilirubin, AST, ALT, ALP, and albumin, and was defined from 3 months after RT until liver metastasis was revealed. RIHT was defined as a late toxicity. Conventionally, RILD is defined as ascites and various elevated liver enzymes (especially ALP), or anicteric hepatomegaly, or severe hepatic failure, or hepatic encephalopathy, which typically occur between 2 weeks to 4 months after RT.

Table 1

Patient and treatment-related characteristics.

Total number of patients	32
Gender	
Male	21
Female	11
Age, yr	
Median	70 (range, 43–82)
PS (ECOG)	
0	27 (84.4%)
1	5 (15.6%)
Histology	
Adenocarcinoma	29 (90.6%)
Cholangiocarcinoma	3 (9.4%)
Primary tumor site	
IHCC	4 (1.3%)
EHCC	28 (87.5%)
Postoperative clinical stage (TNM Classification of Malignant Tumors, 8th edition)	
Stage I	1 (3.1%)
Stage II	8 (25.0%)
Stage IIIA	1 (3.1%)
Stage IIIB	6 (18.8%)
Stage IIIC	14 (43.7%)
Stage IVA	2 (6.3%)
Regional lymph node metastases	
Positive	16 (50.0%)
Negative	16 (50.0%)
Type of resection/operative characteristics	
Lobectomy	25 (78.1%)
Extended lobectomy	4 (12.5%)
Lobectomy + PD	3 (9.4%)
Pathological margin status	
R0	0
R1	16 (50.0%)
R2	16 (50.0%)

ECOG = Eastern Cooperative Oncology Group, EHCC = extrahepatic cholangiocarcinoma, IHCC = intrahepatic cholangiocarcinoma, PD = pancreaticoduodenectomy, PS = performance status, R0 = negative margin, R1 = microscopic positive margin, R2 = macroscopic positive margin.

Table 2

Chemotherapy.

The phase of chemotherapy/ treatment timing	N	
(a) Neoadjuvant	11	GEM (n = 7), GEM + TS-1 (n = 4)
(b) Postoperative, before RT	10	GEM (n = 7), TS-1 (n = 2) GEM+TS-1 (n = 1)
(c) Postoperative, concurrent with RT	7	GEM (n = 2), TS-1 (n = 5)
(d) Postoperative, after RT	14	GEM (n = 2), TS-1 (n = 3) GEM + TS-1 (n = 6), GEM + CDDP (n = 6)

CDDP = cisplatin, GEM = gemcitabine, TS-1 = tegafur/gimeracil/oteracil.

2.4. Statistical analysis

Overall survival (OS), progression-free survival, and local recurrence (LC) rates from the beginning of RT treatment were calculated with Kaplan–Meier curves and differences between curves were tested by the log-rank test. We used univariate logistic regression analysis to assess the relationship between liver DVH and RIHT. Statistical analyses were performed with the Statistical Package for the Social Sciences for Windows, v 23.0 (IBM Institute, Armonk, NY). $P < .05$ was considered significant.

3. Results

Median follow-up time for this cohort was 27 months (range, 4–158 months). Chemotherapy regimens at 4 phases and numbers of patients are shown in Table 2.

The median time between the day of surgery and initiating RT was 83 days (range, 33–310 days), and the median overall treatment time for RT was 37 days (range, 30–49 days). All 32 patients completed RT without interruptions. Median presurgery liver volume was 1152 cm^3 (range, 845–1918 cm^3) and median liver volume at the time of RT (after surgery) was 888 cm^3 (range, 591–1799 cm^3), for a median reduction rate of 21% (range, 1%–44%). Before RT, patients' Child–Pugh (CP) classifications were CP class A: n = 30, CP class B: n = 2; after RT, they were CP class A: n = 23, CP class B: n = 9.

3.1. Survival and tumor control

Two-year effect rates in this cohort were OS: 72.4%, disease-free survival: 47.7%, and LC: 65.3% (Fig. 1). Median survival time (MST) was 40 months.

At the last follow-up date, 16 patients (50%) were alive, 13 (40.6%) had died of cancer, and 3 (9.4%) had died of

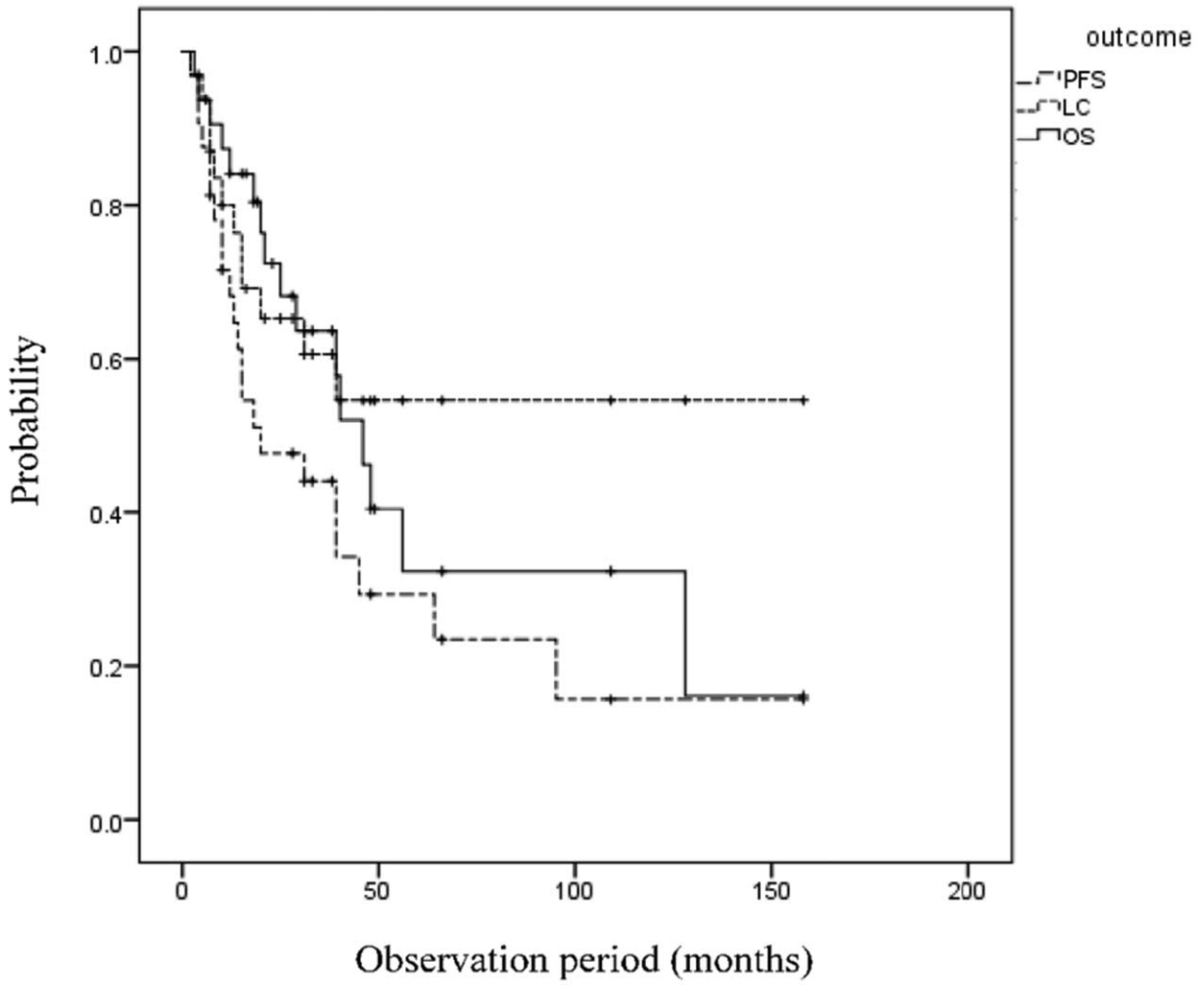

Figure 1. Kaplan–Meier curve of progression-free survival, local recurrence, and overall survival rates. LC = local recurrence, OS = overall survival, PFS = progression-free survival.

non-cancer-related causes that included heatstroke and hepatic failure (n=2). These hepatic failures were suspected RILD, but these were not proved pathologically. Of the 13 patients who had died of cancer, 12 died of distant metastases, and only 1 died of local liver recurrence, with no distant metastasis. The distant metastases were liver metastases (n=7), peritoneal dissemination (n=2), intra-abdominal lymphatic metastases (n=2), and multiple lung and lymph-node metastases (n=1). Of the 12 patients with distant metastases, 6 had controlled primary tumors. Of the 16 patients who were alive at the last follow up, 8 patients were disease-free, 3 patients had both local recurrences and distant metastases, 3 patients had only distant metastases, and the other 2 patients had only local recurrences. Five of 16 patients with recurrences have received chemotherapy. The results of the log-rank test analysis evaluated the relationship among some risk factors and treatment outcome. The OS had statistically significant difference in nodal status ($P=.032$) and "liver reduction rate" >30% ($P=.016$). Twelve (37.5%) patients suffered recurrence within the radiation field (in-field recurrence). Six of 12 patients developed both in-field recurrence and distant metastases.

3.2. Toxicity

Adverse events related to hematology, myelosuppression, and GI were considered acute toxicity, and RIHT as late toxicity (Table 3). Among acute toxicity events, 2 patients developed mild cholangitis during RT. Table 3 also shows patients' hepatic function and RIHT grades after RT.

Among late toxicity events, 2 patients (6.25%) were suspected RILD. Except for these 2, no other treatment-related late toxicities >grade 3 were observed in the other patients. Of the 2 patients with RILD, 1 was suspected about 8 weeks after RT, based on liver dysfunction, ascites, and hepatic encephalopathy but had no evidence of recurrence or distant metastasis; he died at about 6 months after the suspicion of RILD. The other patient was suspected with RILD by hepatic failure and ascites about 9 weeks after the RT, but also had no recurrence or distant metastasis; he died of hepatic failure 8 months after the suspicion. Both patients terminated RT because of cholangitis, at 44 Gy in 22 fractions and 46 Gy in 23 fractions, respectively. They had received chemotherapy in some phases and suffered cholangitis before or after RT repeatedly.

Table 3

Toxicities.

Acute toxicities	Grade 1	Grade 2	Grade 3	Grade 4
Hematology toxicity/myelosuppression				
Leukocytes/leukopenia	12	6	3	0
Neutrophils/absolute neutrophil count	7	4	2	1
Hemoglobin	5	10	1	0
Platelets	7	4	0	1
GI				
Anorexia	10	0	0	0
Nausea	3	0	0	0
Gastritis	4	0	0	0
Duodenal ulcer	1	1	0	0
Late toxicities	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Liver enzyme				
Bilirubin	2	6	1	0
Aspartate transaminase (AST)	12	6	0	0
Alanine transaminase (ALT)	5	5	1	0
Alkaline phosphatase (ALP)	23	6	0	0
Hypoalbuminemia	14	11	0	0
RIHT	13	16	1	0

GI = gastrointestinal, RIHT = radiation-induced hepatic toxicity.

Table 4

The relationship between DVH parameter and grade ≥2 RIHT rates.

	Median ± standard deviation		
	<grade 2 (n=15)	≥grade 2 (n=17)	*P* value
V10	45.2 ± 12.9	60.1 ± 21.9	.250
V20	30.3 ± 16.6	41.1 ± 17	.120
V30	20.3 ± 9.4	27.9 ± 10.5	**.041**
V40	13.6 ± 6.3	18.3 ± 6.6	**.034**
V50	1.5 ± 3.2	2.2 ± 4.6	.420
Mean dose	14.8 ± 4.9	20.2 ± 5.7	**.058**

DVH = dose-volume histogram, RIHT = radiation-induced hepatic toxicity.

3.3. Analysis of DVH and liver volume

Tables 4 and 5 shows the results of univariate logistic regression analysis evaluated the association between the grade ≥2 RIHT and DVH or clinical parameters. The patients who developed grade ≥2 RIHT, showed higher rates of V10 to V50, and mean dose. Especially, there were significantly differences in V30 and V40 ($P=.004$, $P=.003$), respectively. The grade ≥2 RIHT rates differ also significantly by sex ($P=.008$).

Table 5

The relationship between clinical parameters and grade ≥2 RIHT rates.

	Median ± standard deviation		
	<grade 2 (n=15)	≥grade 2 (n=17)	*P* value
Age, yr	70 ± 8.3	70 ± 10.5	.610
Gender (n)			
Male	6	15	**.008**
Female	9	2	
HCV or HBV (n)			
Yes	1	1	.920
No	14	16	
Child-Pugh classification (at RT) (n)			
Class A	14	16	.920
Class B	1	1	
Liver volume, cm^3	884.4 ± 296.1	932.5 ± 216.4	.960
Reduction rate (%)	0.18 ± 0.12	0.22 ± 0.16	.710
Total radiation dose, Gy	50 ± 3.4	50 ± 2.9	.780
Chemotherapy phase (a + b) (n)			
Yes	8	10	.750
No	7	7	
Chemotherapy phase (c) (n)			.077
Yes	1	6	
No	14	11	
Chemotherapy phase (d) (n)			.750
Yes	7	7	
No	8	10	

The phases of chemotherapy: (a) neoadjuvant; (b) postoperative, but before RT; (c) postoperative. HBV = hepatitis B virus, HCV = hepatitis C virus, RIHT = radiation-induced hepatic toxicity, RT = radiation therapy.

4. Discussion

The aim of this study was to analysis the DVH of the remnant liver, to reveal the frequency of toxicity, and to confirm the safety and efficacy of postoperative RT to the remnant liver of CCA. Although other reports have described postoperative RT for CCA (Supplementary Table 6, http://links.lww.com/MD/D146), none of them have evaluated RT of the remnant liver in patients who undergo surgery for CCA.

In the present study, MST was 40 months, 2-year OS was 72.4%, and LC was 65.3%. The 40-month MST was similar to, or longer than, that in previous studies (13–37 months)[6,7,12,13,18–21]; OS was also similar to previous studies.[6,22–24] A few reports clearly address in-field recurrence. In 1 study, among patients who were considered to have negative margin (R0), in-field recurrence was reported to be 17.2%.[12] In another study, among extrahepatic cholangiocarcinoma patients who had surgery and adjuvant chemoradiation, the 5-year locoregional recurrence rate was 38%.[21] In our study, all patients were R1 or R2 resections; the 2-year LC was 65.3% and in-field recurrence (with or without distant metastases) was 37.5%. The major reason for disease-specific death (n = 13) was distant metastasis (n = 12); only 1 patient died from local recurrence. This result concords with reports that distant metastases are common (24%–69%) in CCA.[21,23] Overall, the treatment outcome in our study was comparable to previous reports, even if taking into account that previous studies involved various stages, primary tumor site, radiation field, and with or without chemotherapy. Several studies related lymph-node status (regional lymph nodes metastases) to poor survival.[6,7,13,18] The same result was seen in this study ($P = .032$). Our study also found a relationship between liver reduction rate >30% and treatment outcome ($P = .016$). This result may reflect the fact that patients who need much liver volume resection are usually high-risk patients.

Our acute toxicity results with respect to adverse hematologic and GI events were comparable to previous studies. Reportedly, most patients have grade ≤2 hematologic toxicity and a handful of patients develop grade ≥3 hematologic events.[21–23] The rate of GI bleeding was 2% to 17% [19,23]; gastric ulcers or duodenal ulcers were sometimes found after RT,[22,23] and cholangitis also occurred during and after RT.[19] The reported RILD rate is 9.3% to 36%,[25–27] although most studies focused on patients with HCC or liver metastases, who were sometimes also suffering from cirrhosis. In the present study, the RILD suspected rate in remnant normal-function liver was 6.25%, which was less than in previous reports. These RILD suspected patients had received chemotherapy in some phases and suffered cholangitis before and after RT repeatedly, these factors also had might affect to develop hepatic failure.

Reported risk factors for RILD are mean liver dose, CP classification and having hepatitis B virus or hepatitis C virus.[25–27] Some reports recommend that mean liver dose to patients whose liver volume (ie, liver tissue not affected by HCC or liver metastases) is less than 700 ml should be restricted to ≤23 Gy in 2 Gy per fractions.[29–31] The mortality rates from RILD was reported to range from 10% to 76% in patients with chronic viral hepatitis.[28] As effective treatment of RILD has not been established,[28,32] its prevention is critical. However, only 2 patients suspected RILD in this study, which is too few to draw any conclusions. We, therefore, analyzed RIHT. Of the 32 patients, 30 patients developed RIHT (grade ≤2: 96.6%; grade ≥3: 3.4%). In previous studies, RIHT was reported to be 9.9% to 32%.[33,34] As the definition of RIHT or radiation-induced liver injury/dysfunction is unestablished, it varied in each study and might therefore be difficult to compare. Recently, most reports were about patients with HCC or liver metastases. However, 1 report focused on radiation-induced liver injury in patients with postoperative or locoregional recurrent gastric cancer with nondiseased or normal/healthy livers and also without resection liver; they found V30, V35, and V40 of liver to be predictors of liver function injury.[35] It was similar to our result that V30 ($P = .041$) and V40 ($P = .034$) were related to RIHT. In our study, RIHT rates significantly differed by sex ($P = .0084$). The difference failed to reach statistical significance in the mean liver dose ($P = .058$) and concurrent chemo-radiotherapy ($P = .077$), possibly because of limited patient numbers. We suggest it may be better to take into consideration of these factors for RT of remnant liver.

To our knowledge, this is the first report to analyze the tolerance dose for remnant liver, or to report RILD and RIHT rates in the remnant liver after surgery for CCA. As no criteria are available for the tolerance dose for remnant liver after surgery, our findings can become helpful in radiation planning for these patients.

This study was limited by the small number of patients because the needs of partial liver resection were dependent on tumor invasion, not all the CCA patients undergo both liver resections and RT, and the relatively short median follow-up time (27 months). Further studies are required to validate our findings on acceptable resection rate, and DVH parameters (including mean liver dose and appropriate V30 and V40 doses).

5. Conclusions

In the present study, RT for remnant liver after surgery for CCA led to good local control and acceptable intermediate-term tolerance. We suggest that radiation planning for remnant liver should considered mean, V30 and V40 doses to liver tissue, to prevent radiation-induced liver dysfunction. Further studies are needed to determine indications, long-term efficacy, and possible late toxicities.

Author contributions

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