

## The prognostic significance of R1 resection for extra-hepatic bile duct cancer

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### Background

Not infrequently, curative intent for extrahepatic bile duct cancer inevitably results in R1 resection due to its multifocal nature, cholestatic liver disease, and poor physical condition of the patients. The prognostic value of R1 resection for peri-hilar and mid to distal bile duct cancer remains to be determined.

### Methods

We reviewed literatures to investigate the prognostic significance of R1 resections for hilar bile duct cancer and we compared the survival of 130 patients who underwent R0 (n=102), R1 (n=21), and R2 (n=7) resection for mid to distal bile duct cancer at Kyungpook National University Hospital through retrospective review of medical records. Univariate and multivariate analysis were performed using the clinicopathologic factors and the status of resection margin.

### Results

In literature review of the hilar bile duct cancer, authors showed survival benefit of R1 resection compared to R2 or non resection and similar survival rate of R1 resection compared to R0 resection. Overall 5-year survival rates of the patients of who underwent R0, R1, and R2, resection were 47.1%, 16.8%, and 0% respectively ( $p=0.000$ ). In contrast, among 61 patients who underwent bypass surgery, no patients survived longer than 3 years. On univariate analysis, T stage, lymph node metastasis, perineural invasion, lymphovascular invasion (LVI), microscopic involvement of resection margin, surgical method, and TNM stages were significant prognostic factors. On multivariate analysis lymph node metastasis, LVI, TNM stages, and surgical method were independent prognostic factors.

### Conclusion

Literature review shows that R1 resections for hilar cholangiocarcinoma, if inevitable, can offer better survival than R2 or nonresection. Similarly, our data of mid to distal bile duct cancer also showed the survival benefit of R1 resection compared to R2 or nonresection justifying the role of R1 resection in inevitable cases.

## Introduction

The goal of surgical treatment for the extrahepatic bile duct cancer is to achieve R0 resection but it is not always possible to achieve the goal even after major resections such as pancreaticoduodenectomy (PD) and hepatoapancreaticoduodenectomy (HPD).

R1 resection is defined as the resection of tumor with microscopic residual tumor on any part of remnant tissue. RI resection for extrahepatic bile duct does not necessarily mean limited resection and include R1 bile duct resection with or without liver resection, R1 PD with or without liver resection. The question whether R1 resection irrespective of the reasons for failure to achieve R0 resection offers survival benefit need to be answered since R1 resections are not infrequent clinically.

The reasons for R1 resections may be various. First, multifocality of bile duct cancer is present in 10% of EHBD cancer. In cases of multifocal EHBD cancer, positive distal bile duct margin can be treated by PD, whereas positive uppermost proximal bile duct margin cannot be treated resulting R1 resection if the volume of remnant liver is not sufficient. Thus in some cases of multifocal EHBD cancer the resection ends up with R1 PD or R1 HPD if the uppermost proximal bile duct margin is microscopically involved. Second, if the patients are not in good condition to undergo major resection such as PD and liver resection, surgical option may end up with R1 BDR if any of both resection margins is involved. Third, in many cases, surgeons perform surgery for mid to distal bile duct cancer without relieving the jaundice below 2 mg% and estimation of remnant liver function preoperatively. In this situation, adding liver resection to BDR or PD in case of involvement of proximal margin may be dangerous since it often lead to insufficiency of liver which is already damaged by cholestasis. For these reasons, R1 resections are inevitable in some cases and include R1 PD, R1 BDR, and R1 HPD.

However, surgical outcome of R1 resections for EHBD cancer is largely unknown. In this study, we reviewed clinicopathological features, and surgical outcomes of the patients with EHBD cancer who inevitably underwent R1 resections

## Material and Methods

Overall and disease free survival rate was drawn from 191 patients who underwent surgery at department of surgery, Kyungpook National University Hospital from August 1990 to June 2011. Among these 191 patients, 130 patients received resection (R0, R1, and R2) and remaining 61 patients underwent non-resection surgery such as bypass, cholecystectomy, or exploration only. The status of resection margin and clinicopathological factors were analyzed as variables using univariate and multivariate analysis to determine the prognostic significance of R1 resection and identify prognostic factors using Kaplan-Meier and Cox proportional hazard regression method.

Surgical procedures were determined by the location and extent of the tumor. Among 130 patients, 88 patients (67.7%) underwent pancreaticoduodenectomy, 41 (31.5%) patients underwent bile duct resection, and 1 patient (0.8%) underwent hepatoapancreaticoduodenectomy.

## Results

### 1. Clinicopathological features of patients who underwent R1 resection

Resection rate was 68.1% (R0, R1, and R2, 53.4%, 11.0% and 3.7% respectively). The patients with R1 resection older than the patients with R0 resection (70.1 vs 6.7 p=0.01). BDR was more frequently performed among the patients with R1 resection than the patients with R0 resection (66.7% vs 20.6% p=0.000). Advanced T stage was not more frequent in the patients with R1 resection. Other clinicopathological factors including the level of Ca19-9 were not different between two groups.

**Table 1.** Comparison of clinico-pathological features of between the patients who underwent R0 and R1 resection

Variables		R0(n=102)	R1(n=21)	P-value
	Mean	64.7	70.1	0.010
Age	<65	44(%)	3	0.014
	≥65	58	18	
Sex	M	62	16	0.335
	F	42	6	
	HPD	0	1	
Surgical method	PD	82	6	0.000
	BDR	21	14	
	T1	26	8	
T classification	T2	18	7	0.050
	T3	58	6	
N classification	N0	77	16	1.000
	N1	25	5	
	1a	23	7	
	1b	13	6	
AJCC stage	2a	41	3	0.112
	2b	23	5	
	3	0	0	
	4	2	0	
Perineural Invasion	-	62	11	0.477
	+	40	10	
Lymphovasculular invasion	-	84	16	0.542
	+	18	5	
CA19-9	<37	31	10	0.096
	≥37	51	6	
	Papillary	2	1	
Differentiation	Well	31	6	0.772
	Moderate	53	12	
	Poorly	11	1	

\* PD: Pancreatoduodenectomy, BDR: Segmental bile duct resection, HPD: Hepatopancreaticoduodenectomy.

### 2. Type of surgery and Long term survival of the patients who underwent R1 resection

Type of R1 resection included a case of HPD, 6 cases of PD, and 14 cases of BDR. The survival according to

different type of surgery was not different.

**Table 2.** Type of R1 resection and median survival

Variables	R1 Resection (n =21 )		
	No	Median (month)	p
Type of surgery	R1-HPD(Proximal R1)	1	14.0
	R1-PD	6	23.0
	R1-BDR	14	24.0
	Proximal R1	6	
	Distal R1	4	
	Proximal/Distal R1	4	
Pathology of resection margin	Severe dysplasia	3	24.0
	Invasive carcinoma	18	23.0

### 3. Overall survival of the patients who underwent with resection according to the status of resection margin

According to status of resection margin, the 5-year survival was 47.1% after R0 resection, 16.8% after R1 resection, and 0% after R2 resection ( $p = 0.000$ ). The difference of survival between R1 and R2 was statistically significant, whereas the difference of survival between R1 and R0 was just a little short of statistical significance. The survival of patient with any type of resection was better than that of the patients with no resection.

## Conclusion

R1 resection, if inevitable, can be performed because it offers better survival than that of R2 or no resection. Furthermore, since long term survival can be achieved in some subset of the patients with R1 resection aggressive surgical approach to achieve R0 or R1 resection is justified.

## Discussion

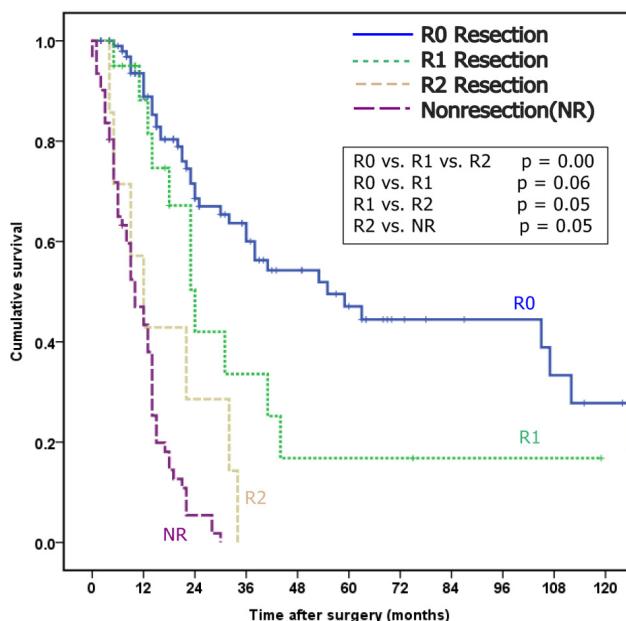
To investigate the prognostic significance of R1 resection for hilar bile duct cancer, we reviewed the literature not from our own data because we were not able to complete the analysis of our own data at this moment of presentation. In the literature review of the hilar bile duct cancer, many authors showed survival benefit of R1 resection for hilar bile duct cancer compared to R2 or non resection (1, 2). Furthermore, Seyama et al., Zervos et al., and Lee et al. (3-5) independently reported that survival after R1 resection was not statistically different from the survival after R0 resection although there are some reports showing the opposite similar results (6, 7).

To investigate the prognostic significance of R1 resection for mid to distal bile duct cancer, we analyzed our own data. In our patients of mid to distal bile duct cancer, the prognosis of the patients with R2 resection was much poorer compared to the patients with R0 and R1 resections. While the patients with R0 and R1 resection showed 5-year survival rate of 47.13% and 16.8%, none of the patients with nonresection or R2 resection survived longer than 3 years (median 10 mo. and 12 mo.).

There is no controversy over the statement that R0 resection is necessary for long term survival of the patients with mid to distal bile duct cancer. However, it is sometimes very difficult to achieve a R0 resection due to short

length of the bile duct, superficial microscopic spread, multifocal tumor, and poor condition of cholestatic liver and the patients. In such cases, R1 resection is inevitable and some authors report that patients with R1 resection survived longer than expected (8-11). In our study, 5-year survival rates after R0-resection was higher than after R1-resection but the difference did not reach the statistical significance (47.1% vs 16.8%; p = 0.0.6)(Figure).

Thus, we may be able to insist that R1 resection, if inevitable, deserve to perform to prolong the survival, considering the data that none of the patients with R2 resection or nonresection survived longer than 36 month.



**Figure.** Overall survival of the patients who underwent with resection according to the status of resection margin ( R0=102, R1=21, R2=7, Non resection=61).

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