

A Proposal for the treatment of locally advanced proximal bile duct cancer

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=한글초록=

진행성 근위부 담도암의 치료를 위한 한가지 방안

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배 경 : 근년에 들면서 근위부 담도암에 대한 관심이 증가하고 있고, 보다 적극적인 치료를 하고 있으나 일반적으로 치료성적이 좋지 않은 것으로 알려져 있다. 특히 근위부 담도암은 해부학적 위치와 담도암의 특성으로 인하여 근치절제율이 낮고 생존율도 낮다. 저자들의 과거 연구결과(1983. 1-1992. 4 ; 121예)에서 비근치절제술의 시행이 단순담도삽관술에 비하여 생존율이 좋았음을 보고한 바 있다. 또 1991년 Marc Mahc 등의 보고 즉, 현미경적 잔류암이 담도암의 절단면에 남아 있는 경우, 수술후 방사선치료를 해서 수술후의 3년 생존율을 57%까지 높였다는 보고가 있었다. **목 적** : 저자들은 국소적으로 진행된 근위부 담도암의 경우에 근치적 절제술의 목적을 가지고 절제를 한 후 현미경적 잔류암이 있는 경우에 수술후 방사선 치료를 해서 환자에게 도움이 될 것인가를 알기 위하여 전향적인 연구를 계획하였다. **대상 및 방법** : 1990년 11월부터 1993년 10월까지 3년동안 1인의 외과의에 의해 국소적 절제를 시행받은 근위부 담도암 45예를 대상으로 하였다. 환자는 치유절제군, 비치유절제군, 그리고 비절제군으로 나누었고 방사선 치료의 유무에 따라 세분하였다. 비치유절제군은 육안적으로 간십이지장인대의 주요혈관에 종양의 침윤이 있었거나 육안적으로 종양이 남아 있지는 않았으나 절제면에 현미경적으로 종양의 침윤이 있었던 예로 분류하였다. 근치적 절제는 되었으나 임파절 전이가 있는 경우에 수술후 방사선치료를 하였다(4500-5900cGy, Mean=5083cGy). 생존율의 측정에는 Kaplan-Meier법을 이용하였다. **결 과** : 45명의 환자중 치유절제가 된 경우는 18예였고 비치유절제군은 13예, 그리고 비절제군은 14예였다. 이중 생존예는 7예였으며 4예는 치유절제군에서 3예는 비치유절제군에서 나왔으며 비절제군에서는 2년이상 생존예가 없었다. 생존율의 조사에서 치유절제군과 비치유절제군간의 유의한 차이는 없었고, 치유절제군과 비절제군의 생존율은 통계적으로 유의한 차이가 있었다. 그러나 중간생존값에 있어서는 치유절제군이 22개월, 비치유절제군이 13개월, 비절제군은 10개월로 시간경과에 따른 생존율의 수치와는 차이가 있었다. 치유절제군을 방사선 치료의 유무에 따라서 구분하고 대상의

모든 환자에서 방사선치료를 시행한 비치유절제군간의 생존율비교에서 통계적인 차이는 없었으며 중간 생존기간은 27개월, 19.5개월, 13개월로 나타났다. **결론** : 근위부 담도암에 있어 절제술의 시행이 환자를 위한 최선의 치료로 생각된다. 또한 담도암이 국소적으로 진행된 경우, 병변의 절제가 가능하면 절제후 방사선치료를 함으로써 환자에게 도움이 될 것으로 생각한다.

Introduction

In recent years, aggressive surgery has been increasingly used to treat proximal bile duct cancer; however, it has not improved its survival rate. Surgery remains the basic treatment of this cancer but resection is only possible in approximately 10-30% of patients¹⁾, and the survival rate has not exceeded²⁾ five years. The reasons for the low resectability and survival rates are due to anatomical location and characteristics of bile duct cancer.

We analyzed both the effects of resective modality of proximal bile duct cancer on prognosis and the effects of postoperative radiotherapy on survival of patients with microscopic residual tumors following resection, in order to determine whether noncurative resections have better survival rates than biliary drainage only and whether postoperative radiotherapy is helpful to patients with positive resection margin³⁾.

Patients and Methods

Between November 1990 and October 1993, 45 patients with cancer of the proximal bile duct were treated by one surgeon. The ages of the patients ranged from 18 to 77 years(mean 66 years). There were 28 men and 17 women. On admission, all patients had obstructive jaundice. Shortly after admission, the jaundice was relieved by percutaneous transhepatic biliary drainage or intrahepatic bile duct cannulation, reducing the total bilirubin level.

This study was performed in a prospective nonrandomized fashion and the operation method was used to skeletonize the hepatic hilum without hepatic resection. According to operative findings or pathologic reports, the patients were divided into three groups: curative, 16 patients; noncurative

resection, 15 patients; and nonresection, 14 patients. Noncurative resection was defined as patients with positive resection margin or minimal residual tumors adjacent to major vessels. Postoperative external radiotherapy was done with curative intent in 23 patients after complete resection with positive lymph nodes(n=8), or after noncurative resection(n=15), and with palliative results in nine patients with nonresection.

Doses of external radiation ranged from 4500 to 5900 cGy with a mean dose of 5083 cGy. Survival curves were drawn using Kaplan-Meier survival analysis. Comparison between curves was assessed using the log-rank test. A P value below 0.05 was considered significant.

Results

Regular follow-up information was available for all 45 patients. Duration of mean follow-up was 41 months. For the entire group, the overall survival was 53.3% at 12 months, 24.4% at 24 months, and 15.2% at 36 months. The mean and median survival was 20 months, and 13 months, respectively(Fig. 1). The resectability for all patients was 69%(31/45)

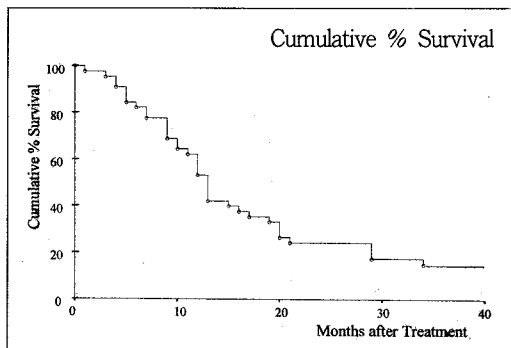


Fig. 1 Cumulative survival curves for patient with proximal bile ductcancer(n=45). The mean and median survival are 20 months, 13 months

Table 1 Mode of Treatment

Procedure	Number	%
Resection	31	69
curative	16	
noncurative	15	
Drainage	14	31
internal	1	
external	13	
Biopsy only	0	

but the noncurative resectability in all resections was 48% (15/31). In the nonresection group, drainage procedure was employed: external drainage via T-tube in 13 cases, internal drainage in only one case (Table 1). The local recurrence rate between curative resection and noncurative resection with external radiation was not statistically significant (Table 2). The survival curve for patients who underwent resection was compared with that of patients who could not undergo resection. The patients without resection had significantly shorter survival times ($p=0.0037$, Fig. 2). Mean and median survival was 24.8 months and 16 months, respectively, in patients treated with resection but 10 months and 11 months, respectively, after nonresection. Prognosis was poor in patients treated for nonresective palliation since overall survival was 50% at 12 months, 0% at 24 months and mean survival was 11 months. The last patient died at 24

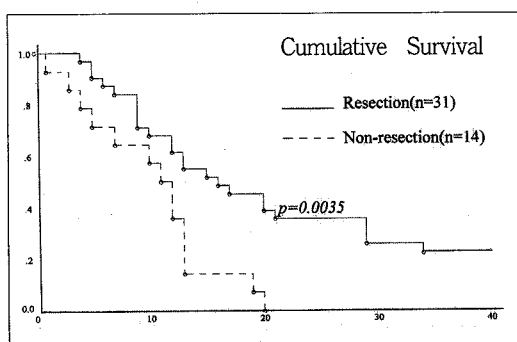


Fig. 2 Cumulative survival curves for patient with proximal bile duct cancer according to operation.

Table 2

	Recurrence Patterns of Resected Cases (n=31)		
	Curative (n=16)		Noncurative (n=15)
	RT(+)	RT(-)	RT(+)
Liver	5	3	3
Local	2	1	4*
Disease-free	2	2	3

* $p>0.05$ vs. local recurrence in curative resection

noncurative resection group treated for external radiation, whereas curative resection as well as noncurative resection groups show longer survival than that of the nonresection group with statistically significant data ($p<0.05$, Fig. 3).

Six clinicopathologic factors were analyzed and the prognosis was significantly related to one analyzed by univariate method. The only significant variable was operation type, resection or nonresection. The following factors were not significantly associated with prognosis: age, sex, lymph node involvement, perineural invasion, and histologic type (Table 3). There were seven patients who survived without recurrence and the characteristics of these patients are shown in Table IV. Four of seven were patients with curative resection, and three were patients with noncurative resection; patients with nonresection did not live more than 2 years.

Discussion

Proximal bile duct cancer shows that slowly

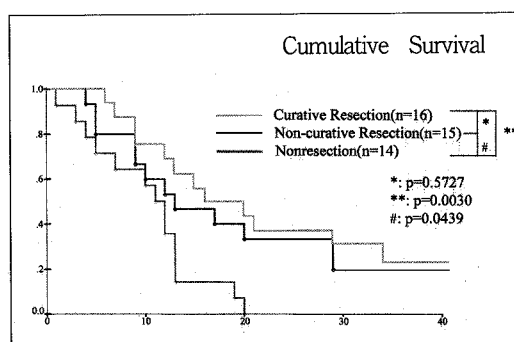


Fig. 3 Cumulative survival curves for patient with proximal bile duct cancer according to operation.

biliary obstruction and its consequent cholangitis and liver failure represent the most common causes of death in these patients⁵⁾.

Because proximal bile duct is located nearby major vessels, and bile duct has thin walls, carcinoma of the proximal bile duct easily involves the surrounding tissues, such as the portal vein, hepatic artery and parenchyme of the liver around the hepatic hilum. It can spread along the periductal lymphatic network, perineural space, and periductal venules; and it may infiltrate the bile duct wall submucosally over a wide area. It has been repeatedly emphasized that tumor cells often remain after apparent microscopically complete radical resection¹⁾.

In our series, the rate of positive resection margin was 48%(15/31). In the series by Beazley et al, only

4 of 16(25%) patients obtained curative resection⁶⁾. Mizumoto et al reported that 10 of 11 patients maintained positive resection margin by local resection¹⁾. Bismuth et al also indicated that improved survival in hilar cholangiocarcinoma can be achieved by resection with minimal morbidity and zero mortality rates, if histologically free resection margins are obtained and local excision

without hepatic resection is sufficient for type I lesions only⁷⁾.

The local recurrence was more frequent when the resection margin was closer to the tumor, and local recurrence may be due to cancer cells that remain in the surgical margins of the bile duct. Histologic examination of resected specimens has demonstrated a positive correlation between absence of residual tumor in the resection margins and long-

Table 3
Univariate analysis of prognostic factors affecting the patient survival.

Factor	No. of patients	p value
Age	0.6948	
Sex	0.1032	
Male	28	
Female	17	
Lymph node metastasis		0.0539
Present	10	
Absent	21	
Perineural invasion		0.9950
Present	9	
Absent	22	
Histologic type		0.5083
Papillary	3	
Well-differentiated	13	
Moderate-differentiated	13	
Poorly-differentiated	4	
Operation		0.0035
Resection	31	
Nonresection	14	

Table 4. Characteristic of survivors without recurrence

Sex/age	op.type	R.M	L/N	histology	outcome	comments
M/55	curative	-	-	W/D	5year	RT(-)
M/18	curative	-	-	W/D	3year,10mo	RT(-)
M/56	curative	-	-	W/D	3year	RT(-)
M/64	curative	-	-	W/D	2year,7mo	RT(-)
F/64	noncurative	-	+	P/D	3year,5mo	RT(-)
M/69	noncurative	+	-	W/D	3year,5mo	RT(-)
M/49	noncurative	+	-	W/D	3year	RT(-)

R.M.;resection margin, W/D; well differentiated,

M/D;moderate differentiated, P/D;poorly differentiated

term survival¹⁵⁸). Hadjis and associates¹⁷ insisted that the difference in the survival times between patients with histologic clearance and those with microscopically positive or close (<1mm) resection margin was marginally significant statistically. Not only are the mucosal margins important in this regard but also the transverse margins, as pointed out in a paper by Ogura and associates¹⁶. However, the results of other reports^{13,18} indicated that microscopically positive resection margins did not affect prognosis in patients in whom the disease had been excised.

Since the first report in 1973 by Longmire et al, major hepatic resection and replacement of the complete hepatoduodenal ligament has been anatomically and experimentally feasible¹⁰. The reported clinical results from Japan are also promising^{11,12}. Comparisons of the most relevant series, local resection before 1980 and resections with partial hepatectomy since 1980, show that the addition of major liver resection provides a 5-year survival rate more than twice as long (17% vs. 7%), at the cost of an operative mortality twice as high (15% vs. 8%)¹⁹. The mean survival time has hardly improved with addition of a major liver resection⁹. Also, in our series, major liver resection did not improve overall survival(data not shown).

Surgery offers the only chance at a cure, and removal of all gross tumor probably provides the longest survival; but curative resection of these tumors is a reflection of the propensity for early local invasion of unresectable vital structures that lie in immediate proximity to the bile duct. There are several methods of delivering radiation to tumor beds: external irradiation, internal radiation and intraoperative radiation(IORT). Herskovic et al¹⁹ introduced intraductal¹⁹²iridium as a therapeutic approach for bile duct cancer. The principal advantage of¹⁹² iridium therapy is that it can be given with low morbidity and relatively little inconvenience to the patient. However, no definitive increase in survival has been documented using this modality and the principal deterrent to enthusiastic application of this therapy is lack of evidence of efficacy. IORT was investigated by some groups and seems to be of interest in improving local control²¹. High dose IORT to unresectable gross tumors while minimizing the dose on surrounding normal structures have been encouraging, but occasionally severe complications were experienced in porta hepatis, especially hepatic artery. Several reports demonstrated that external radiation therapy was of interest in palliation¹⁹ and could even be curative in some patients²⁰. Fortner et al¹³ suggested that

postoperative external radiotherapy might influence survival of patients with positive resection margin. In our series, patients with positive microscopic margins of resection had the same survival as patients with negative microscopic margins, infer ring that the adjuvant external radiotherapy had a positive effect on survival.

We recommend postoperative external irradiation in patients with locally advanced proximal bile duct cancer following resection, if possible.

Conclusion

The resection is the treatment of choice for locally advanced proximal bile duct cancer, if resectable. The noncurative resection followed by radiotherapy may be beneficial to patients with locally advanced proximal bile duct cancer.

References

- Mizumoto R, Kawarada Y, and Suzuki H. Surgical treatment of hilar carcinoma of the bile duct. *Surg Gynecol Obstet* 1986;162:153-158
- Molt P, Hopfan S, Watson RC, Botet JF, Brennan MF. Intraluminal radiation therapy in the management of malignant biliary obstruction. *Cancer* 1986;57:536-544
- Lim DJ, Kim MW, Kim BR. Result of operation for carcinoma of the proximal bile duct-the role of palliative resection. *J Kor Surg Soc* 1994;46:853-858
- Mahe M, Romestaing P, Talon B, Ardiet JM, Salerno N, Sentenac I, Gerald JP. Radiation therapy in extrahepatic bile duct carcinoma. *Radiotherapy and Oncology* 1991;21:121-127
- Ottow RT, Sugarbaker PH, August DA. Treatment of proximal bile duct carcinoma; an overview of techniques and results. *Surgery* 1985;97:251-262
- Beazley RM, Hadjis N, Blumgart HL. Clinicopathological aspects of high bile duct cancer. Experience with resection and bypass surgical treatment. *Ann Surg* 1984;199:623-636
- Bismuth H, Nakache R, Diamond T. Management strategies in resection for hilar bile duct cholangiocarcinoma. *Ann Surg* 1992;215:31-38
- Bengmark S, Ekberg H, Evander A, Klover-Stahl B, Tranberg KG. Major liver resection for hilar cholangiocarcinoma. *Ann Surg* 1988;207:120-125
- Hayes JK, Sapozink MD, Miller FJ. Definite radiation therapy in bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 1988;15:735
- Hadjis NS, Blenkharn JI, Alexander N, Benjamin IS, Blumgart LH. Outcome of radical surgery in hilar cholangiocarcinoma. *Surgery* 1994;107:597-604
- Ogura Y, Takahashi K, Tabeta M, Mizumoto R. Clinicopathological study on carcinoma of the extrahepatic bile duct with special focus on cancer invasion on the surgical margins. *World J Surg* 1994;18:778-784
- Fortner JG, Vitelli CE, Maclean BJ. Proximal extrahepatic bile duct tumors analysis of a series of 52 consecutive patients treated over a period of 13 years. *Arch Surg* 1989;124:1275-1279
- Bhuija MMR, Nimura Y, Kamiya J, Kondo S, Nagino M, Hayakawa N. Clinicopathologic factors influencing survival of patients with bile duct carcinoma: Multivariate statistical analysis. *World J Surg* 1993;17:653-657
- Boerma EJ, de Boer HHM, van der Heyde MN, van Haelst UJGM. Hemihepatectomy and replacement of the afferent hepatic blood supply in the dog. Resection of liver and hepatoduodenal ligament. *HPB Surg* 1989;1:101-105
- Mimura H, Kim H, Ochiai Y, etal. Radical

- block resection of hepatoduodenal ligament for carcinoma of the bile duct with double catheter bypass for portal circulation. Surg Gynecol Obstet 1988;167:527-529
16. Nimura Y, Haykawa N, Kamiya J, Kondo S, Nagino M, Kanai M. Hilar cholangiocarcinoma - Surgical anatomy and curative resection. J Hep Bil Pancr Surg 1995;2:239-248
17. Boerma EJ. Research into the results of resection of hilar bile duct cancer. Surgery 1990;108:572-580
18. Herskovic A, Heaston D, Engler MJ, Fishburn RI, Jones RS and Noell KT. Irradiation of biliary carcinoma. Radiology 1981;139:219-222
19. Meyer WC, Jones RS. Internal Radiation for bile duct cancer. World J. Surg. 1988;12:99-104
20. Iwasaki Y, Todokori T, Fukao K, Ohara K, Okamura T and Nishimura A. The role of intraoperative radiation therapy in the treatment of bile duct cancer. World J. Surg. 1988;12:91-98
21. Mittal B, Deutsch M and Iwatsuki S. Primary cancers of extrahepatic biliary passages. Int J Radiat Oncol Biol Phys. 1985;11: 849-854