

The Role of Radiotherapy in the Treatment of Extrahepatic Bile Duct Carcinoma

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Twenty-seven patients with unresectable extrahepatic bile duct carcinoma (n=21) or with microscopic evidence of tumor rest after aggressive surgery for extrahepatic bile duct carcinoma (n=6) between 1985 and 1990 were given radiotherapy consisting intentionally external radiotherapy and/or intraluminal therapy using Gamma-Med 12i (192-Ir) high dose rate (HDR) remote control afterloading system following bile drainage procedures and Gianturco stent insertion. The objectives of this study has been to assess the feasibility and effects on survival of a combination of external radiotherapy and brachytherapy with which we hope to achieve optimal loco-regional control for patients with unresectable extrahepatic bile duct tumors.

Sixteen patients were men and eleven were women, and the mean age was 58 years (34-70). 10MV X-ray was used for radiation therapy, with the total dose ranging from 45 Gy to 55 Gy, and intraluminal brachytherapy performed after external radiotherapy, with the dose of total 15 Gy. The minimum follow up was 12 months.

Failure were predominantly local-regional, without distant failure. Median survival was 10 months; 2-year actuarial survival rates was 21%. Median survival for common hepatic duct (CHD) cancer was 9 months; for common bile duct (CBD) cancer, was 16 months. And median survival for incomplete surgery/external radiotherapy group and external/intraluminal radiotherapy group was 10 months; for external radiotherapy alone group, was 6 months. Use of chemotherapy and/or hyperthermia were not affected in survival.

Therefore, our result is that the survival rates in the group of external/intraluminal radiotherapy were comparable with ones in the group of incomplete resection/external radiotherapy, and so we believe that the aggressive local and regional radiotherapy can improve the quality of life and the survival length.

Key Words: Extrahepatic bile duct tumors, Intraluminal brachytherapy

INTRODUCTION

The extrahepatic bile duct tumors tend to be small, grow slowly, remain sharply localized, and develop distant metastasis late. Despite the tendency of these tumors to grow slowly and manifest their presence early by obstructive jaundice, the prognosis has been poor^{1,2,4,5,12,18,26,41}. Irrespective of the treatment received, almost all patients die from hepatocellular failure and/or sepsis from high-grade biliary obstruction^{1,4,5,12,18,26,31,41}. In recent years, attention has been focussed on the possibilities that radiotherapy offers in the treatment of the extrahepatic bile duct tumors³⁶. Until the beginning of the 1980s, the only treatment modality considered potentially curative was radical surgery^{1,9,12,16,19,36}.

Although these lesions are frequently small at the time of diagnosis, there are not only difficult to diagnoses, but also often invasive of adjacent vascular structures. Therefore, merely 10~41% of patients are eligible candidates for resection and mortality rates for this form of treatment are not negligible (approximately 10%)^{2,3,9,12,13,14,16,19,22,23,26,28,30,36,37,41}. Despite advances in surgical technique during the past decades, cure rates for carcinomas of the extrahepatic biliary system have remained disappointingly low. Approximately 5~19% of surgical patients survive five years after radical resection^{3,5,6,9,19,29,30}.

It is estimated that even after intentionally curative resection, the local recurrence rate is about 25% and mean survival is 16~39 months^{9,12,13,16,19,22,26,28,30,36,37}. Usually the possible treatment is surgical bypass with the intent of symptomatic

relief^{12,16,17,19,22,26,28,41}). When palliative surgery was possible the reported average survival was 4 to 10 months. When palliative surgery for common hepatic duct cancer was not possible, the reported average survival was 1 to 4 months^{1,16,19,26}. The development of various technics of biliary drainage, including the recent use of percutaneous transhepatic cannulation and endoscopic retrograde biliary drainage (ERBD), allows palliative treatment even in inoperable patients^{11,17,21,23,29,32,33,41,43,44}.

Radiation therapy for biliary obstruction had been abandoned for a long time due to the concept that bile duct tumors were relative radioresistant and poor radiation tolerance of adjacent tissues such as liver, kidney, duodenum. Therefore low dose external irradiation had been used for a palliative intent without definite success^{1,2,3,7,15,17,23,36,38,39,41,42,44,47}. In order to give high dose in a short time to the central part of the tumor, internal radiotherapy has been proposed for a palliative goal^{10,14,17,23,25,27,34,41,46}. Therein, external-beam therapy, intraluminal treatment with 192-Ir or radium needles and intraoperative radiotherapy^{6,8} have been applied separately or in combination.

Several studies reported a mean survival of 9~12 months with some long-term, possibly cured survivors³⁶. Radiotherapy was also worthwhile for the patients who had successful palliative surgery and can achieve local control and forestall tumor extension and recurrence of bile duct obstruction by tumor^{1,12}. Detailed analysis of modes of tumor spread of the extrahepatic biliary system, based on findings at exploration or autopsy, indicates that a significant percentage of patients present with only local or regional disease and are therefore poten-

tially curable by local treatment³. Therefore, the combination of tumor resection and external and internal irradiation may well lead to cure in some of these patients¹².

The objectives of our work has been to assess the feasibility and effects on survival of a combination of external radiotherapy and brachytherapy with which we hope to achieve optimal loco-regional control for patients with unresectable bile duct tumors and to compare with the treatment results for incomplete resection and postoperative radiotherapy group.

MATERIALS AND METHODS

1. Patients Characteristics

Twenty three patients with extrahepatic bile duct tumors were referred to the Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine between 1985 and 1990. Patients referred to our clinic and thus included in this study were: (a) unfit for surgery due to extensive invasion on preoperative evaluation (n=13); (b) those with a tumor appearing to be unresectable at laparotomy (n=8); (c) those with microscopic residum after aggressive surgery (n=6).

Sixteen patients were male and 11 were female; the mean age was 58 years (range 34~70 years) and age distribution is listed in Fig. 1. Clinical symptoms and signs are listed in Table 1; diagnostic procedures in Table 2. Tumor localizations (established by means of ultrasonography, computerized tomography (CT scan), endoscopic retrograde cholangiopancreatography (ERCP),

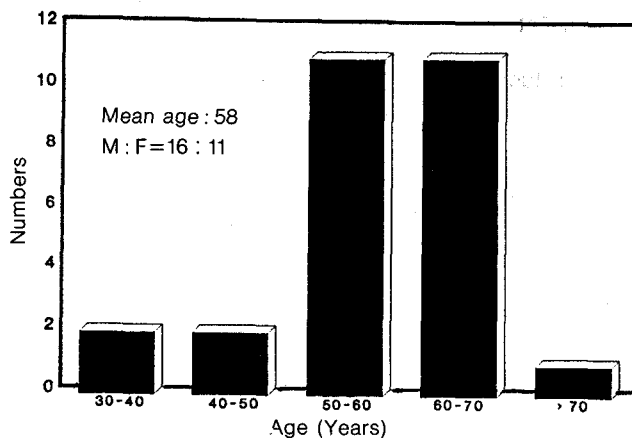


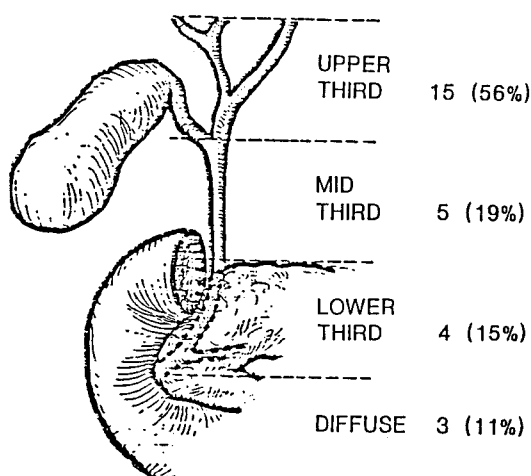
Fig. 1. Age distribution (1985~1990, 27 Patients).

Table 1. Clinical Signs and Symptoms

Symptoms/Signs	Number	Percentage (%)
Jaundice	24	89
Abdominal Pain & Tenderness	18	67
Anorexia	17	63
Pruritus	11	41
Change in urine/stool	9	33
Weight Loss	9	33
Malaise	9	33
Nausea/Vomiting	6	22
Hepatomegaly	5	19

Table 2. Diagnostic Studies

Procedures	No. of Patients
Percutaneous Transhepatic Cholangiography (PTC)	27
Endoscopic Retrograde Cholangiopancreatography (ERCP)	17
Abdominal Ultrasonography	19
Abdominal Computed Tomography	20
Liver Scan	2
Barium Studies	1
Angiography	2

**Fig. 2.** Anatomic distribution.

percutaneous transhepatic cholangiography (PTC) etc.) are shown in Fig. 2: upper third extrahepatic

Table 3. Treatment Modalities

Group	Treatment
I	Incomplete resection and postoperative radiotherapy
II	External radiotherapy alone
III	External radiotherapy and ILRT*

* ILRT : Intraluminal Radiotherapy

Table 4. Patients Characteristic Following Treatment Modality

	Group I (n=6)	Group II (n=13)	Group III (n=8)
Age (years)			
Mean	55	57	62
Range	34-68	39-69	55-70
Sex			
Male	4	7	5
Female	2	6	3
Location of Tumor			
Upper 1/3	3	7	5
Mid 1/3	1	3	1
Lower 1/3	1	1	2
Diffuse	1	2	0

bile duct (n=15), mid-third (n=5), lower third (n=4), and diffuse (n=3). Cytologic or histologic proof of the malignant character of the tumor was obtained (either by endoscopic route or at laparotomy) in eighteen patients. Prior to radiotherapy, adequate bile drainage was obtained by percutaneous transhepatic route in most patients.

2. Treatment

The patients were divided to three groups by the treatment modality (Table 3): (a) group 1 (n=6) was the patients with microscopic residuum after segmental resection with and without lymph node dissection and postoperative radiotherapy; (b) group 2 (n=13) was the patients with external radiotherapy alone; (c) group 3 (n=8) was the patient with combined external radiotherapy and intraluminal brachytherapy. The distributions between 3 group patients were no difference (Table 4).

The external radiotherapy target volume, determined with the aid of CT scan, PTC, and ERCP, encompassed the porta hepatis, common bile duct,

celiac nodes, and regional lymph nodes (hepatoduodenal ligament and superior pancreaticoduodenal nodes). The external radiation was delivered in total 45~55 Gy, 25~30 fractions of 1.8 Gy given over 6 weeks (Fig. 3). Before brachytherapy, patients were referred to consulting radiologist for insertion of Gianturco stent and Gamma-Med tube with inner diameter of 1.9 mm. Gianturco stent was inserted into the bile duct through drainage

catheter to prevent from developing the radiation fibrosis after intraluminal brachytherapy.

Intraluminal brachytherapy was performed at 4~6 weeks after finishing the external radiotherapy, using high dose rate (HDR) Ir-192 remote control afterloading system (Gamma-Med 12i), under the antibiotic prophylaxis and was controlled by fluoroscopy.

At the session, a dose of 5 Gy, calculated at a

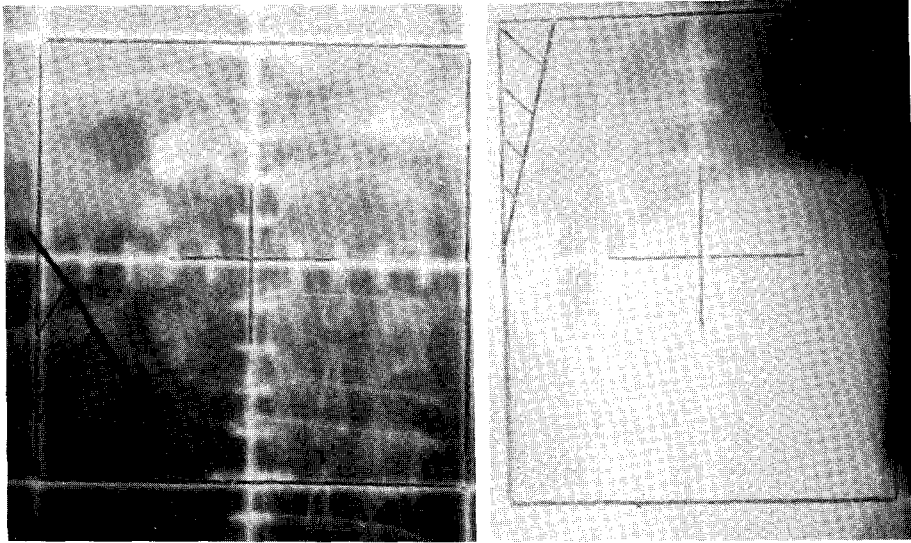


Fig. 3. Field arrangement of external irradiation; include primary tumor and surrounding regional lymph nodes through 4 box technique using 10 MV linear accelerator.

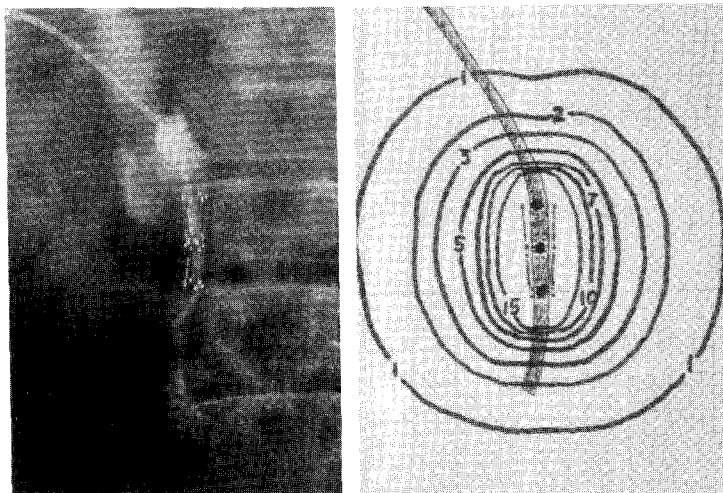


Fig. 4. Intraluminal brachytherapy: high dose rate (HDR) Ir-192 remote control afterloading system (Gamma-Med 12i), left-abdominal X-ray after Gamma-Med tube insertion and right-dose planning after Gianturco stent insertion.

point 1 cm from the margin of the Gamma-Med tube, was delivered. Thus, totally, 15 Gy was given in 3 fractions of 5 Gy (Fig 4). After brachytherapy was completed, percutaneous transhepatic biliary drainage (PTBD) catheter was removed when possible.

RESULTS

1. Failure Patterns

Locoregional control was defined as no evidence of disease progression in the time of last follow up. If not, it regarded to the locoregional failure.

The failure patterns were mostly locoregional failure without distant metastasis (Fig 5). Locoregional failure rates for each treatment group was; group 1 was 67% (4/6), group 2 was 79% (10/13)

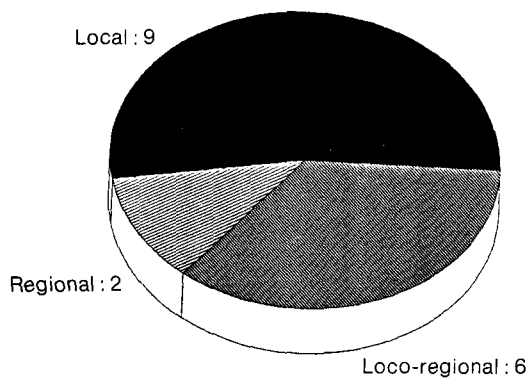


Fig. 5. Failure patterns.

and group 3 was 38% (3/8) respectively (Table 6). Although group 3 was better results than group 1 and 2, there was no significant difference ($p > 0.05$) because of small number of patients and short follow up periods.

2. Survival rates

The survival rates of entire patients (total 27 patients) is presented in Fig. 6. Median survival was 10 months; 2-year actuarial survival rates was 30%. 2-year actuarial survival rates by sites of tumor involvement revealed in Fig. 7; distal bile duct tumors ($n=9$) was better than proximal bile duct tumors ($n=18$) (66% vs 18%). But there was no significant difference ($p > 0.05$). 2-year actuarial survival rates by each treatment group were as follows (Fig. 8); group 1 was 56%, group 2 was 18%, and group 3 was 50%. Survival between group 1 and group 3 was no significant difference ($p > 0.05$). The use of chemotherapy was not affected to the local control and survival.

Table 5. Treatment Morbidity

External radiotherapy (n = 13)	
Gastrointestinal symptom	5*
Fever (> 38.0°C)	3
Sepsis	1
External radiotherapy and ILRT (n = 8)	
Gastrointestinal symptom	2
Fever (> 38.0°C)	4

* including duodenitis (1) and upper GI bleeding (1)

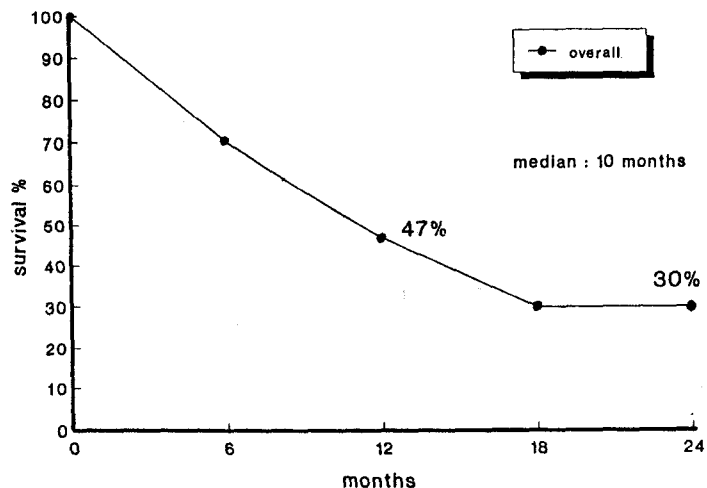


Fig. 6. Overall actuarial survival rates.

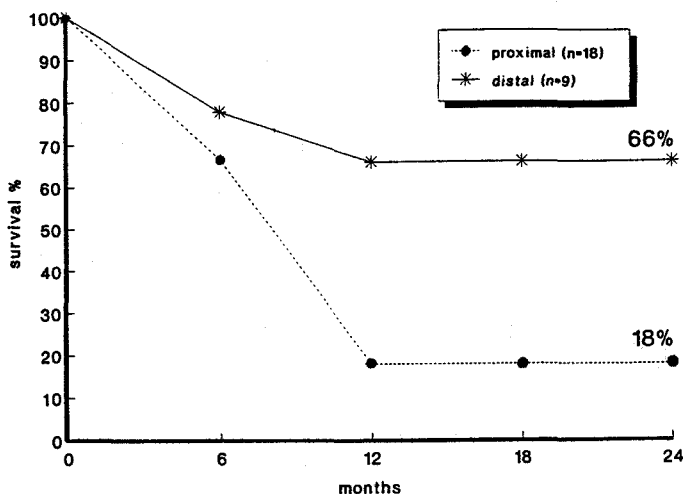


Fig. 7. 2-year actuarial rates for patients with proximal & distal disease.

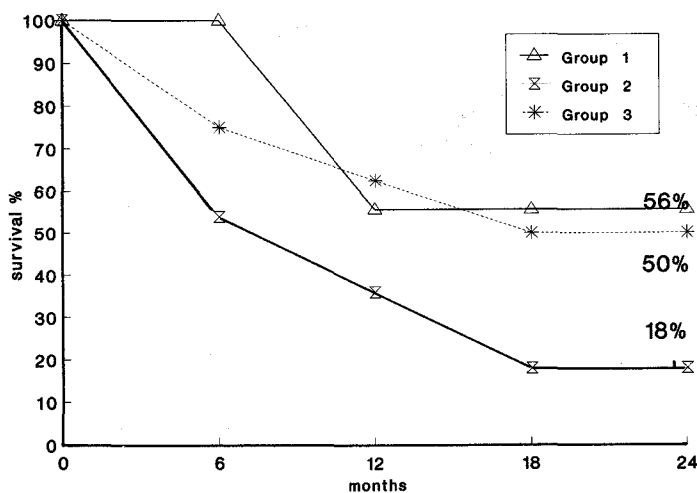


Fig. 8. 2-year actuarial survival rates for each treatment groups.

3. Treatment Morbidity (Table 5)

During the period of external radiotherapy, 7 patients required medication for gastro-intestinal symptoms (including 1 patient with duodenitis discovered by fiberoptic gastroscopy and 1 patient with upper gastrointestinal bleeding), 3 patients were treated with antibiotics for fever, probably due to cholangitis, and 1 patient died of sepsis. Periods of fever occurred shortly after insertion of Gamma-Med tube for intraluminal brachytherapy in 4 out of 8 patients and could be controlled with antibiotics. External radiation dose were ranged

Table 6. Locoregional Failure Rates

	Group I (n=6)	Group II (n=13)	Group III (n=8)
Local Failure	2	5	2
Regional Failure	1	1	0
Loco-regional Failure	1	4	1
Overall	4/6 (67%)	10/13 (77%)	3/8 (38%)

over 50 Gy in most patients with gastrointestinal symptoms.

DISCUSSION

Despite the tendency of the extrahepatic bile duct tumors to grow slowly and manifest their presence early by obstructive jaundice, the prognosis has been poor^{1,2,4,5,12,18,26,41}. Irrespective of the treatment received, almost all patients die from hepatocellular failure and/or sepsis from high-grade biliary obstruction^{1,4,5,12,18,26,31,41}. The management of malignant obstruction of the bile duct remains a taxing problem for physician in all oncologic disciplines.

If possible, radical surgical resection of extrahepatic bile duct tumors remains the treatment of choice, with a median survival approaching 16~39 months^{12,16,26,28}. Also, 5-year survival rates for curative resection were ranged from 5 to 19%^{19,30}. Surgical morbidity and mortality for curative surgery, regardless of approach, ranges from 10~20% and remains high despite in jaundice patients preliminary biliary decompression^{3,5,6,9,19,28,30}. Unfortunately, only 10~41% of these patients are resectable at the time of diagnosis^{12,19,26,30}, and the median survival of unresectable patients with no further therapy is 3~15 months^{12,19,23,26,39}. In conclusion curative surgical resection offers the best probability of prolonged survival and the best quality of life. However, the majority of patients are suitable only for a palliative procedure and the best palliation is achieved by a surgical bypass procedure. Alexander et al¹⁹ reported that the rates of performing bypass surgery and surgical drainage were 76%; 5-year survival rates were 0%.

The development of various technics of biliary drainage allows palliative treatment even in inoperable patients^{11,17,21,23,32,33,41,43,44}. Recent interest has centered on nonsurgical palliation with percutaneously and endoscopically stents. Numerous technical innovations, including internal prostheses, continued to be developed. Relief of jaundice and pruritus by these techniques, is effective in unresectable bile duct tumors; however, cholangitis is a frequent accompaniment, and survival remains short, with median survivals ranging from 2 to 5 months²⁵.

Prior to the mid-1970's, radiation therapy played no role in this disease. Standard reference texts cited the mistaken belief that adenocarcinomas are "radioresistant"^{1,18,36}. But radiation therapy as a modality of local treatment has been reported to be of palliative benefit in several reports of malignant

biliary obstruction. Although criteria for response have differed, reported response and palliation rates have varied from 20% to 100%^{1,2,3,7,15,17,18,23,25,36,38,39,41,42,44,47}. Reported mean or median survivals have ranged from 7.3 to 15 months in these studies^{1,3,18,38,39}. Radiotherapy was also worthwhile for the patients who had successful palliative surgery and can achieve local control and forestall tumor extension and recurrence of bile duct obstruction by tumor^{1,12}. Therefore, the combination of tumor resection and external and internal irradiation can add to those with resectable lesions with high likelihood of microscopic residual disease, and also those with unresectable or gross residual disease after surgery^{12,44}. Our results appeared that in the 6 patients with postoperative adjuvant radiotherapy for microscopic residuum after incomplete resection, median survival was 10 months; 2-year survival rates 56%. This results were comparable with other reports.

In order to give high dose in a short time to the central part of the tumor, intraluminal brachytherapy has been proposed for a palliative goal^{10,14,17,23,25,27,34,41,46}. The advantage of intraluminal brachytherapy is two-fold: first, an exceedingly high dose of radiation can be given precisely at the point of biliary obstruction, with little effect on normal structures in the area. Furthermore, the patient is usually left with patent anatomic bile drainage without the need for prosthetic devices^{10,14,17,25,27,34,41,46}. But of concern is the possibility of radiation induced fibrosis and stricture of the bile duct¹¹. Therein, external radiotherapy and intraluminal brachytherapy using high dose rate (HDR) remote control afterloading system (Gamma-med 12i) with insertion of Gianturco stent for the purpose of preventing the radiation-induced fibrosis have been applied^{6,8,36}.

Molt et al noted that radiation dose due to the gamma emission of encapsulated Ir¹⁹² decreased rapidly in tissue, thus allowing delivery of high doses of radiation to a well-defined and limited volume while minimizing exposure to adjacent structures²⁵.

Since then, Green et al¹¹ reported 4 patients with common hepatic duct carcinoma. Survival from the time of surgery ranged from 7~17 months. Although these patients all had relief of obstructive jaundice, autopsy subsequently revealed gross disease at the initial site of obstruction in 3/4 patients. Pilepich et al⁹ described 6 patients with common bile duct tumor treated with T-tube drainage and postoperative external radiotherapy (4000

~6000 cGy) following T-tube insertion alone (4 patients) or following radical surgical resection (2 patients). The 3 patients were without evidence of disease 6 months, 26 months, and 4.5 years following therapy. Two of the 3 survivors had received 6000 cGy, and the authors therefore recommended high-dose external radiotherapy for patients with common bile duct lesions.

Lees et al⁵⁾ reported that in patients with localized tumors at the bifurcation, average survival was increased from 0.4 to 1.7 years with the addition of external radiotherapy to palliative bypass or intubation. Smoron³⁸⁾ and Hishikawa et al¹⁵⁾ have reported improved survival rates with external radiotherapy at doses of greater than 4000 cGy in patients with unresectable biliary primary lesions as compared with lower doses (respectively, 15 months vs. 2.5 months: 10.3 months vs. 3 months).

Fletcher et al¹⁴⁾ described 8 patients with unresectable common hepatic duct tumors irradiated with Ir¹⁹² placed via U tubes. Total delivered dose was 4000~7800 cGy over 48 hours calculated at 0.5 cm from the wire. There were no acute complication from the procedure, and 6/8 patients were reported living 2, 4, 5, 16, 22, and 23 months following Ir¹⁹² treatment. Conroy et al¹⁰⁾ advanced this "intracavitary alone" approach by placing Ra²²⁶ needles in a Ring biliary drainage catheter. A dose of approximately 20000 cGy was delivered to the bile duct walls of 6 patients (approximately 14000 cGy at 1 cm from the needles). It was anticipated that this high dose would cause dense periductal fibrosis so rigid that subsequent patency could not be maintained without any catheter or stent in place. Five of 6 patients had died at the time of the report and the sole patients alive 6 months after treatment had required reinsertion of the Ring catheter because of recurrent obstructive jaundice. Thus, although reports are conflicting, it would appear that intracavitary irradiation alone is inadequate in providing long-term symptom-free survival, despite relatively high doses. This is because the volume irradiated using this technique rarely encompasses the entire tumor bulk, and subsequent regional regrowth of disease may still compress the periductal sterilized area. Herskovic et al¹⁷⁾ reported treating 10 patients with 5000 cGy to the bile duct wall using Ir¹⁹² sources placed in external drainage catheter, followed by a 4 MV rotational external-beam boost to the surrounding tumor volume in 7 patients for a combined minimum tumor dose of 5800 cGy. Chitwood et al⁴⁰⁾ reported that 6/7 and no evidence of recur-

rence as measured by repeated cholangiograms 3 ~13 months after Ir¹⁹² placement. Buskirk et al⁴²⁾ have treated 16 patients. Five received Iridium-192 boosts following external beam irradiation. Four were alive without disease at early follow-up. In the reports of Fletcher et al¹⁴⁾, median survival of 19 treated patients was 11 months, with 47% surviving more than 1 year and 9/19 alive at the time of reporting. Mornex et al¹⁷⁾ reported survival ranging from 1 to 19 months (median, 8 months) among seven patients with localized Klatskin and common bile duct cancers, with four alive at 4 to 11.5 months. They suggested that intraluminal radiotherapy permits symptomatic palliation without excessive side effects for the patients. Johnson et al²⁹⁾ employing intraluminal radiotherapy in combination with external radiotherapy, observed a median survival from treatment of 5.5 months in seven patients with bile duct cancer. Three of 7 patients survived from 8.5 to 12.5 months. Our results was that median survival and 2-year survival rate for external radiotherapy alone were 6 months and 18%; for external radiotherapy and intraluminal brachytherapy using Gamma-Med 12i (Ir¹⁹²) high dose rate (HDR) remote control afterloading system, 10 months and 50%, respectively. This results is comparable with postoperative adjuvant irradiation for microscopic residuum after incomplete resection.

Adjunctive chemotherapy have not been usually helpful in local control and prolonging survival but the role of chemotherapy in future must be defined by prospective controlled studies^{9,20,45)}. In six of 27 patients, chemotherapy using 5-fluorouracil containing regimen were performed. There is no effect of improving survival and local control.

CONCLUSION

Patients with unresectable extrahepatic bile duct tumors cannot be adequately treated with external radiotherapy alone, because of the poor tolerance of surrounding normal tissues. The use of brachytherapy techniques to boost the local tumor dose appears to increase duration of survival, to improve the quality of life, and to be well-tolerated, efficacious in terms of significant palliation and local control.

We propose that the role of radiotherapy in the management of these tumors should be evaluated systemically as follows;

- 1) postoperative radiotherapy be given after curative surgery especially in those patients with

inadequate surgical margins and/or locally aggressive tumors to increase the length and quality of survival by decreasing the incidence of local recurrences.

2) combined external and intraluminal radiotherapy be given after palliative or exploratory surgery, and when palliative surgery has failed, to increase the effectiveness of palliation and to increase local control.

3) combined external and intraluminal radiotherapy be used for relief of obstructive jaundice in patients with unresectable extrahepatic bile duct tumors and in whom surgery is refused and/or contraindicated.

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국문초록 =

간외담도종양에서 방사선치료의 역할

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1985년부터 1990년까지 연세대학교, 연세암센터 치료방사선과에 내원하였던 27명의 간외담도종양환자를 대상으로 외부방사선조사 및 관내 근접조사(intraluminal brachytherapy)를 병용하였을 경우 적절한 국소관해율을 얻을 수 있는지에 대한 후향적 분석을 하였고 이러한 치료방법에 대한 결과를 불완전한 절제술후 방사선치료를 시행한 군의 치료성과 비교분석하였다.

16명은 남성이었고 11명은 여성이었으며, 평균나이는 58세(34~70세)였다. 외부방사선치료는 10 MV Linear Accelerator, 4 분조사방법을 이용하였고 총 조사량은 45~55 Gy이었다. 관내 근접조사는 외부방사선조사후 시행하였고 Ir-192를 사용한 고선량치료기기인 Gamma-Med 12i를 이용하여 총 15 Gy를 조사하였다. 최소 추적조사기간은 12개월이었다. 치료방법에 따라 3개의 군으로 대별해보았는데, 1군(6명)은 불완전 절제술후 미시적 잔류암존재로 방사선치료를 시행했던 경우이고 2군(13명)은 수술불가능하여 방사선치료 단독으로 치료하였던 경우이며, 3군(8명)은 외부방사선조사와 관내근접조사를 병용하였던 경우로 분류하였다.

치료실패요인은 대부분 국소실패였고 원격전이는 관찰되지 않았다. 중앙생존기간은 10개월이었고 2년 생존율은 30%이었다. 각 치료군에 따른 치료실패율은 1군 67%(4/6), 2군 79%(10/13), 3군 38%(3/8)이었으며 중앙생존기간은 각각 10개월, 6개월, 10개월이었다. 또한 2년 생존율은 각각 56%, 18%, 50%로서 종합적으로 1군과 3군간의 생존율과 중앙생존기간은 의미있는 차이는 없었다.

따라서 본 저자들은 간외담도종양 환자의 경우 외부 방사선치료만으로는 만족할 만한 결과를 얻을 수 없었으며 외부방사선 치료와 관내근접조사를 병용하였을 경우 수술적 절제술이 시행되었던 경우와 비슷한 치료성적을 얻었기에 이를 보고하는 바이며 향후 이러한 결과를 바탕으로 생존율을 향상시키기 위해 적극적인 방사선치료 방법이 모색되어야 하리라 생각하는 바이다.