

Radiotherapy of cholangiocarcinoma: the roles for primary and adjuvant therapies

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Summary. A total of 22 patients with cholangiocarcinoma who had been treated with external radiotherapy between 1978 and 1989 were analyzed. Of the 22 patients, 18 had cancer of the hepatic hilus (Klatskin) and 4 had intrahepatic biliary cancer; all but 2 of the subjects had advanced disease. In all, 16 patients underwent primary irradiation for unresectable tumors, 4 were subjected to adjuvant irradiation after gross tumor resection, and 2 received preoperative irradiation followed by gross tumor resection. The mean initial irradiation dose was 52.0 Gy (range, 26–78 Gy). The TDF (time-dose-fractionation) for the entire course of radiotherapy ranged from 49 to 154 (mean, 100). The median survival of all patients was 10 months, and the cumulative 1-year survival value was 37.7%. The external radiotherapy proved to be effective in the treatment of cholangiocarcinoma in terms of palliation and survival.

The objective of the present study was to assess the value of external radiotherapy as locoregional therapy for cholangiocarcinoma.

Patients and methods

Patients. A total of 22 patients with cholangiocarcinoma were referred to the Department of Radiotherapy at the National Medical Center Hospital between 1978 and 1989. Patients with a history of postoperative recurrence and those who had received less than 20 Gy were excluded from this study. The histological diagnosis of 15 patients was adenocarcinoma; materials for tissue diagnosis were not obtained from the remaining 7 subjects. The 22 patients included 14 men and 8 women whose mean age was 63.5 years (range, 45–85 years) and who had been diagnosed as having intrahepatic cholangiocarcinoma ($n = 4$) or hilar cholangiocarcinoma (Klatskin tumor, $n = 18$). Two patients had localized disease, but the others all had advanced disease. The patients' characteristics are summarized in Table 1.

Treatment. In all, 16 patients underwent primary irradiation for unresectable tumors in the presence or absence of palliative surgery, 4 were subjected to primary irradiation after gross tumor resection, and 2 received preoperative irradiation followed by gross tumor resection. All patients were treated with high-energy (6-, 10-, or 18-MV) X-rays. The initial dose varied between 26 and 78 Gy (78 Gy was the combined dose of preoperative and postoperative irradiation), the mean value being 52.0 Gy. AP-PA parallel opposed fields were used, with the field size ranging from 16 (4×4) to 162 (12×13.5) cm² and the average being 61.8 cm². The patients tolerated the radiotherapy well, and four subjects

Introduction

Despite recent advances in diagnostic imaging modalities such as ultrasound (US) and computed tomography (CT), most patients with cholangiocarcinoma have advanced disease at diagnosis and tumor resectability is low. Furthermore, even after curative resection has been performed, the local recurrence rate is high and the prognosis remains poor. Adenocarcinoma has long been considered to be radioresistant, but some recent reports justify the use of radiotherapy for bile duct cancer. External radiotherapy has been applied solely or in combination with brachyther-

Table 1. Patients' characteristics and treatment

Characteristic	Hepatic hilus	Intrahepatic	Total
Sex (M/F)	10/8	4/0	14/8
Mean age in years (range)	63.0 (45–85)	65.5 (46–78)	63.5 ± 9.9
Resection (n)	4	2	6
Initial radiotherapy:			
Dose (Gy)	50.9 (26–78)	56.8 (45–64)	52.0 ± 12.6
Field size (cm ²)	58.8 (16–162)	76.0 (36–121)	61.8 ± 32.3
TDF (total course)	97.9 (49–154)	110.3 (85–152)	100 ± 25

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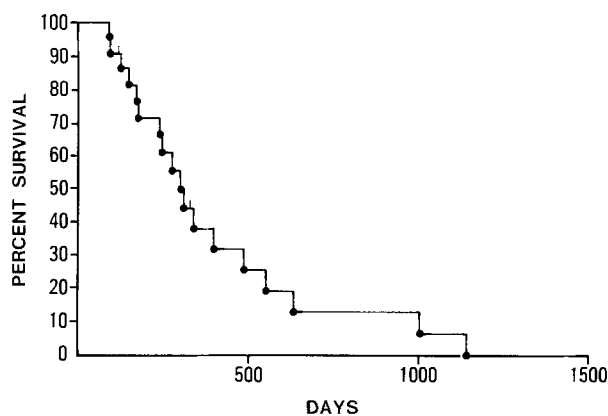


Fig. 1. Cumulative survival curve generated for patients with cholangiocarcinoma ($n = 22$)

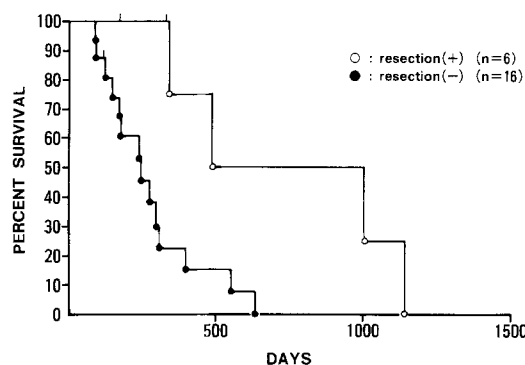


Fig. 2. Cumulative survival curves constructed for cholangiocarcinoma patients treated in the presence and absence of gross tumor resection

received additional irradiation (36–53 Gy; mean, 45.5 Gy) for palliation. For purposes of comparison, we performed time-dose-fractionation (TDF) conversion on all radiation doses. The TDF for the entire course of radiotherapy ranged from 49 to 154 (mean, 100). The usefulness of this therapy was evaluated on the basis of its feasibility, the local response, the patients' survival, and the postmortem examination findings.

Results

Feasibility

The initial external radiotherapy was well tolerated by the patients, and radiotherapy was discontinued under 40 Gy in only four subjects due to nausea and vomiting in two cases and to cholangitis in one case. The acute side effects of the radiotherapy were minimal except in these three patients. In one other case, the primary irradiation was altered to preoperative irradiation with 31 Gy.

Local response

The responsiveness to the external irradiation was evaluated by pre- and posttreatment cholangiograms. In all, 14 patients were evaluable, and improvement on the cholangiogram was noted in 7 subjects (50%). One patient

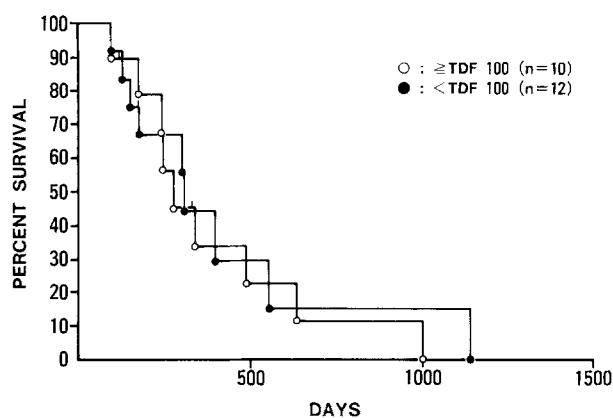


Fig. 3. Cumulative survival curves generated for cholangiocarcinoma cases as a function of the TDF

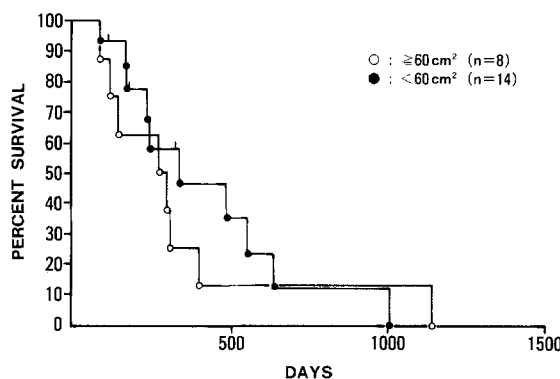


Fig. 4. Cumulative survival curves constructed for cholangiocarcinoma patients as a function of the field size

could be discharged without the need for PTCD (percutaneous transhepatic cholangiographic drainage) after radiotherapy.

Survival

The cumulative survival curve generated for all patients is presented in Fig. 1 (Kaplan-Meier method). The median survival for the entire group was 10 months, and the cumulative 1-year survival value was 37.7%. A significant difference in survival was found between patients who underwent gross tumor resection and those who did not (Fig. 2). Two patients survived for more than 2 years after the start of therapy; both had undergone gross tumor resection. All patients who did not undergo gross tumor resection died within 2 years. No difference in survival was found between patients who received a radiation dose of <100 TDF and those who received ≥100 TDF (Fig. 3). Similarly, no difference was detected between patients with radiation fields of <60 cm² and those with fields of ≥60 cm² (Fig. 4). The period of survival was shorter in four patients with intrahepatic cholangiocarcinoma, including two who had undergone gross tumor resection, than in patients with cholangiocarcinoma located at the

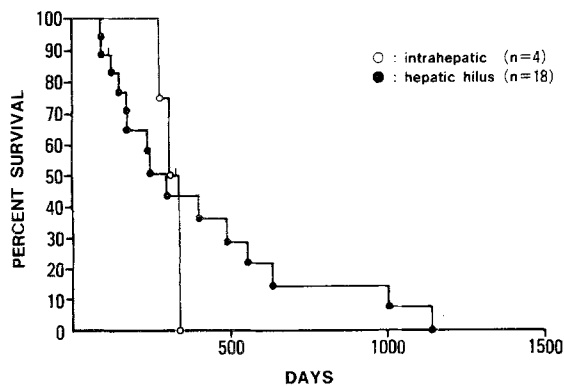


Fig. 5. Cumulative survival curves generated for cholangiocarcinoma cases as a function of the tumor location

hepatic hilus. All but one patient with the latter tumor died within 1 year (Fig. 5).

Postmortem examination findings

Seven patients underwent postmortem examinations (Table 2). Persistent carcinoma was detected in all of these patients within the irradiated field. Most subjects showed macroscopically and microscopically dense fibrosis in the irradiated portion. Two of the seven patients who had undergone gross tumor resection experienced local recurrence. Six patients showed evidence of invasion to adjacent structures such as the liver, kidney, and adrenal gland. Regional lymph node metastases were found in all but two patients, and distant metastases were also detected in two others. Tumor thrombosis was found in the portal vein in two patients and in the common bile duct in one subject. Massive hemorrhage into the common bile duct was noted in the latter patient, and his death was attributed to hemorrhagic shock. One patient died of upper gastrointestinal bleeding due to a stomach ulcer; although he had received a total dose of 154 TDF, the field of initial radiotherapy did not include the stomach. Additional radiotherapy of 45 Gy

was performed for palliation using multiportal techniques (case 3). The major causes of death were liver failure and/or liver abscess.

Discussion

The mortality of patients with cholangiocarcinoma is higher in Japan than in Western countries. Furthermore, both the morbidity and the mortality have increased in recent years. The resectability of bile duct cancer remains approximately 20%–35% due to the proximity of vital structures and their early invasion [3, 4]. A review of the literature by Kopelson et al. [7] revealed that 26% of patients developed local recurrence after undergoing curative surgery. The 5-year survival value remains less than 5% in most series.

Response

Evaluation of the treatment response of bile duct cancer using CT or US is somewhat difficult. A local response to primary irradiation as evaluated from cholangiograms was recognized in 50% of the patients in our series. However, this improvement was minimal except in one patient who no longer required PTCD after irradiation. In patients with complete obstruction of the bile duct, recanalization was frequently observed after intraoperative radiotherapy [13]. Actually, tumor regression does not result in improvement of the biliary passage. One reason may be the development of fibrosis in the irradiated portion. Green et al. [6] reported that at autopsy, one of four patients showed extensive fibrosis of the common hepatic and common bile ducts after radiotherapy, but repeated T-tube manipulation was surmised to have been the cause. Higher doses of irradiation may have a greater likelihood of causing fibrosis. Other factors such as swelling of the bile-duct wall and atrophy of the bile duct must also be considered [2]. Moreover, the type of tumor growth seems to affect the treatment response.

Table 2. Postmortem examination findings

Patient, age (years), sex (M/F)	Loc.	Rec. ^a	Infiltration	Metastasis	Cause of death	Survival (months)
1. Y. T. 47 M	H	+	Liver, pancreas, ileum, PV thrombus	LN, right kidney and adrenal gl.	Liver abscess, pulmonary congestion	33
2. K. K. 59 M	H	–	Tumor thrombus (PV, SV)	LN (hepatoduodenal)	Liver failure (liver abscess)	18
3. Y. K. 65 M	H	+	Right kidney and adrenal gl.	LN (superior celiac)	GI bleeding (stomach ulcer)	16
4. T. U. 46 M	I	–	GB, duodenum, peri-CBD, tumor thrombus (CBD)		Hemorrhagic shock	10
5. M. I. 72 F	H	–	CBD, pancreas, right kidney and adrenal gl., transverse colon	LN, liver, lung, adrenal gl., ovary	Peritonitis carcinomatosa	8
6. K. N. 65 F	H	–	Intrahepatic bile duct		Acute hemorrhagic pancreatitis	8
7. K. N. 78 M	H	–	Liver, portal vein	LN (hilus, para-aorta)	Liver abscess	5

^a Rec. = recurrence: +, after resection; –, no resection

Loc., Location; H, hilus; I, intrahepatic; PV, portal vein; SV, splenic vein; adrenal gl., adrenal gland; CBD, common bile duct; LN, lymph node

Survival

Significant palliation can be achieved by biliary decompression, e.g., using PTC, resulting in prolongation of life and relief of the symptoms of obstructive jaundice. Almost all of our patients tolerated the radiotherapy well. Mittal et al. [8] reported that the median survival of patients receiving radiation doses of ≥ 70 TDF was longer (11 months) than that of patients receiving < 70 TDF (4.4 months). In our series, the TDF values were higher than those reported by other investigators, and all but three patients in this study received > 80 TDF. No significant survival benefit was noted for the group receiving > 100 TDF. Smoron [11] has recommended a total radiation dose of 4500 rad. In regard to the irradiation fields, we did not see a difference in survival between those measuring < 60 cm² and those measuring ≥ 60 cm².

Generally, a wide field that includes the lymphatic drainage is recommended, but few reports have stated the actual field size. Smoron [11] recommended fields measuring 12×12 cm or less, but the details were not described. Our results seemed to arise from the relatively small median field size used and from the smaller fields irradiated in patients who had undergone gross tumor resection (mean, 41.5 cm²).

Fields and Emami [5] recommended that the initial external radiotherapy deliver 4500–5000 cGy to a large volume of tissue encompassing the main sites at risk of recurrence in patients with completely resected tumors. In our autopsy findings, local failure of the primary tumor was recognized in all of the patients, even after gross tumor resection. Further investigation is needed to determine the optimal field size for adjuvant therapy as well as primary therapy.

Intrahepatic cholangiocarcinoma is not common, and it represents about 0.5% of primary liver tumors in the United States [14]. There have been few reports on radiotherapy for intrahepatic cholangiocarcinoma. In 1960, Phillips and Murikami [9] reported on one patient with intrahepatic cholangiocarcinoma who received radiotherapy with 250-kV X-rays but showed no response. Stillwagon et al. [12] obtained a median survival of 6.5 months in patients with nonresectable intrahepatic cholangiocarcinoma using external radiation and ¹³¹I-labeled anti-CEA. In our series, all but one patient died within 1 year. Although the present series included only a small number of such cases, no proven benefit from radiotherapy has been shown for this tumor.

Pilepich and Lambert [10] reported that two patients with common bile duct cancer survived with NED (no evidence of disease) for 6 and 26 months following T-tube insertion and radical radiotherapy with 6000 rad. In the present series, two patients survived for more than 30 months after undergoing gross tumor resection, but all of the patients who were not subjected to gross tumor resection died within 2 years.

Other reports have shown improved survival for patients receiving combined external radiotherapy and intracavitary brachytherapy [1, 5] or intraoperative radiotherapy [1, 13]. Considering the surrounding normal tissue

tolerance, the use of brachytherapy or intraoperative radiotherapy would be reasonable for achieving higher local tumor control. However, external radiotherapy alone has also been shown to provide palliation and some degree of life prolongation, as well as the occasional cure of cholangiocarcinoma. The dose-limiting factor is the surrounding normal tissue tolerance, especially in the upper gastrointestinal tract. Buskirk et al. [1] did not recommend that doses in excess of 5500 rad be delivered unless the tumor volume was small. Additional radiotherapy increases the risk of bleeding from the upper gastrointestinal tract.

Cholangitis and liver abscess are special and lethal conditions related to cholangiocarcinoma, as shown in autopsy examinations. Intensive therapy for these conditions must be developed. In the present series, contrary to our expectation, no cure was obtained in patients who had residual disease after undergoing gross tumor resection. Further therapeutic advances are required for the improvement of local tumor control and survival in patients with cholangiocarcinoma.

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