

External Radiation Therapy Combined with Hyperthermia in the Carcinoma of Extrahepatic Biliary System

Hoon Sik Bae, M.D.

*Department of Therapeutic Radiology, Kangdong Sacred Heart Hospital,
College of Medicine, Hallym University, Seoul, Korea*

From January 1986 to September 1990, 7 patients with carcinoma of the extrahepatic biliary system received external radiation therapy combined with hyperthermia. Of the 3 patients with extrahepatic bile duct cancer, two were primary cholangiocarcinoma and one was metastatic peripancreatic carcinoma. Of the 4 patients with carcinoma of the gallbladder, two were locally advanced and unresectable carcinoma and the remaining two were local-regional recurrence after cholecystectomy. They were all pathologically proven adenocarcinoma.

The radiation dose received ranged from 3000 cGy/2weeks to 5040 cGy/7 weeks. The hyperthermia was done once or twice a week and 4 to 12 sessions in total. The tumor response was confirmed by T-tube cholangiography, percutaneous transhepatic cholangiography and CT scan. 6 out of 7 (86%) showed partial regression of the tumor. The median survival time was 7 months (range 4~11 months). 6 out of 7 patients were dead: one died of septicemia, 4 of primary disease, one of distant metastases. Only one out of 7 patients is still alive but new metastatic lesion was found.

There was not any treatment related deaths. There was also no evidence of treatment related problems with liver, stomach and duodenum, although the observation period was short.

Key Words: Bile duct cancer, Gallbladder cancer, Radiotherapy, Hyperthermia

INTRODUCTION

Carcinomas of the gallbladder or extrahepatic bile ducts are uncommon, but devastating malignancies. Most series report overall 5-year survival less than 10%^{1,2)}. Surgery remains the mainstay of treatment. Approximately 10~30% of tumors are resectable at presentation^{3,4)}, and local regional recurrence rate is 25~60% after curative resection^{6,7)}. 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 potentially curable by local treatment^{4,8)}. In the past, these lesions have been considered resistant to radiation⁹⁾. Several reports have suggested palliative benefit from external beam radiation therapy in primary or metastatic malignant obstruction of the biliary tract^{1,3,4,10~14)}. Early experience with external radiation therapy demonstrated good palliation with occasional long term survival, and a suggestion of better results with higher dose¹²⁾. External radiation therapy has been used as a palliative agent, but only low doses of 40 to 50 Gy in 4 to 6

weeks can be delivered due to the general and local tolerance^{10~14,16)}. In order to give high dose to the central part of the tumor, several groups used external-beam radiation therapy followed by intracavitary radiation therapy, usually with Ir-192^{2,14,17~20)}.

Some reports with intraoperative irradiation are also encouraging²¹⁾. However, in view of the limited tolerance of the duodenum and reported complications such as duodenitis, bleeding, gastric ulcer, et al. after radical irradiation^{22~24)}, the use of radiation dose modifier such as hyperthermia can improve the local control rate with safety^{25~27)}.

The present report describes personal experience with the use of irradiation combined with hyperthermia for primary and metastatic carcinoma of the extrahepatic bile duct and gallbladder.

METHODS AND MATERIALS

1. Patient Selection

From January, 1986 to September, 1990, 10 patients with carcinoma of the extrahepatic bile duct or gallbladder were referred to the Depart-

ment of Therapeutic Radiology, Maryknoll Hospital, Pusan. Among them one patient was dropped during treatment due to poor general condition, and the other 2 patients had no histological proof. The remaining 7 patients were considered eligible for this study (Table 1). The average age of patients was 64 years. The male to female ratio was 5:2.

2. Pathology

All patients had histologically proven adenocarcinoma: 1) poorly differentiated--3 (43%); 2) moderately differentiated--1 (14%); 3) well differentiated--3 (43%). Two patients had cholangiocarcinoma of extrahepatic bile duct. Four patients had carcinoma of the gallbladder. One patient had peripancreatic and pericholedochal metastases from stomach cancer (Fig. 3).

3. Surgical Management

4 patients were locoregionally advanced and considered unresectable at exploration, 2 patients were local-regional recurrences after cholecystectomy, and one patient was medically contraindicated for exploration: One underwent ultrasound-guided biopsy and percutaneous transhepatic bile drainage; Two underwent biopsy only;

Four underwent exploratory laparotomy and one of them underwent T-tube choledochostomy also.

4. Radiation

Radiation and hyperthermia was initiated as soon as the surgical wound had healed and patients had stabilized which was usually 2 to 3 weeks postoperatively. Radiation was delivered with Cobalt-60 teletherapy unit. The external therapy target volume usually encompassed the tumor or tumor bed and major nodal chains (cystic or hilar lymph node near the junction of the cystic and common hepatic duct, superior pancreaticoduodenal node, celiac nodes or to a group of retroduodenal nodes and nodes around the origin of the superior mesenteric artery). The size of radiation fields were between 8×8 and 13×13 cm. Tumor volume was defined by cholangiogram (usually obtained through the T tube and PTBD tube), UGI series, CT, and position of the surgical clips. Total external radiation dose was 3000~5040 cGy, and daily fractions were 180~300 cGy. External radiation was usually given opposed anterior-posterior portals, and last 360~540 cGy was added using AP-PA shrinking fields.

Table 1. Patient Characteristics and Clinical Course

Case	Age/Sex	Site	Tumor Extent	External Radiation (cGy/Fraction/Day)	Hyperthermia (No/Day)	Current Status	Survival from Tx to death or last follow-up
1	59/M	CHD	Bifurcation of the CHD, left lobe of liver	4500/25/33	11/38	died of sepsis	7 months
2	62/M	GB	GB, T-colon, duodenum, abdominal wall	5000/25/43	10/26	died of primary disease	11 months
3	60/M	GB	GB, Porta hepatis, Rt lobe of liver, Peripancreatic LNs	3000/10/14	8/34	died of primary disease	4 months
4	71/M	CHD	CBD, Duodenum	4860/27/44	10/36	died of primary disease	6 months
5	70/F	GB	GB, Rt lobe of liver, Porta hepatis, T-colon, peritoneum	5040/28/50	4/15	died of primary disease	7 months
6	58/F	GB	GB, Porta hepatis, Abdominal wall	5040/28/50	7/51	alive with progressive disease	11 months
7	65/M	Stomach	Peripancreatic and pericholedochal tissue	4500/25/35	12/43	died of distant metastases	4 months

CHD: common hepatic duct, GB: gallbladder, CBD: common bile duct, T: transverse, LN: lymph node, Rt: right, Tx: treatment

5. Hyperthermia

Hyperthermia was applied approximately 30 minutes after irradiation. 8 MHz radiofrequency capacitive heating machine (Thermotron RF-8, Yamamoto Vinyter Co., Osaka, Japan) was used for hyperthermia. The radiofrequency is applied through a pair of electrodes placed on opposite sides of the body and power is distributed locally or regionally through interaction of electric fields produced between the parallel-opposed electrodes. The surface of the body of the treated site was precooled before hyperthermia down to approximately 25°C so that excessive heating of the skin and subcutaneous fat can be avoided.

Temperature was measured directly using the single point microthermocouple (Sensortek Inc.,

NJ) implanted during operation in 5 of 7 patients. The remaining 2 patients were measured indirectly; microthermocouple guiding through the T-tube and percutaneous transhepatic catheter.

Hyperthermia was applied regionally once a week or twice a week in 3 days interval. The total numbers of hyperthermia for each patient ranged from 4~12 and it was depended on achieved maximal temperature and performance status. The maximum monitored temperature was kept at 41~43°C for 30~40 minutes.

RESULTS

1. Toxicity

Overall acute tolerance to combined modality

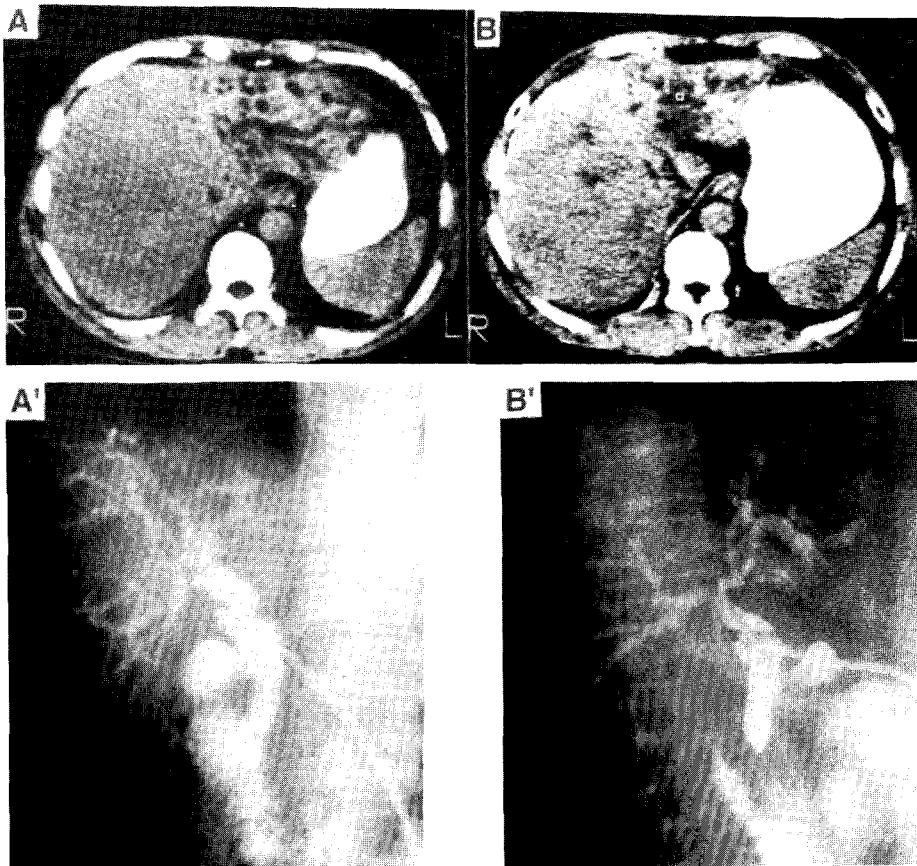


Fig. 1. Pretreatment CT scan (A) and T-tube cholangiogram (A') shows dilated intrahepatic biliary trees in the left lobe of the liver and non-visualization of the left extra-hepatic duct. After external irradiation of 4500 cGy combined with hyperthermia the dilated intrahepatic biliary trees are relieved (B) and the left extrahepatic duct are recanalized (B').

treatment was good as judged by symptoms, hematologic parameters and necessity for medical support. There was not any treatment related deaths. The planned course of treatment was not

significantly altered as a result of gastrointestinal side effects. One patients who had local-regional metastases from stomach cancer showed transient diabetic ketoacidosis.

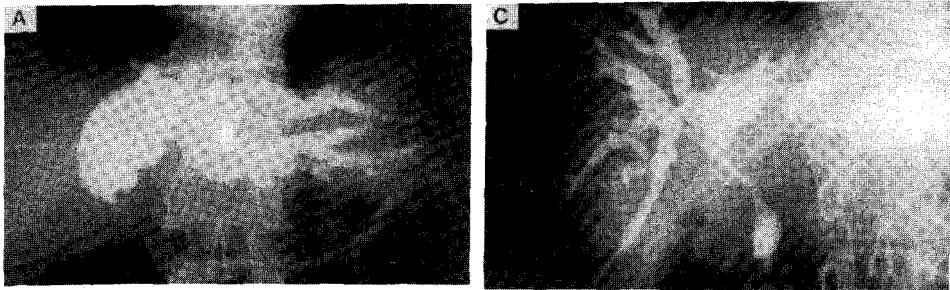


Fig. 2. Pretreatment percutaneous transhepatic cholangiogram shows complete obstruction of the common bile duct (A). Thread-like recanalization of the common bile duct is noted after external irradiation of 2520 cGy combined with 5 times of hyperthermia (B), and partial relief of the common bile duct after 4860 cGy of external irradiation combined with 10 times of hyperthermia is seen. (C)

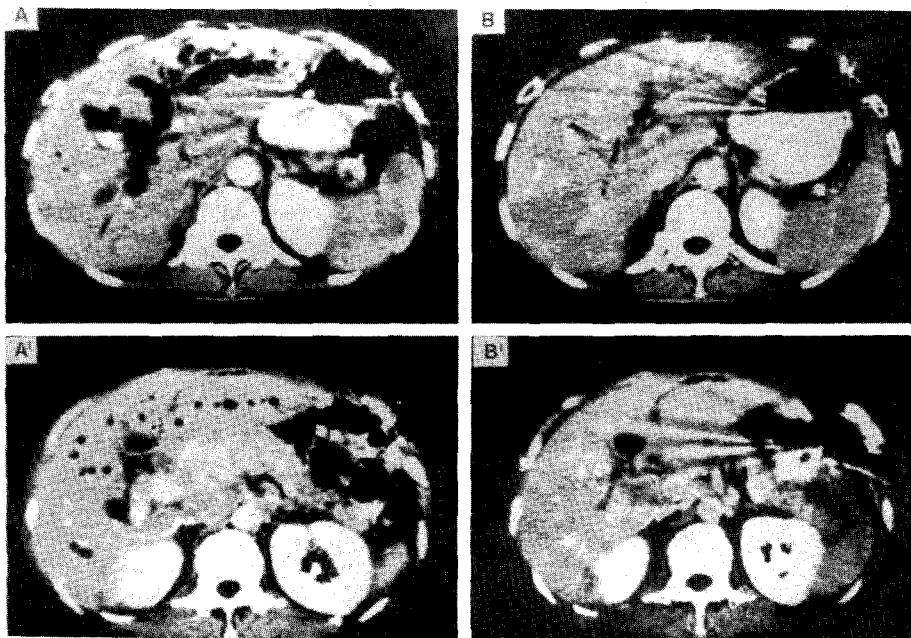


Fig. 3. Pretreatment CT scan shows markedly dilated intrahepatic biliary trees (A) due to metastatic mass in the peripancreatic area. (A') After 4500 cGy of external irradiation and 12 times of hyperthermia the dilated intrahepatic biliary trees and peripancreatic mass are almost normalized. (B, B')

2. Response

Three patients had jaundice before combined treatment. Jaundice was disappeared two to three weeks after start of treatment. The tumor response was evaluable in all 7 patients. The patients were followed by T-tube cholangiography (Fig. 1), percutaneous transhepatic cholangiography (Fig. 2), and CT scan (Fig. 3). The follow-up studies were checked in the middle of treatment, at completion of the treatment and 1 month after the treatment.

Objective responses observed within 1~2 months after treatment were categorized as: 1) complete response (CR), complete regression of all clinically detectable disease; 2) partial response (PR), at least a 50% reduction in tumor volume; 3) no response (NR), less than 50% volume reduction. None achieved CR. 6/7 (86%) showed PR. 1/7 (14%) showed NR.

3. Survival

As of September 1990, 1 of the 7 patients remain alive. She who had suffered from local-regional recurrence 5 months after cholecystectomy showed PR, but recently new metastatic lesion was found out of the treated field. The remaining 6 patients were dead 4 to 11 months after treatment (Fig. 4). The median survival of gallbladder cancer patients was 8.3 months, and of cholangiocarcinoma patients was 5.7 months. The median survival by response was 7.7 months in responders and 4 months in nonresponder. The cause of death

was confirmed in 6 patients: one died of septicemia, 4 of progressive primary disease, and one of distant metastasis.

DISCUSSION

Bile duct. Extrahepatic bile duct (EHBD) carcinoma is rare and represents approximately 9% of all new cancers in the digestive tract²⁸. Surgery remains the primary treatment modality for carcinoma of the EHBD. Unfortunately, curative surgery is possible in only 20~40% of patients^{3,29}. Approximately 80% of patients undergoing "curative" resection succumb to local-regional recurrence³⁰. Unresectable patients can be expected to survive a median of 3 months³¹. Most of the cases involve a rather scirrhous type of cancer. fibrous component is almost always dominant. The tumor grows diffusely locally, under the mucosa, along the nerves, venules, arteries, and lymphatics, and can extend far beyond macroscopic margins. It has also a tendency to affect the portal vein, especially at the confluence where the duct and vein are very close. This is the reason why, despite the fact that distant metastases are rare and late, radical resection is often not possible³².

These tumors are often multicentric and diffuse in the biliary tract³. Lymph node involvement is present in 41%³. These patients are severely disabled and uncomfortable from jaundice, cachexia, intense pruritus, painful hepatomegaly, malabsorp-

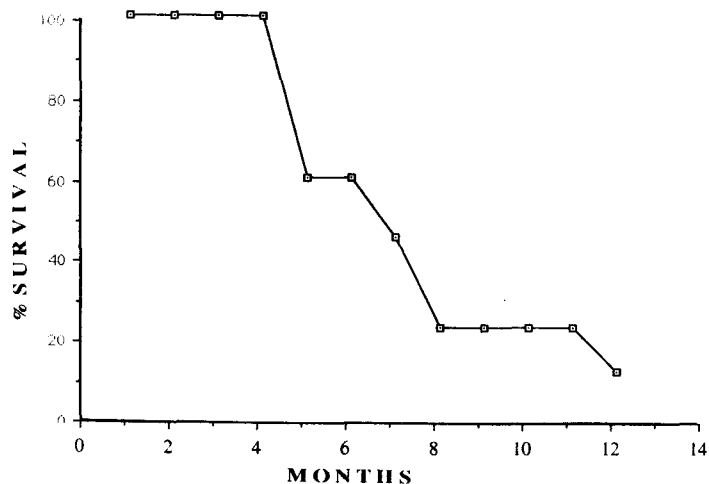


Fig. 4. Survival curve for the entire group.

tion, and coagulopathies²⁰). Patients die not from extensive distant nor hepatic metastatic disease but from local recurrence with extensive unrelieved biliary obstruction leading to hepatocellular failure³). Therefore one must infer that localized disease is still present even after curative surgery³).

As a result, many palliative efforts with varying treatment modalities have been explored for these unresectable cholangiocarcinoma patients, as well as for those patients with obstruction of a portion of the biliary tree from porta hepatis lymph node metastasis or pancreatic malignancies. Palliative procedures can improve the duration and quality of survival of patients with unresectable tumors. Biliary decompression, by any of several techniques, can alleviate anorexia and forestall sepsis and hepatic failure.

Early reports^{3,4,12,33}) suggest excellent palliation and extended survival by addition of external radiotherapy (ERT), with the possibility of occasional cure. Pilepich and Lambert reported 2 longterm survivors (26 and 50 months) of 6 patients receiving 40~60 Gy⁴). Mittal et al²³), in a retrospective review, has suggested improved survival for higher dose, patients receiving ≥ 70 TDF showing a longer median survival (11 months) than patients receiving < 70 TDF (4 months). Radiation therapy can play a role in the palliative management of these tumors with improvement of jaundice and pain³⁴). In this study three patients with extrahepatic bile duct cancer were received 45~48.6 Gy of ERT combined with 10~12 sessions of hyperthermia. All showed partial response, and their median survival was 5.7 months.

The development of percutaneous transhepatic biliary drainage allows the placement of interstitial source, usually Ir-192, into biliary ducts which are stenosed by tumor. With this technique, a high dose can be delivered to the tumor and normal tissues are spared. Pilepich and Lambert already reported median survival of 8 months (1 to 19 months), among 7 patients with 4 alive from 4 to 11.5 months⁴). Fletcher et al. reported median survival of 11 months among 19 patients with 47% surviving more than one year¹⁷). Fletcher et al. have used intracavitary Ir-192 alone for irradiation of tumor¹⁹). However, because of the propensity for mucosal and lymphatic spread of these tumors, intracavitary irradiation alone is unlikely to treat the entire tumor volume: 3/6 patients for Conroy¹⁸), 10/19 patients for Fletcher¹⁹). Recent studies have emphasized the use of intracavitary radioisotope implantation or intraoperative radiotherapy, usually delivered as a

supplement to ERT. Molt et al²) reported median survival of 4.5 months after ERT (29 Gy in 8~11 fractions)+ brachytherapy (mean dose 26 Gy) and 2.65 months after external irradiation alone (29 Gy in 8~11 fractions). For Hayes et al³⁵), median survival was 13.2 months after external irradiation alone (mean dose 38.6 Gy). For Fields and Emami³¹) median survival was 15 months for 8 patients who received both external irradiation (range 44~50.4 Gy) and brachytherapy (range 9.5~27.5 Gy) against 7 months for 9 patients who had only external irradiation (range 9.5~27.5 Gy) against 7 months for 9 patients who had only external irradiation (range 44~63.6 Gy, median 50.4 Gy. Smoron¹²) reported improvement in survival for patients receiving external irradiation ≥ 40 Gy (median 15 months) versus < 40 Gy (median 2.5 months) and the same conclusions were made by Hishikawa⁶). Johnson²⁰) related a mean survival of 16.1 months from laparotomy with bypass and 8.3 months from radiotherapy completion in seven patients with unresectable tumors treated by external irradiation (mean dose 50 Gy) and brachytherapy (mean dose 10.2 Gy).

Autopsies were performed in three patients and none showed evidence of biliary obstruction. Buskirk et al²²) reported only one local failure among seven patients treated with a combined external + transcatheter Ir-192 or intraoperative radiotherapy (IORT) approach. Veeze - Kuijpers et al³⁶), with this approach (external irradiation 30 Gy/15 fractions or 40 Gy/16 fractions + brachytherapy 15 or 25 Gy) reported at 3 years survival rate of 38% in 11 patients with positive margins after complete gross resection. Buskirk et al²²), Fields and Emami³¹) reported improved local control with combined ERT and local boost treatment. Fields and Emami³¹) recommended adjuvant postoperative ERT for all patients with "completely resected" tumors, as these are at high risk of local-regional relapse. For patients with unresectable tumor, Fields and Emami recommended ERT followed by external-beam or Ir-192 boost. Johnson et al²⁰), Fields and Emami³¹) recommended that patients with unresectable cholangiocarcinomas, distal common duct obstruction from pancreatic carcinoma, or more proximal CHD obstruction from metastatic carcinoma should be treated with radical surgical resection if possible. If unresectable, however, they should have a biliary drainage procedure followed by 4500~5000 cGy using external-beam megavoltage fields encompassing tumor and the porta hepatis, entire extrahepatic biliary tree, and

regional lymphatics (pancreaticoduodenal and celiac). Simulation and implant films are taken with contrast material in the stomach and duodenum to allow sparing of sensitive tissues not at risk for tumor involvement. Normal tissue tolerance limits the dose that can safely be delivered with external beam techniques. Three or 4 weeks following the external-beam treatment, a line source of Ir-192 may be positioned via a transcatheter under fluoroscopic control through the site of obstruction, and an additional 6,000~10,000 cGy may be delivered to a point 0.5 cm from the line. This appears to be well-tolerated, efficacious in terms of significant palliation and local control, and may modestly improve survival rates for these patients²⁰. IORT was investigated by several groups and seems to be of interest to improve local control^{20,21,22,37}. A single dose of 2500~3000 cGy could produce a recanalization of a completely obstructed bile duct. As to the one-year survival rate in Todoroki et al. series²¹, the IORT group of unresectable carcinoma had the successful outcome of 63%. Iwasaki et al³⁷. reported 14 patients who benefited from this technique: 2 are alive with non-evidence of disease at 37 and 80 months after curative resection, four survived longer than 13.5 months after non-curative resection and one patient survived 26 months after biliary drainage + IORT without resection. From these studies it appears that external irradiation may be effective in improving local control with doses more than 40 Gy and that brachytherapy may be an appropriate technique to boost the unresected or tumor bed. IORT when feasible can be done on the tumor bed for incomplete resection or on the porta hepatis after complete excision. This technique allows to protect critical organs such as stomach and duodenum.

Flickinger et al³⁸) reported improved survival rate for extrahepatic biliary duct cancer after liver transplantation with postoperative radiation therapy; 2 of 12 patients underwent orthotopic liver transplantation are alive 50 months without disease.

Consideration may be given to incorporating a systemic chemotherapeutic agent during the initial external-beam treatment. The effectiveness of chemotherapy is difficult to assess because of contradictory reports. Kopelson et al³) reported a median survival of 10 months for patients receiving combined radiotherapy-chemotherapy with 5-fluorouracil and 5.2 months after radiotherapy alone. The potentials of combined radiotherapy

and chemotherapy with 5-fluorouracil for bile duct carcinoma need to be assessed in larger series.

Gallbladder: Carcinoma of the gallbladder constitutes about 60% of malignant tumors of the extrahepatic biliary tract, while carcinoma of the proximal bile ducts and those of the ampulla of Vater and distal common bile duct each comprise about 20%⁴¹. The efferent lymphatics of the gallbladder drain to the cystic or hiatal lymph node near the junction of the cystic and common hepatic duct and from there to the superior pancreaticoduodenal node. This node drains to the celiac nodes or to a group of retroduodenal nodes and then to nodes around the origin of the superior mesenteric artery. Perineural invasion was found usually with high-grade lesions⁴¹.

Involvement of the liver usually follows a sequence in which there is initially direct local invasion by the primary disease, followed by appearance of satellite nodules in the immediate vicinity of the infiltrative mass. Subsequently, diffuse nodules may appear in the right lobe of the liver. The most common finding is local infiltration in the vicinity of the primary lesion, and this has occurred at the time of diagnosis in at least half of the patients⁴¹. It appears that one of the most frequent reasons for deeming a lesion unresectable at surgery is liver involvement. Thus in any patient with direct gross or microscopic extension through the GB wall or with definite or clinically undetected lymph node metastases, there will be increased risk for microscopic residual disease and therefore local recurrence after surgery³¹.

Because of this early nodal and hepatic involvement, more extensive surgical procedures have been proposed, ranging from wedge resection of the hepatic GB combined with en bloc nodal dissection to hepatic lobectomy. Such surgery has a high mortality, ranging from 14% with wedge liver resection to 35% with right hepatic lobectomy³¹. However, most patients fail despite extended surgery, and 75% of recurrences are local³¹. Clearly, further therapy is indicated for patients with microscopic residual disease after simple cholecystectomy. Fields and Emami³¹) suggested that adjuvant radiotherapy may have a role in the care of patients with a high likelihood of microscopic residual disease after surgery. Of 3 patients with microscopic transmural or nodal involvement after simple cholecystectomy, 2 are alive without evidence of disease at 22 and 27 months. In this study 4 patients with gallbladder cancer were received 30 ~50.4 Gy of ERT combined with 4~10 sessions of

hyperthermia. 3 out of 4 (75%) showed partial response and their median survival was 8.3 months. There are few other reports of the use of adjuvant irradiation for carcinoma of the GB. Smoron¹²⁾ reported on a single patient with invasive squamous cell carcinoma confined to the muscularis and receiving adjuvant radiotherapy followed by 5-FU, alive at 6 years. Pilepich and Lambert⁴⁾ reported on two patients irradiated for tumors with serosal and lymphatic extent. At the time of report, one was alive without evidence of disease at 17 months; the other had died of tumor 1 year after treatment. Treadwell and Hardin³⁹⁾ reported on 41 patients with GB cancers incidentally found at cholecystectomy. Those receiving adjuvant irradiation and/or chemotherapy showed a significant increase in survival over those not receiving adjuvant therapy.

Patients who have high risk of microscopic residual disease after complete resection of gross disease are likely to benefit from adjuvant irradiation. Silk et al⁴⁰⁾ suggested that doses of 4500 ~5000 cGy to the tumor bed and regional lymph nodes are likely to provide local-regional tumor control, and for some patients, cure. Control of gross residual disease would require higher doses, which could be delivered with brachytherapy or intraoperative techniques.

Hyperthermia: The biological rationale for the use of hyperthermia alone or in combination with radiotherapy or chemotherapy, to treat malignant tumors, have been well established. The effect of local hyperthermia alone is reported to produce response in 51% of patients⁴¹⁾ and when combined with radiation, the complete response rate is often more than doubled in comparing with radiation alone⁴²⁾. When considering delayed complication of curative radiation onto duodenum, stomach and liver, combination of hyperthermia with radiation can increase the response rate. And furthermore, when the radiation dose could be reduced, the delayed complication also could be prevented. Hiraoka et al²⁵⁾, Bae²⁷⁾ suggested the usefulness of radiofrequency hyperthermia combined with radiotherapy for the treatment of refractory deep-seated tumors. In agar phantom and human tumor study, Song et al⁴³⁾ demonstrated that radiofrequency capacitive heating is potentially useful. In the phase 1 trial of Minnesota University⁴⁴⁾, radiofrequency capacitive hyperthermia was useful and response rate was depended with combined total radiation dose; the response rate of the full-dose radiotherapy group and low-dose group was 69% vs 43%,

respectively.

Complications.: The most common complications are ulcers. Gastric and duodenal ulcers seem to be more frequent for patients receiving more than 50 Gy with external irradiation or external irradiation plus a transcatheter boost^{20,24,31,36)}. Sometimes ulcers can make symptomatic upper gastrointestinal bleeding within 2 years after treatment^{20,31,36)}. Mahe et al²⁴⁾ recommended prophylactic use of cimetidine although its efficiency has never been proved. Conroy et al¹⁸⁾, Kopelson et al³⁾ reported periductal biliary fibrosis after radiation, which may, in itself, be a contributory factor in renewed obstruction. Conroy et al¹⁸⁾ recommended draining catheter left behind to minimize fibrotic stenosis.

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= 국문초록 =

간외 담관계암의 방사선치료와 온열치료의 병용요법

한림대학교 의과대학 부속 강동성심병원 치료방사선과

배 훈 식

1986년 1월부터 1990년 9월까지 7예의 간외담도계 암 환자를 대상으로 외부 방사선치료와 온열치료를 병행하였다. 7예중 3예는 간외담도암으로 이중 2예는 원발성 담도암 이었고 1예는 위암에서 담도주위로 전이된 암이었다. 7예중 나머지 4예는 담낭암으로 이중 2예는 담낭 절제후 국소적으로 재발된 암이었고 나머지 2예는 원발성 담낭암 이었다. 그리고 7예는 모두 선암으로 확인 되었다. 조사된 방사선의 양은 3000 cGy/2주 조사한 1예를 제외하고 6예에서는 4500~5040 cGy/6~7주 조사되었다. 온열치료는 모든 환자에서 방사선치료후 30분 이내에 시행되었으며 방사선치료 기간동안 주 1회 내지 2회씩 총 4회에서 12회까지 시행되었다.

치료효과의 판정은 T-관 담도촬영술, PTC, 그리고 CT등의 소견으로 하였으며 7예중 6예(86%)에서 부분관해를 보였으며 완전관해는 없었다. 7예중 6예는 4개월에서 11개월 이내 사망하였으며 나머지 1예는 현재 11개월째 생존하고 있으나 치료부위 밖에서 국소전이가 관찰되었다. 그리고 7예환자의 정중생존기간은 7개월이었다.

사망환자 6예의 사망원인으로는 원발성 담도암환자 1예에서 폐혈증, 전이성 담도암환자에서 원격전이, 나머지 4예에서는 원발병소의 진행이 확인되었다. 관찰기간이 짧았으나 모든 환자에서 치료에 잘 적응하였으며 간, 십이지장, 위내의 합병증은 없었고 전이성 담도암 환자에서 일과성 카보닐산혈증이 관찰되었다.