Analysis of Failure After Curative Irradiation of Extrahepatic Bile Duct Carcinoma

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Thirty-four patients with subtotally resected or unresectable carcinoma of the extrahepatic bile ducts received radiation therapy; a minimum of 45 Gy (external beam) to the tumor and regional lymph nodes ± 5-fluorouracil (5-FU). Seventeen patients received an external beam boost of 5 to 15 Gy to the tumor, and a specialized boost was used in the remaining 17 patients (iridium-192 transcatheter seeds in 10 and intraoperative radiation therapy [IORT] with electrons in seven). The median time to death in all 34 patients was 12 months (range, 4 to 98 months). The only patients who survived longer than 18 months were those either with gross total or subtotal resection before external irradiation (2 of 6) or who received specialized boosts (^{192}Ir, 3 of 10; IORT, 3 of 7). Local failure was documented in 9 of 17 patients who received external beam irradiation alone ± 5-FU, 3 of 10 patients who received an ^{192}Ir boost, and 2 of 6 patients who received an IORT boost with curative intent.

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CARCINOMA OF THE extrahepatic bile ducts is an uncommon malignancy associated with a high mortality rate.[1,2] Of all bile duct neoplasms, 15% to 20% occur proximally in the porta hepatis, 30% are found in the proximal common bile duct, and 50% develop in the distal common bile duct.[3]

These tumors are usually well-differentiated adenocarcinomas and are associated with fibrosis (scirrhous carcinomas) in one third of patients.[3] The predominant route of dissemination is by direct extension within a rich lymphatic network in the submucosa, with extraductal involvement of surrounding organs, or to lymph nodes in the porta hepatis and celiac axis.[1,4] Intra-abdominal spread involving the peritoneal surface or ovaries was noted in only 7 of 77 patients (9%) initially explored at the Lahey Clinic.[5]

Because of the anatomic location of these tumors and the operative limitations, most of these carcinomas are either unresectable or there is gross or microscopic disease present after attempted resection.[6] Of the 15% to 30% of patients who are able to undergo potentially curative resection, a local recurrence develops in approximately 50%.[2]

Because local progression of tumor is the most common cause of treatment failure and death in these patients,[4,7] we began a program of aggressive local irradiation alone or in combination with 5-fluorouracil (5-FU) or with specialized radiation boost techniques. When lesions were unresectable, percutaneous transhepatic biliary drainage was used for decompression[8] followed by irradiation delivered with curative intent. External beam irradiation was used to treat the tumor or tumor bed and regional lymph nodes. When technically feasible, a supplemental boost dose was given to unresected or residual disease with either transcatheter iridium-192 or an intraoperative electron source.

Materials and Methods

From January 1980 through December 1984, 34 patients with a diagnosis of carcinoma of the extrahepatic bile ducts received irradiation delivered with curative intent in the Division of Radiation Oncology of the Mayo Clinic in Rochester, Minnesota.

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Clinical Features

The median age of the patients was 66 years (range, 35 to 86 years). Twenty of the patients were men, and 14 were women. Symptoms at presentation included pruritus in 18 patients, anorexia and weight loss in 16, right upper quadrant pain in 13, nausea in 9, fever in 4, and vomiting in 2. Two patients had a history of chronic ulcerative colitis. The duration of the symptoms ranged from 4 days to 3 years (median, 5 weeks). Physical findings included jaundice in 30 patients, right upper quadrant tenderness in 9, fever in 3, hepatomegaly in 1, and palpable gallbladder in 1.

Investigations

Thirty-three of the thirty-four patients had increased values on liver function tests. Serum alkaline phosphatase levels ranged from 235 to 2259 U/L (normal, 90 to 240 U/L). Serum aspartate aminotransferase values ranged from 33 to 366 U/L (normal, 12 to 31 U/L). Direct and total bilirubin values ranged from 0.4 to 22.5 mg/dL (normal, 0 mg/dL) and 0.9 to 31.3 mg/dL (normal, $\leq$1.1 mg/dL), respectively.

Chest radiographs were negative for metastasis in all 34 patients. Twenty-seven of the thirty-four were evaluated by percutaneous transhepatic cholangiograms (PTHC). All the PTHC studies were abnormal and showed an intraluminal component of tumor. Right upper quadrant ultrasonograms showed dilated ducts in 17 of 20 patients evaluated. Dilated bile ducts were noted also in 18 of 19 patients evaluated by computed tomography (CT) of the abdomen. Endoscopic retrograde cholangiopancreatography (ERCP) showed tumor obstruction of bile ducts in four patients. Neither ultrasonography nor CT studies were useful in determining the extraductal component of disease for the purpose of planning radiation therapy.

Pathology

A tissue diagnosis could not be secured before irradiation in three of the 34 patients; however, the findings on PTHC were diagnostic in each. One of these patients was surgically explored, and several biopsy specimens were negative for tumor. At autopsy, a histologic diagnosis of squamous cell carcinoma was obtained. The other two patients were not surgically explored. Needle biopsies and bile cytology were negative for tumor in these two patients (both died of tumor progression). A review of the tissue of the remaining 31 patients disclosed grade 1 adenocarcinoma in 5 patients, grade 2 in 19, grade 3 in 4, and grade 4 in 1. Two tumors were diagnosed as adenocarcinoma but were not assigned a specific Broders' grade.

Tumor Location and Surgical Treatment

Tumor extent was variable. Eighteen of the thirty-four patients had contiguous tumor in the right hepatic duct, left hepatic duct, and common hepatic duct. Tumor was located in the common hepatic duct in five patients, the common bile duct in four, the right hepatic duct and common hepatic duct in three, the common hepatic and common bile duct in two, and the right hepatic duct in one. One additional patient had contiguous involvement of the right hepatic, left hepatic, common hepatic, and common bile ducts.

Surgical exploration was performed in 31 of the 34 patients. Biopsy only was performed in 24 patients. Subtotal resection and formation of a hepaticojejunostomy or choledochojejunostomy was performed in six patients. A right hepatic lobectomy was performed in one patient with tumor confined to the right hepatic lobe and duct. Lymph node sampling was performed in eight patients, and a lymphadenectomy was performed in one patient. Six of these nine patients had lymph node involvement with tumor. Percutaneous transhepatic biliary tube decompression alone was performed in the three patients who were not surgically explored.

Treatment With Radiation Therapy

The volume of the radiation field and the total dose varied within the patient population (Table 1). Since January 1981, all patients received external beam irradiation with 10-MV photons by using a four-field technique designed to deliver 45 Gy in 1.8-Gy fractions to the tumor and regional lymph nodes. Treatment fields included a margin of 3 to 5 cm beyond ductal involvement as demonstrated on PTHC. The porta hepatis, pancreaticoduodenal, and celiac lymph nodes were routinely included in the initial volume to receive 45 Gy. Thirty patients also received an external beam boost of 5 to 15 Gy to the tumor volume plus a 2- to 3-cm margin. In most patients, the external beam boost doses were limited to 55 Gy when a portion of the small intestine or stomach was within the boost field. The total dose to the volume receiving external beam boost was usually limited to 50.4 Gy if a specialized radiation boost was planned.

The method of achieving a boost to the residual or unresected tumor was dependent on tumor location, operative procedure, and the presence of dose-limiting organs. The options for accomplishing the boost to the tumor included: (1) intraoperative irradiation, (2) ^{192}Ir implant, and (3) additional external beam irradiation. Starting in July 1981, an attempt was made to supplement the external beam irradiation with intraoperative electron beam irradiation (IORT) or transcatheter ^{192}Ir whenever feasible. If the patient had a choledochoenterostomy or

TABLE 1. *Radiation Therapy Volume and Dose Data*

External Beam Dose (Gy)*	External ± 5-fluorouracil		External + Specialized Boost†	
	Subtotal Resection of Tumor (no.)	Unresected Tumor (no.)	^{192}Ir Boost (no.)	IORT (no.)
Tumor and lymph nodes				
45	6/6	11/11	10/10	7/7
Boost to tumor				
5	—	1	8	3
10	2	5	—	—
15	4	3	—	—
Before operation				
5	—	—	—	4

* Majority treated with 1.8-Gy fractions 5 days/week.
† Transcatheter ^{192}Ir dose of 20 to 25 Gy at 0.5- to 1.0-cm radius; IORT dose of 15 to 20 Gy in one fraction.
IORT, intraoperative radiation therapy.

hepaticoenterostomy, the boost was given with external beam irradiation, with one exception. An ^{192}Ir boost was used in only one of these patients because the small intestine would have been within the radiation boost target volume, and the risk of radiation damage manifesting as ulceration or necrosis was thought to be excessive.

Seventeen of the twenty-seven patients with unresected tumors had either an IORT supplement with a single dose of 15 to 20 Gy (7) or transcatheter ^{192}Ir boost (10). Six of seven with IORT boosts were treated with curative intent. In one, the treatment was defined as palliative because the lesion was 6.0 × 6.5 cm. Translesional stents (transhepatic catheters or U-tubes) were left in place in all 17 because the combined external beam and boost dose to the bile duct was of sufficient magnitude to produce significant progressive fibrosis.[9–12] In 10 patients, ^{192}Ir seeds were placed into the percutaneous transcatheter biliary drainage tube and guided to the tumor site at fluoroscopy. A dose of 20 to 25 Gy was delivered to a 0.5- to 1.0-cm radius, depending on the initial tumor volume and proximity of dose-limiting structures (stomach, duodenum ± esophagus). Single ^{192}Ir strands with differential spacing or double ^{192}Ir strands of different lengths were occasionally used to maximize dose penetration in regions of gross tumor (highest risk of extraductal disease) and to decrease the depth of penetration proximally and distally where only an intraluminal component was likely (Fig. 1).

Chemotherapy

Seven of the thirty-four patients received concomitant 5-FU therapy during their course of external beam radiation. Doses of 500 mg/m^2 were given intravenously for 3 consecutive days during week 1 and, on some occasions, during week 5 of external beam irradiation. Concomitant 5-FU was not given during external irradiation in any of the 17 patients who received an IORT boost or transcatheter ^{192}Ir.

Results

Survival

All of the 34 patients are dead, with a median time to death of 12 months (range, 4–98 months) (Table 2). When interval survival was analyzed by treatment method, the only patients who survived more than 18 months had subtotal surgical resection before external radiation (2 of 6 patients, 33%) or had specialized radiation boosts for unresectable lesions (3 of 10, 30% with ^{192}Ir; 3 of 7, 43% with IORT). The only patients who survived more than 48 months were two patients who had specialized radiation boosts (Table 3).

Sites of Failure

Autopsy information was available on four patients, and reoperative data were available on three patients. The sites of failure of the remaining patients were analyzed from a review of the clinical records and radiologic studies available.

Extra-abdominal distant metastasis developed in 3 of the 34 patients (9%): 1 in the lungs, 1 in multiple osseous sites, and 1 in the mediastinum and supraclavicular lymph nodes.

Diffuse peritoneal carcinomatosis developed in 7 of the 34 patients (21%). A recurrence developed in the surgical scar in two patients. In one patient, recurrence developed on the anterior abdominal wall and in another recurrence developed in the skin at the entrance site of the percutaneous transhepatic biliary tube. Hematogenous metastasis to the liver developed in one additional patient.

Seven of the nineteen patients (37%) who had a subtotal resection of tumor, dilatation of the bile ducts with probes, or curettement of the bile ducts during the surgical procedure had peritoneal dissemination of disease (5), a recurrence in the surgical incision (1), or both (1). In one additional patient who had a biopsy only, peritoneal dis-

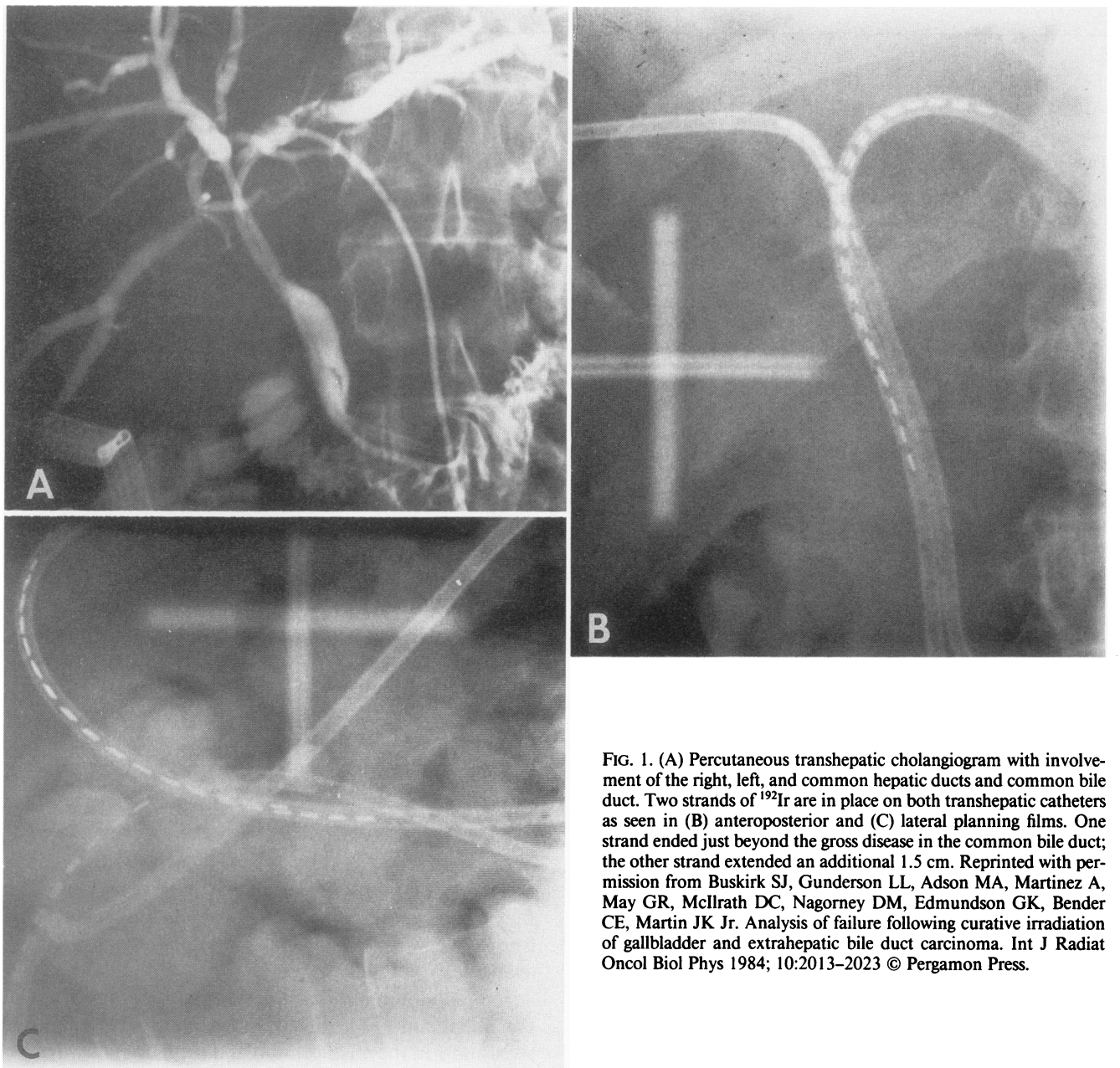

FIG. 1. (A) Percutaneous transhepatic cholangiogram with involvement of the right, left, and common hepatic ducts and common bile duct. Two strands of ^{192}Ir are in place on both transhepatic catheters as seen in (B) anteroposterior and (C) lateral planning films. One strand ended just beyond the gross disease in the common bile duct; the other strand extended an additional 1.5 cm. Reprinted with permission from Buskirk SJ, Gunderson LL, Adson MA, Martinez A, May GR, McIlrath DC, Nagorney DM, Edmundson GK, Bender CE, Martin JK Jr. Analysis of failure following curative irradiation of gallbladder and extrahepatic bile duct carcinoma. Int J Radiat Oncol Biol Phys 1984; 10:2013–2023 © Pergamon Press.

semination of disease also developed. Peritoneal failure was not noted in the 17 patients who received an ^{192}Ir or IORT boost.

Local failure was documented in 9 of 17 patients (53%) who received external beam irradiation alone ± 5-FU. Local failure was also documented in 3 of 10 patients (30%) who received an ^{192}Ir boost and in 2 of 6 patients (33%) who received an IORT boost with curative intent. In the patient who died at 36 months of a pulmonary embolus, serial transcatheter cholangiograms had not demonstrated any evidence of local failure; this was identified only at autopsy.

The immediate cause of death in several patients with no definite evidence of disease progression appeared to be cholangitis with or without associated sepsis, abscess, or diminished hepatic function due to intermittent obstruction of the percutaneous transhepatic drainage tubes. It is possible that undocumented disease progression or treatment-related fibrosis[9] led to some of these complications.

Acute Radiation Sequelae

Acute side effects during the course of external beam irradiation included nausea (17), weight loss greater than

TABLE 2. *Survival and Sites of Failure According to Treatment*

Subtotal Resection + External Beam Radiation	External Beam Radiation Alone	External Beam Plus Interstitial ^{192}Ir Boost	External Beam Plus Intraoperative Electron Boost
Dead WD, 39 mo (RF-PS)	Dead WD, 16 mo (LF)	Dead SU, 98 mo	Dead WD, 60 mo (LF)
Dead WD, 38 mo (LF)	Dead WD, 16 mo (LF, RF)	Lost to follow-up; SU, 18 mo	Dead WD,* 36 mo (LF)
Dead WD, 13.5 mo (LF-PS)	Dead WD, 16 mo (RF-PS)	Dead SU, 18 mo	Dead SU, 20.5 mo
Dead WD, 11 mo (DM)	Dead WD, 14 mo (LF-RF)	Dead WD, 15 mo (LF)	Dead SU, 16 mo
Dead WD, 10 mo (LF-PS)	Dead WD, 12 mo (LF)	Dead WD, 12 mo (LF, DM)	Dead SU, 9 mo
Dead WD, 5.5 mo (PS)	Dead WD, 12 mo (PS)	Dead SU, 12 mo	Dead WD,† 6 mo (LF, CF)
	Dead WD, 9 mo (PS)	Dead SU, 12 mo	Dead (sepsis), 4 mo
	Dead WD, 9 mo (LF, RF, DM)	Dead SPC, 12 mo (TI)	
	Dead WD, 8 mo (SFU)	Dead WD, 10 mo (LF)	
	Dead WD, 6 mo (SFU)	Dead SU, 10 mo	
	Dead WD, 5 mo (LF)		

* Died of pulmonary embolus; local tumor found at autopsy.

† Because of large tumor size, treatment was identified as palliative intent.

CF, central failure in IORT field; DM, distant metastasis; IORT, intraoperative radiation therapy; LF, local failure; PS, peritoneal seeding; RF, regional failure, SFU, site of failure uncertain; SPC, second primary carcinoma; SU, status uncertain; TI, tumor implant; WD, with disease.

3 kg (8), emesis (7), and diarrhea (2). Intermittent fever secondary to cholangitis was noted in 11 patients.

Major Radiation Complications

Most of the major radiation-related complications were due to inclusion of the stomach, duodenum, or small intestine within the treatment field. Significant upper gastrointestinal bleeding occurred in seven patients 2 to 12 months after completion of radiation therapy. Duodenal ulcers developed in seven patients, hemorrhagic antral gastritis in three, gastric ulcers in two, and a bleeding friable esophagus in one. Gastric outlet obstruction developed in one additional patient.

Clinically significant radiation-induced hepatitis may have occurred in 1 of the 34 patients. This patient had ascites that responded well to diuretic therapy.

A detailed analysis of the external radiation dose delivered to the distal stomach and duodenum ± jejunostomy was performed in the 24 patients who received external beam irradiation alone or external beam irradiation plus IORT (stomach and duodenum displaced away from the IORT boost). The estimated total external beam dose to these sites ranged from 45 to 61.2 Gy. Eighteen patients received 55 Gy or less to these sites. Duodenal ulcers developed in 2 of the 18 patients (11%). In two of six patients (33%) who received a dose of more than 55 Gy, duodenal ulcers with upper gastrointestinal bleeding developed.

Four of the ten patients who received external beam irradiation followed by an ^{192}Ir boost had significant complications, including upper gastrointestinal bleeding (4), hemorrhagic antral gastritis (3), duodenal ulcers (3), and a bleeding friable esophagus (1). We were not able to accurately reconstruct the interstitial boost dose delivered to the stomach and duodenum in this group of patients. Therefore, no accurate dose–complication table could be generated.

Discussion

Survival

The exact impact of our aggressive treatment approaches on disease-free survival is uncertain because the immediate cause of death in several patients appeared to be related to problems with percutaneous transhepatic drainage tubes (ascending cholangitis plus sepsis with patent tubes, repetitive obstruction of tubes resulting in infection, or chronic hepatic dysfunction). Because autopsy information was available in only four patients, the exact incidence of death from tumor *versus* tube-related prob-

TABLE 3. *Duration of Survival by Treatment Method*

		12 mo		18 mo		24 mo		36 mo		48 mo		60 mo	
Treatment	Total	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
XRT ± 5-FU	11	6	55	—		—		—		—		—	
Resection + XRT	6	3	50	2	33	2	33	2	33	—		—	
XRT + ^{192}Ir	10	8	80	3	30	1	10	1	10	1	10	1	10
XRT + IORT	7	4	57	3	43	2	29	2	29	1	14	1	14

5-FU, 5-fluorouracil; IORT, intraoperative radiation therapy; and XRT, external radiation.

lems is uncertain. In an attempt to decrease the morbidity from the tube-related problems, considerations under evaluation in our institution include the use of prophylactic antibiotics, placement of the catheter tip proximal to the ampulla, or dilation of tubes by using surgical decompression with formation of hepaticojejunostomies proximal to the level of tumor obstruction.[13]

The only long-term survivors in this series were patients who had gross total or subtotal surgical resection before external irradiation or those with specialized irradiation boosts for unresectable lesions. Whether the improved survival at or beyond 18 months in these three treatment groups is due to more aggressive treatment, compared with external irradiation ± 5-FU, is uncertain because of patient selection. Patients with specialized boosts for unresectable lesions did as well as those in whom the surgeon thought resection was feasible, but residual disease was pathologically identified at resection margins.

Sites of Failure

Distant Metastasis. The analysis of sites of failure suggests that the risk of extra-abdominal progression of disease is low. Only 3 of the 34 patients (9%) had documented extra-abdominal metastasis.

Peritoneal Failure. Peritoneal carcinomatosis ultimately developed in 7 of the 34 patients (21%). In 7 of the 19 patients (37%) who had subtotal resection of tumor, dilatation of the bile ducts with probes, or curettement of the bile ducts, peritoneal carcinomatosis (5), a failure in the surgical incision (1), or both (1), developed, suggesting tumor implantability. We believe that increased emphasis needs to be placed on avoiding duct violation or tumor transection to secure a diagnosis. We currently obtain transabdominal thin-needle biopsy specimens after tube placement in the majority of patients. Positive biopsy results are obtained in more than 90% of cases. An alternative approach would be to use low-dose preoperative irradiation (5 Gy × 1, 3.5 Gy × 3, or 2 Gy × 5 fractions) before the initial surgical procedure (biopsy or attempt at resection) in an attempt to alter implantability of tumor cells during the operative procedure.[14,15]

For patients who present after surgical transection or duct violation, phase I and II studies with whole abdominal radiation, intraperitoneal radiocolloids (*i.e.*, ^{32}P), or intraperitoneal chemotherapy need to be conducted to see if one can decrease the incidence of peritoneal failure.

Local-regional Failure. Routine lymph node sampling or dissection was not performed in this series; however, 6 of the 31 surgically explored patients (19%) had lymph node involvement with tumor. Because of the relatively high incidence of regional lymph node involvement with tumor, these areas did receive 45 Gy in all 34 patients in the hope of controlling this subclinical disease.[16,17]

Local failure was documented in 9 of 17 patients (53%) who received external beam irradiation alone ± 5-FU chemotherapy. In contrast, local failure was documented in only 3 of 10 patients (30%) who received an ^{192}Ir boost and 2 of 6 patients (33%) who received an IORT boost with curative intent (1 of 2 had no evidence of disease clinically, with local failure documented at autopsy). These figures are probably falsely low in all treatment groups, however, because reoperative or autopsy information was available in only 7 of 34 patients (21%). In the interval of 6 to 18 months from initiation of treatment, patient symptoms and diagnostic radiographic changes caused by radiation fibrosis from the specialized boosts can mimic local tumor persistence or progression.[9] For example, in the one patient who survived 98 months, the question of local progression was raised on at least two occasions in the initial year of follow-up. In view of these uncertainties, only patients with progressive changes on serial cholangiograms are coded as local failures.

Local persistence or progression occurred in at least 5 of 16 patients (31%) treated with curative intent. Although we will continue using specialized boosts whenever feasible, we think it is reasonable to evaluate the concomitant use of radiation dose modifiers, including sensitizers and transcatheter hyperthermia. In future studies, we intend to stress the need for autopsies to more accurately assess the impact of our locally aggressive measures and the need for future changes in technique.

Radiation Complications. The major complication of this treatment regimen has been the development of significant upper gastrointestinal bleeding in 7 of the 34 patients (21%). On the basis of dose *versus* complication data generated in this analysis, we do not recommend that doses in excess of 55 Gy be delivered to the stomach or duodenum in the treatment of biliary duct or upper abdominal malignancies unless the volumes are small or the patient has been informed of increased risks. In an adjuvant setting, with tumor-free resection margins, additional risks from doses of more than 55 Gy would be unreasonable. With unresectable or residual disease, such risks may be warranted because complications from uncontrolled tumor are excessive. In the two groups of biliary patients in which an increased incidence of gastrointestinal complications exists (*i.e.*, external beam dose of greater than 55 Gy or external beam plus a transcatheter boost), the use of prophylactic medications (antacids, sucralfate, H_2 blockers) should be considered, although the efficacy in this setting is unproven.

When a transcatheter boost is to be used, every attempt should be made to optimize delivery of dose to the tumor while sparing as much normal tissue as possible. Options include differential spacing and variation of the intensity of ^{192}Ir seeds in the regions of the gross tumor and decreasing the external dose to 40 to 45 Gy because the

transcatheter boost will deliver 5 to 10 Gy to areas of subclinical disease.

Intraoperative radiation therapy has a theoretical advantage over either external beam or transcatheter boosts because it is technically possible to displace the stomach and duodenum from the treated area and one can more accurately determine the extraductal component of disease. However, IORT may not be applicable if the intrahepatic component of tumor is significant. If residual disease remains in the porta hepatis after resection and if an IORT electron boost is not feasible, an alternative radiation technique for the boost may be iodine-125 in absorbable suture.[18]

Conclusions and Future Possibilities

We are disappointed that all patients are dead, with a median survival of 12 months. Although extra-abdominal failure is uncommon, peritoneal failure is frequent after surgical tumor manipulation or transection. With proper patient selection, the ability to achieve local-regional control should impact on the survival of these patients if deaths from malignant causes can be eliminated or minimized. Therefore, although we will continue to use the aggressive local treatment approaches discussed in this manuscript, we plan to evaluate radiation-dose modifiers and to intensify our post-treatment supportive measures in the hope of improving the survival of patients with this disease with acceptable treatment-related morbidity.

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