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Perihilar Cholangiocarcinoma

Postoperative Radiotherapy Does Not Improve Survival

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Objective

The aims of this analysis were to determine prospectively the effects of surgical resection and radiation therapy on the length and quality of survival as well as late toxicity in patients with perihilar cholangiocarcinoma.

Background

Retrospective analyses have suggested that adjuvant radiation therapy improves survival in patients with perihilar cholangiocarcinoma. However, in these reports, patients receiving radiotherapy tended to have smaller, often resectable tumors, and were relatively fit. In comparison, patients who have not received radiotherapy often had unresectable tumors, metastatic disease, or poor performance status.

Methods

From 1988 through 1993, surgically staged patients with perihilar cholangiocarcinoma and 1) no evidence of metastatic disease, 2) Karnofsky score >60, 3) no prior malignancy or radiotherapy, and 4) a patent main portal vein were analyzed. Fifty patients were stratified by resection (n = 31) *versus* operative palliation (n = 19) and by radiation (n = 23) *versus* no radiotherapy (n = 27).

Results

Patients undergoing resection had smaller tumors (1.9 ± 2.8 *vs.* 2.4 ± 2.1 cm, $p < 0.01$) that were less likely to invade the hepatic artery (3% *vs.* 42%, $p < 0.05$) or portal vein (6% *vs.* 53%, $p < 0.05$). Multiple parameters that might have affected outcome were similar between patients who did and did not receive radiation therapy. Resection improved the length (24.2 ± 2.5 *vs.* 11.3 ± 1.0 months, $p < 0.05$) and quality of survival. Radiation had no effect on the length (18.4 ± 2.9 *vs.* 20.1 ± 2.4 months) or quality of survival or on late toxicity.

Conclusions

This analysis suggests that in patients with localized perihilar cholangiocarcinoma, resection prolongs survival whereas radiation has no effect on either survival or late toxicity. Thus, new agents or strategies to deliver adjuvant therapy are needed to improve survival in these patients.

Multiple retrospective analyses[1-7] have suggested that radiation therapy augments survival in patients with perihilar cholangiocarcinoma. However, in all of these retrospective reports, patients receiving radiotherapy tended to have more favorable, often resectable tumors, and were relatively fit. These radiated patients, expected to have good outcomes, have been compared with patients with unresectable tumors, metastatic disease, or poor performance status who did not receive radiotherapy. Thus, the fact that patients receiving radiotherapy in these analyses have survived longer is not surprising. However, conclusions based on these uncontrolled data may be misleading.

To more objectively assess the benefit, if any, of adjuvant radiotherapy, we prospectively analyzed surgically staged patients with perihilar cholangiocarcinoma, all of whom met predetermined eligibility criteria. During a 5-year period, 50 patients met these criteria, whereas 34 were excluded. Patients were stratified by resection *versus* operative palliation and by radiation therapy and no radiotherapy. Radiation ranged from 45 to 63 Gy and consisted of external beam plus iridium IR-192 seeds for resected patients and external beam plus cone down port for palliated patients. Major outcome parameters included length of survival, quality of survival, and late toxicity.

METHODS

Study Design

To be eligible for inclusion in this analysis, patients were surgically staged and found to have cholangiocarcinoma localized to the perihilar biliary tree, with no evidence of intraperitoneal or distant metastases. All patients required histologic confirmation of malignancy. Patients were included with either resected, partially resected, or unresected tumor, but were stratified on the basis of extent of resection. A Karnofsky Performance Status[8] of at least 60 at the time of hospital discharge was required for inclusion. In addition, patients had to be fit to begin radiation therapy within 8 weeks after surgery. A serum creatinine of less than 2.5 mg percent and left renal function demonstrated by contrast enhanced computerized tomography, intravenous pyelography, or renal scan was the final requirement for patient eligibility.

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Conversely, patients were excluded if they had 1) evidence of liver, peritoneal, or distant metastases; 2) a Karnofsky Performance Status of less than 60; 3) prior or concomitant malignant disease or radiotherapy; 4) angiographic or magnetic resonance imaging evidence of total occlusion of the main portal vein; or 5) cholangiographic evidence of bilateral involvement of secondary intrahepatic biliary radicals (Bismuth Type IV).[9] Patients also were excluded if they died after surgery. Patients who met these inclusion and exclusion criteria were evaluated by members of the Johns Hopkins Division of Radiation Oncology. A balanced view of the potential advantages and disadvantages of radiation therapy were explained to the patients who then decided whether to receive treatment.

Patient Characteristics

From August 1988 through July 1993, 84 patients with perihilar cholangiocarcinoma were evaluated. Thirty-four patients were excluded because of metastatic disease (n = 16), Karnofsky Performance Status less than 60 (n = 6), prior cancer or radiotherapy (n = 5), hospital mortality (n = 3), portal vein occlusion (n = 3), or creatinine levels greater than 2.5 mg percent (n = 1). The remaining 50 patients were considered eligible for postoperative radiotherapy. Thirty-one of these patients (62%) had complete or partial tumor resection, whereas 19 eligible patients (38%) underwent palliative procedures. Fourteen of the resected patients (45%) and nine of the palliated patients (47%) received postoperative radiation therapy. Thus, 23 patients (46%) received radiation, and 27 patients (54%) did not.

Several differences were apparent when the resected patients were compared with those undergoing palliative surgery. However, the patients receiving radiation were almost identical to those who did not receive radiotherapy. Multiple patient characteristics for the four major subgroups are presented in Table 1. No significant differences were noted with respect to age, gender, race, associated diseases, presenting symptoms, or physical findings. Two patients, who were resected and did not receive radiotherapy, had primary sclerosing cholangitis. One resected patient, not receiving radiation, also had ulcerative colitis. Cirrhosis was documented in only one patient undergoing palliative surgery, followed by radiation therapy. None of these patient characteristics were significantly different when patients were stratified by type of surgery or whether radiation was administered.

Laboratory data were analyzed both on initial hospital admission and on the day before surgery. In general, both hematocrit and liver function values diminished during this interval. Preoperative laboratory data are

Table 1. PATIENT CHARACTERISTICS

	Resection n = 31 (%)	Palliation n = 19 (%)	Radiation n = 23 (%)	No Radiation n = 27 (%)
Age, Gender, Race				
Age (mean yr)	63 ± 2.1	62 ± 2.3	61 ± 1.9	64 ± 2.4
Female	65	68	61	70
Caucasian	94	89	96	89
Associated Diseases				
Diabetes	13	5	13	7
ASCVD	3	16	4	11
Sclerosing cholangitis	6	0	0	7
Symptoms				
Jaundice	81	89	87	81
Abdominal pain	42	42	43	41
Fever/chills	32	26	26	33
Physical Findings				
Jaundice	68	74	83	59
Tenderness	29	42	43	26
Hepatomegaly	0	11	9	0

ASCVD = atherosclerotic cardiovascular disease.

presented in Table 2. The only significant differences were that resected patients had higher serum albumin values, whereas patients receiving radiotherapy tended to have lower hematocrit levels. No significant preoperative differences in laboratory data were observed between the resected or the palliated patients who did or did not receive radiotherapy.

Radiologic Evaluation

A summary of the radiologic evaluation is presented in Table 3. As might be expected, resected patients had fewer bile duct segments involved[10] and were less likely to have portal vein encasement on angiogram. Patients receiving radiation were more likely to have the tumor seen on computerized tomography but not on magnetic resonance imaging scan. Similarly, radiation patients were more likely to have hepatic artery—but not portal vein—encasement. However, these differences were no longer statistically significant when the resected or palli-

Table 3. RADIOLOGIC EVALUATION

	Resection n = 31 (%)	Palliation n = 19 (%)	Radiation n = 23 (%)	No Radiation n = 27 (%)
Ultrasound				
Performed	52	37	39	52
Tumor seen	0	0	0	0
CT Scan				
Performed	94	84	87	93
Tumor seen	14	31	40*	4
MR Scan				
Performed	16	26	26	15
Tumor seen	40	40	33	50
Cholangiogram				
Performed	97	95	96	96
Segments involved	2.2 ± 0.2†	3.1 ± 0.2	2.8 ± 0.2	2.3 ± 0.2
Angiogram				
Performed	100	100	100	100
HA involved	10	26	30*	4
PV involved	6†	32	9	22

CT = computerized tomography; MR = magnetic resonance; HA = hepatic artery; PV = portal vein.
* $p < 0.05$ *vs.* no radiation.
† $p < 0.05$ *vs.* palliation.

Table 2. PREOPERATIVE LABORATORY DATA

	Resection n = 31	Palliation n = 19	Radiation n = 23	No Radiation n = 27
Hematology				
Hematocrit (%)	34.7 ± 0.9	32.5 ± 1.0	32.4 ± 1.2*	35.3 ± 0.7
WBC count (K/mm^3)	9.3 ± 0.5	8.8 ± 0.7	9.2 ± 0.7	9.1 ± 0.5
Platelets (K/mm^3)	399 ± 22	379 ± 36	407 ± 30	379 ± 24
Protime ratio	1.2 ± 0.1	1.0 ± 0.0	1.2 ± 0.2	1.1 ± 0.0
Liver function				
Bilirubin total (mg, %)	3.3 ± 0.7	4.3 ± 1.0	3.0 ± 0.5	4.2 ± 1.0
Alkaline phosphatase (IU/L)	386 ± 63	363 ± 74	368 ± 64	385 ± 70
AST (IU/L)	75 ± 11	105 ± 21	74 ± 10	90 ± 17
ALT (IU/L)	71 ± 11	123 ± 31	92 ± 22	90 ± 17
Albumin (g, %)	3.5 ± 0.1†	3.1 ± 0.1	3.3 ± 0.1	3.4 ± 0.1
Renal function				
Creatinine (mg, %)	1.2 ± 0.2	0.9 ± 0.0	0.9 ± 0.1	1.2 ± 0.2

WBC = white blood cell; IU = international units; AST = aspartate aminotransferase; ALT = alanine aminotransferase.
* $p < 0.05$ *vs.* no radiation.
† $p < 0.05$ *vs.* palliation.

ated patients who did or did not receive radiation were analyzed.

Preoperative Biliary Drainage/Biopsy

Percutaneous transhepatic biliary stents were placed preoperatively in all 50 eligible patients. The most frequent complications were cholangitis (30%), pancreatitis (14%), bacteremia (10%), and hemorrhage (8%). These complications did not differ between any of the treatment pairs. The average length of preoperative drainage was 30 ± 8 *versus* 13 ± 2 days in the resected and palliative patients ($p = 0.10$), respectively. The length of preoperative drainage time did not differ (20 ± 4 *vs.* 26 ± 8 days) in the radiation and no radiation groups. Attempts to establish a tissue diagnosis preoperatively were performed in 16 of the patients (32%) and were successful in 7 of these (44%), or 14% of the entire group. The percentage of patients undergoing biopsies (39% *vs.* 26%) or establishing tissue diagnoses (44% *vs.* 43%) did not differ in the radiation and no radiation groups.

Operative Procedures and Findings

The operative procedures and findings are presented in Table 4. Twenty-one patients (42%) underwent complete gross resection of the tumor, including three patients (6%) who had liver resections. An additional ten patients (20%) underwent partial tumor resection. Twelve patients (24%) were palliated by placing large bore transhepatic stents through the tumor into a Roux-en-Y choledochojejunostomy. The resective and palliative procedures were distributed evenly between the radiation and no radiation groups. Vascular and tissue invasions were less common in the resected patients. However, the radiation and no radiation groups were comparable with respect to vascular and tissue invasion. Similarly, these parameters did not differ when the resected and palliated patients who did and did not receive radiation were compared.

Postoperative Complications

Postoperative complications were monitored carefully and grouped into infectious and noninfectious categories. A wound infection was defined as a wound draining pus from which bacteria were isolated on culture. Cholangitis was defined as fever greater than 38.5 C more than 3 days after surgery without another source. Pneumonitis occurred when a new infiltrate appeared on chest x-ray in association with a fever and pathogenic organisms on sputum culture. A urinary tract infection was defined as greater than 10^5 organisms/mL. A liver abscess occurred when a new low-density area appeared in the liver on computerized tomography scan, in association with fever, and was found to contain pus and bacteria when drained. Other complications, such as bile fistula, pancreatitis, gastrointestinal or intra-abdominal hemorrhage, and renal failure, have been previously defined.[11]

Tumor Characteristics

Various characteristics of the tumor as determined by cholangiography, operative evaluation, or pathologic examination are presented in Table 5. The distribution of the tumors by Bismuth Type[9] was not significantly different when stratified by either resection or radiation. Average tumor size as measured in resected patients was smaller than estimated from cholangiograms and operative observations in palliated patients. Tumor size did not differ in radiated and nonradiated patients. Only four patients (8%) had papillary tumors. Microscopic resection margins were negative in 9 of the 31 resected (29%) patients. Lymph nodes were examined pathologi-

Table 4. OPERATIVE PROCEDURES AND FINDINGS

	Resection n = 31 (%)	Palliation n = 19 (%)	Radiation n = 23 (%)	No Radiation n = 27 (%)
Resection				
Performed	100*	0	61	63
Complete	68*	0	39	44
Partial	32*	0	22	19
Hilar	90*	0	57	56
Liver	10	0	4	7
Palliation				
Performed	0*	100	39	37
Roux-en-Y CDJ	0*	63	22	26
Cholecystectomy	0	11	0	7
Biopsy only	0*	26	17	4
Vascular Invasion				
Hepatic artery	3*	42	30	7
Portal vein	6*	53	22	26
Tissue Invasion				
Liver	29	47	48	26
HDST/LN	16†	42	26	26
Gallbladder	16	21	17	19
Duodenum	3†	21	4	15
Pancreas	0	5	4	0

CDJ = choledochojejunostomy with large bore transhepatic stents; HDST/LN = hepatoduodenal soft-tissue/lymph nodes.
* $p < 0.01$ *vs.* palliation.
† $p = 0.05$ *vs.* palliation.

Table 5. TUMOR CHARACTERISTICS

	Resection n = 31 (%)	Palliation n = 19 (%)	Radiation n = 23 (%)	No Radiation n = 27 (%)
Bismuth type				
Type I	26	11	9	30
Type II	48	42	48	44
Type III	26	47	43	26
Tumor size				
Size (cm)	1.9 ± 0.1*	2.8 ± 0.1	2.4 ± 0.2	2.1 ± 0.2
Pathologic type				
Adenocarcinoma	90	95	96	89
Papillary	10	5	4	11
Margins				
Positive	71	NA	87	78
Negative	29*	0	13	22
Lymph nodes†				
Positive	21	NA	13	29
Negative	79	NA	87	71

NA = not applicable.
* $p < 0.01$ *vs.* palliation.
† n = 15 (Data were available in only 14 resection, 1 palliation, 8 radiation, and 7 no radiation patients).

cally in 15 patients and were positive in only 3. The radiated patients did not differ from the patients not receiving radiation, with respect to tumor margin or lymph node status.

Radiation Therapy

Simulation was performed in the supine position, and orthogonal radiographs were obtained in both the supine and cross-table positions. Four-field, three-field, or rotational techniques were used at the discretion of the managing radiotherapist. Shaped blocks were used to shield uninvolved liver and kidneys. Fourteen patients with resected tumors received external beam radiation therapy, mean 46 Gy (range 40–60 Gy) in 5 weeks with 1.8 Gy fractions. Eight of these 14 patients also received iridium IR-192 implants approximately 2 weeks later, with an average tumor dose of 13 Gy (range 2–18 Gy). Thus, resected patients received a mean total dose of 54 Gy. Nine patients with unresectable tumors received external beam radiation therapy, mean 50 Gy, followed by 2 weeks rest, and then a cone down port or iridium IR-192 in two patients, for a total dose of 51 Gy.

Follow-Up

Follow-up was performed every 3 months for the first year and at least every 6 months thereafter. Follow-up was complete in all 50 patients. Evaluation included a history, physical examination, a chemistry panel, an estimate of the Karnofsky Performance Status by the study nurse, and usually, a chest x-ray, a cholangiogram, and a computerized tomography or magnetic resonance imaging scan. An estimate of tumor progression and toxicity was made at each time point on the basis of these studies. The number of hospital admissions and total hospital days were recorded as objective measures of quality of survival. An Overall Karnofsky Score (OKS) also was calculated by adding individual scores for each month and dividing by the months of survival. This OKS was then used to calculate quality adjusted life months = mean survival (months) × OKS/100 as another estimate of quality of survival. The Radiation Therapy Oncology Group radiation morbidity scoring criteria were used to measure late kidney, duodenal, small intestine, and liver toxicity.

Statistical Analysis

All data are presented as percentage of patients or mean ± SEM. Percentages were compared by Fisher's Exact test, and means were analyzed by Student's t test. Survival curves were constructed by the Kaplan-Meier technique and were compared by the log-rank test. Cox's Proportional Hazards Survival analysis was employed to determine whether resection, radiation, and multiple other parameters affected survival.

RESULTS

Morbidity

Infectious complications were common after surgery, but did not differ significantly between resected and palliated patients or between patients who would subsequently receive or not receive radiotherapy. The most frequent infections included wound infection (26%), bacteremia (10%), cholangitis (8%), pneumonitis (6%), and urinary tract infection (6%). One resected patient developed a liver abscess. Biliary fistulas developed in 8%, pancreatitis developed in 4%, and renal insufficiency developed in 2%. No patient developed significant gastrointestinal or intra-abdominal hemorrhage. The postoperative hospital stay did not differ between resected and palliated patients (15.3 ± 1.7 *vs.* 13.7 ± 1.5 days) or between radiated and nonradiated patients (13.7 ± 1.6 *vs.* 15.6 ± 1.8 days). The mean Karnofsky score at discharge among these four subgroups was 79, 77, 79, and 77, respectively.

Table 6. SURVIVAL LENGTH AND QUALITY

	Resection n = 31	Palliation n = 19	Radiation n = 23	No Radiation n = 27
Length				
Mean (mos)	24.2 ± 2.5*	11.3 ± 1.0	18.4 ± 2.9	20.1 ± 2.4
Median (mos)	20*	11	14	15
Alive	26%	11%	22%	19%
Quality				
Karnofsky score	82.4 ± 1.3†	75.7 ± 2.8	80.7 ± 1.7	79.3 ± 2.1
QALM (mos)	19.9 ± 2.1†	8.6 ± 0.8	14.9 ± 2.3	15.9 ± 1.6
Admissions/mo	0.19 ± .03†	0.36 ± .08	0.21 ± .04	0.29 ± .06
Hospital days/mo	1.15 ± .24	2.04 ± .52	1.44 ± .36	1.52 ± .35

Karnofsky score = average of monthly scores; QALM = quality adjusted life months = mean survival (mo) X Karnofsky score/100.
* $p < 0.05$ *vs.* palliation.
† $p < 0.02$ *vs.* palliation.

Survival Length

The length and quality of survival are presented in Table 6. Both the mean and median survival were significantly longer ($p < 0.05$) in the resected compared with the palliated patients. On the other hand, radiation did not affect the mean or median survival. These same trends are depicted in actuarial survival in Figure 1. Among resected patients, radiation had no effect on mean (23.9 ± 4.0 *vs.* 24.5 ± 3.3 months), median (20 *vs.* 20 months), or actuarial survival (Fig. 2A). Similarly, among palliated patients, radiation had no effect on mean (9.8 ± 1.4 *vs.* 12.7 ± 1.3 months), median (8 *vs.* 12.5 months), or actuarial survival (Fig. 2B).

A univariate analysis of 33 parameters, including age, gender, race, associated diseases, presenting symptoms, laboratory data, cholangiographic extent, length of preoperative biliary drainage, resection, type of operation, tumor type, tumor margins, and radiation therapy, was performed. In this univariate analysis, diabetes ($p < 0.03$, Hazard Ratio 0.29) and jaundice ($p < 0.03$, Hazard Ratio 0.20) were negative factors. Resection ($p < 0.001$, Hazard Ratio 5.92) favorably affected survival, whereas radiation ($p = 0.95$, Hazard Ratio 1.02) had no effect on survival. With multiple regressions, diabetes remained a negative factor ($p < 0.01$, Hazard Ratio 0.16); resection was the only positive factor ($p < 0.001$, Hazard Ratio 4.21); and radiation still had no effect ($p = 0.84$, Hazard Ratio 0.93).

Survival Quality

The OKS, quality adjusted life months, and admissions and hospital days per month of survival are presented in Table 6 and Figure 3. Resection was associated with a higher OKS ($p < 0.02$) and quality adjusted life months ($p < 0.02$) and fewer admissions ($p < 0.02$) and hospital days ($p = 0.08$). Radiation had no beneficial or adverse effects on these various measures of quality of

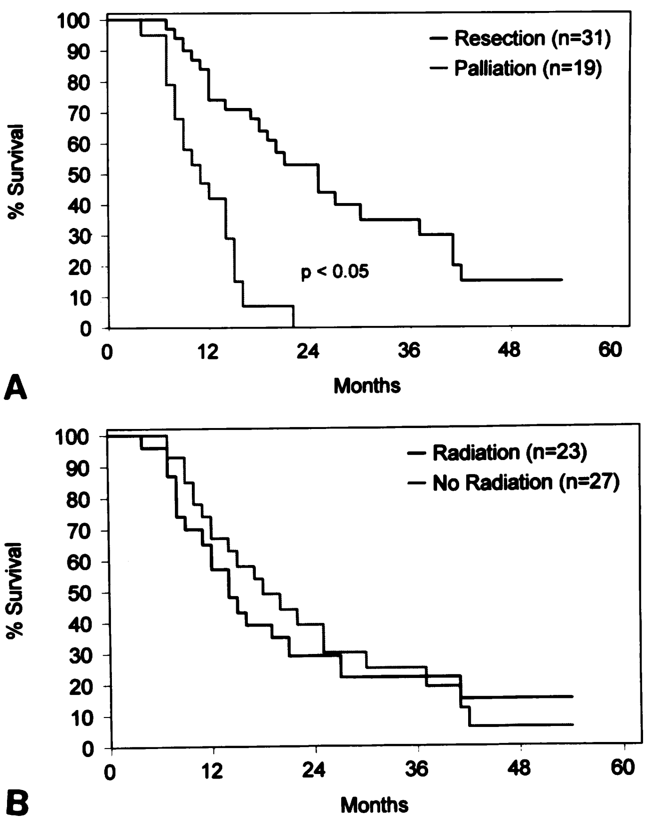

Figure 1. (A) Actuarial survival of resection and palliation patients is shown. (B) Actuarial survival of radiation and no radiation patients is shown.

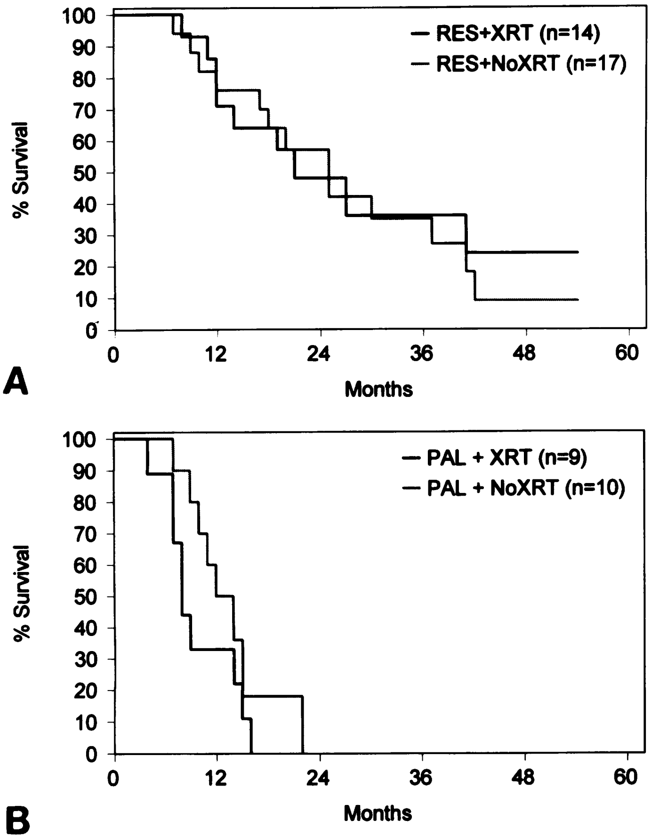

Figure 2. (A) Actuarial survival of resection (RES) patients with and without radiation is shown. (B) Actuarial survival of palliation (PAL) patients with and without radiation is depicted.

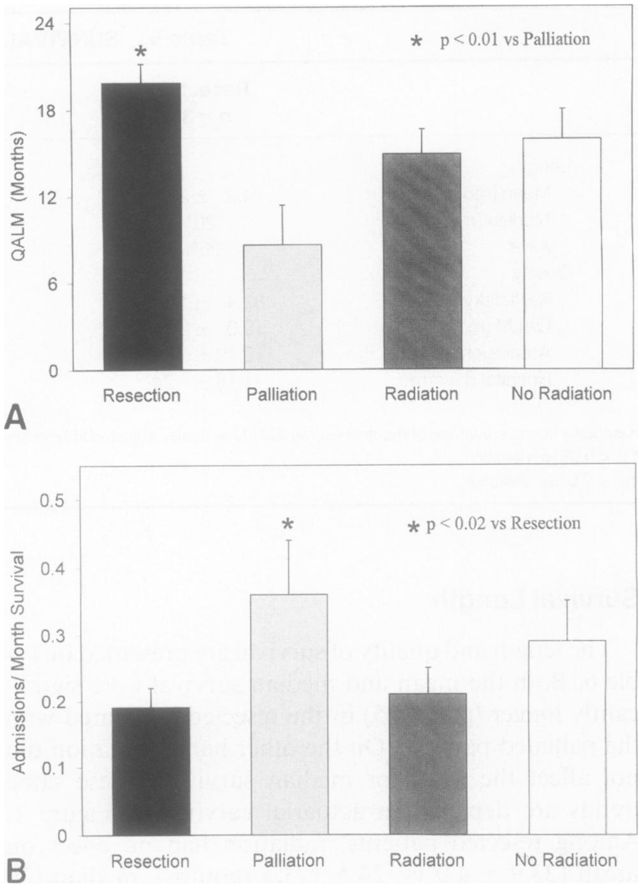

Figure 3. (A) Quality adjusted survival by type of management is shown; QALM = quality adjusted life months. (B) Admissions per month of survival by type of management are depicted.

survival. Similarly, in both the resected and palliated subgroups, radiation had no effect on the quality of survival.

Toxicity

A summary of the kidney, duodenal, small intestine, and liver toxicity is presented in Figure 4. The data represent Radiation Therapy Oncology Group toxicity levels ≥ Level 2. Only one resected, nonradiated patient developed late renal insufficiency. Five patients (10%) developed late duodenal obstruction, but this problem was not significantly more common in radiated *versus* nonradiated patients. Small intestinal problems occurred in seven patients (14%), but were no more common in radiated patients. Late liver toxicity occurred in 25 patients (50%), but was not affected by either resection or radiation. Liver abscesses were late problems in 13 patients (26%), but also were not affected by resection (29% *vs.* 21%) or radiation (26% *vs.* 26%). Neither liver toxicity nor liver abscesses were different in resected or palliated patients who did or did not receive radiation.

DISCUSSION

Perihilar cholangiocarcinoma is a rare tumor with a poor prognosis. Because of proximity to the hepatic ar-

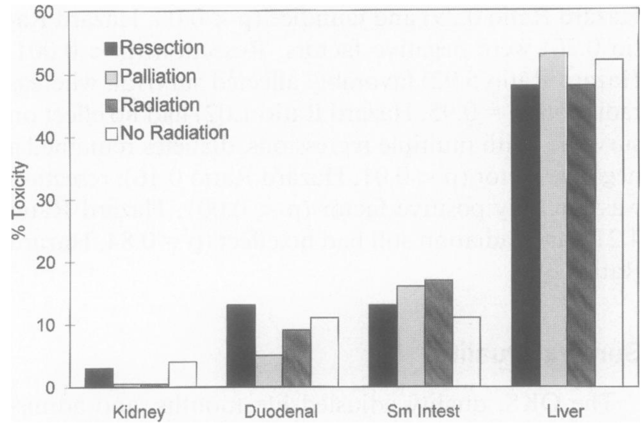

Figure 4. Kidney, duodenal, small intestine (sm intest), and liver toxicity by type of management are shown.

tery and portal vein as well as frequent liver invasion, complete resection with negative microscopic margins is unusual. As a result, radiation therapy frequently has been recommended both as adjuvant therapy for resected patients and as primary treatment for patients with unresectable tumors. However, most reports on the effects of radiation have not been controlled. Moreover, several retrospective analyses[1–7] that compare radiated and nonradiated patients have not stratified by tumor resection or have included patients who were never eligible for radiation because of metastatic disease or poor performance status.

This report included only patients who were staged by clinical and radiologic evaluation and surgical exploration. Patients with metastatic disease, poor performance status, occluded portal vein, or extensive bilateral intrahepatic involvement were excluded from this analysis. Patients were stratified by tumor resection, and the patients who did and did not receive radiation therapy were comparable by multiple parameters that may have affected outcome. Resection improved both the length and quality of survival. However, radiation had no effect on the length or quality of survival or on late toxicity.

The observation that resection improves survival in patients with perihilar cholangiocarcinoma is not new.[1,2,6,12–20] Factors that have been suggested to enhance survival after resection include negative microscopic margins, negative lymph nodes, and papillary tumor type. Debate continues as to the role of liver resection in achieving negative margins.[21] However, some of the best survival data have been reported after hilar plus major liver resection.[2,12,20–25] On the other hand, operative mortality is increased in most series in which liver resection has been added to local hilar resection.[21] Thus, major liver resection may be advisable if hospital mortality can be kept below 5%.

In the current series, postoperative radiation therapy did not improve survival in either resected or palliated patients. A number of possible theories can be proposed to explain this observation. The first issue to be addressed is whether the dose of radiation was adequate. Several reports[4,6,7,17,26] have documented improved survival for those patients receiving more than 40 Gy. In this present study, however, the mean dose was 54 Gy in resected and 51 Gy in the palliated patients. The fact that toxicity was not increased in the radiated patients suggests that even higher doses may have been tolerated. Nevertheless, the doses of radiation received by the patients in this analysis were certainly within the range previously recommended and claimed to be helpful.

A second issue that may have inhibited the influence of radiation in this study was that radiation was given alone without concomitant sensitizing chemotherapy. Several reports[16,26–29] suggest that the combination of radiation and chemotherapy may be more effective than radiation alone. However, the median and mean survivals reported with these multimodality regimens were less than those observed in either the radiation or no radiation groups in this analysis.

Some authors have claimed that radiation is most likely to be helpful if all microscopic margins are negative. In this study, the majority of patients had positive margins, and some of the resected patients had gross tumor left behind. In this setting, radiation may not have been as effective because of the high percentage of patients with residual tumor. Another factor that may have diminished the potential beneficial effects of radiation in this study was the long-term use of transhepatic stents. This regimen is designed to prevent recurrent jaundice and to minimize biliary sepsis. However, the fact that the nonradiated patients in this analysis were all eligible for radiation and therefore, were an appropriate control group, probably is more important than the potential influence of chemotherapy or the long-term stenting factor.

In addition to external beam radiation therapy, numerous reports suggest that brachytherapy, usually with iridium IR-192,[1,4,7,15–17,30–32] intraoperative radiation therapy,[3,33–35] or charged particles[2,36] may be beneficial for patients with hilar cholangiocarcinoma. Although intraoperative radiation therapy and charged particles were not employed in this series of patients, one of the largest experiences with iridium IR-192 brachytherapy for cholangiocarcinomas has been gained at Johns Hopkins.[1] Thus, the majority of resected patients who were radiated in this series also received iridium IR-192 seeds, which provided an average additional local dose of 13 Gy to the tumor bed.

The issue of quality of survival in patients with hilar cholangiocarcinoma has been addressed by several authors.[13,14,37] However, no consensus has been reached as to a uniform measure of quality in these patients. The number of hospital admissions and hospital days per month of survival has been used as an objective measure of quality in a previous report from this institution.[37] In addition to these parameters, Karnofsky Performance Scores were prospectively estimated in this analysis.[38] An Overall Karnofsky Score was then calculated and used to adjust survival to quality adjusted life months.[39] This method of estimating quality of life has not been used previously in patients with cholangiocarcinoma and needs to be validated. Moreover, the Karnofsky score has been criticized because it is unidimensional and does not include a patient assessment of quality. Nevertheless, this methodology was useful in comparing groups of patients in this study.

Several reports[1,3,27,34,36,40] have suggested that significant duodenal toxicity may occur after radiation of patients with hilar cholangiocarcinoma. However, most of these analyses have not provided any control data. Recurrent tumor, as well as radiation, also may cause duodenal obstruction or bleeding. Similarly, progressive tumor growth may contribute to late hepatic failure and sepsis. In this study, both duodenal and hepatic toxicity were the same in radiated and nonradiated patients. This observation suggests that late tumor effects may be responsible for some of the toxicity that previously has been attributed to radiotherapy.

This prospective study suggests that postoperative radiation has no effect on either the length or quality of survival. Thus, to improve outcome, new agents or strategies to deliver adjuvant therapy are needed. Possible strategies include increasing the dose or fields of radiation; adding fluorouracil or other chemotherapeutic agents, such as cisplatin; or switching to a preoperative, neoadjuvant approach. In addition, more research needs to be done on the effect, if any, of hormones such as cholecystokinin or somatostatin on the growth of human cholangiocarcinomas. Ideally, prospective randomized trials should be performed to determine whether new strategies or agents are beneficial.

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Discussion

DR. R. SCOTT JONES (Charlottesville, Virginia): Dr. McDonald, Dr. Copeland, Members, and Guests. Dr. Pitt has presented for us this morning a carefully studied and expertly managed series of patients. This represents one of the more difficult clinical problems confronting the general surgeon with an interest in biliary disease. And I would simply say that we have had an interest in whether or not radiation therapy has any influence in the outcome of patients with cholangiocarcinoma since the mid/early 1970s and have employed both radium therapy as well as external beam radiation therapy in a small number of patients since that time.

A couple of years ago, Dr. William Meyers of Duke and I looked at a combined series of patients from both Duke University and the University of Virginia in Charlottesville. This was a retrospective analysis of a heterogenous group of patients, and we found no evidence from that material to support the conclusion that radiation therapy had any efficacy in the management of this terrible disease.

Dr. Pitt has now provided another analysis with a larger group of carefully studied patients that leads to the same conclusion.

I would go on to add that a review of the literature at the present time, or relatively recently, reveals also no convincing evidence for efficacy of chemotherapy in the management of extrahepatic biliary cancer.

What I am coming to is that if we looked at the history of other cancers early in this particular session, we were given information to suggest fairly conclusively that a combination of radiation therapy and chemotherapy does have therapeutic efficacy in carcinoma of the pancreas, and we have just heard evidence in the prior paper supporting the use of combined chemotherapy and radiation therapy in treatment of carcinoma of the rectum.

What I am coming to, obviously, is that I think the logical challenge for us or project for us for the future would be to investigate the question of whether a combination of chemotherapy and radiation therapy may have efficacy.

This is a difficult kind of project to propose because the numbers of cases are relatively small, making clinical trials very difficult. But I would like to suggest that before we abandon all concepts of adjuvant therapy for bile duct cancer, that we need to at least contemplate a trial with combined therapy.

I will close this by complimenting Dr. Pitt on an excellent study. He has given a great deal of thought over a long period of time to this very difficult clinical topic, and perhaps he and his colleagues have the largest experience of this in North America.

And their outcomes and the results that they show are presently better than any from any institution. So thank you very much for the privilege of the floor, and thank you, Dr. Pitt, for sharing with us this excellent information.

DR. ROBERT E. HERMANN (Cleveland, Ohio): Dr. McDonald, Dr. Copeland, Members, and Guests, I will try to be brief. I, too, enjoyed this carefully done paper by Dr. Pitt and his colleagues. It does address the important issue of biliary cancer, a disease which is terribly difficult to manage and cure.

There is no question that if you can completely resect perihilar cholangiocarcinoma, you have the best survival. But in this series, as in most other series of patients, resection margins were positive in 71% of those patients resected. And so with residual disease present in most patients, it seems that some adjuvant therapy does appear to be warranted.

In the study that we reported some years ago, and comparable to many others in the literature, we did find some improvement in survival, limited to about an eight-months improvement in patients radiated as compared to those not radiated.

So I'd like to ask Dr. Pitt two questions. One is similar to that of Dr. Jones. Since so many patients have residual disease and radiation in your experience does not add any benefit, what do you plan to do now? You tantalize us with the last sentence on your conclusion slide, that new strategies need to be planned. What are your new strategies?

Second, since these tumors rarely metastasize, has your group had any experience with total bile duct and liver hepatectomy with a liver transplant? This would get around the resection margin positivity, which is almost always up in the liver, and then perhaps give adjuvant therapy in this setting.

I enjoyed this paper very much. Thank you.

DR. HENRY A. PITT (Closing Discussion): I would like to thank Dr. Jones and Dr. Hermann for evaluating our analysis. I think that we probably have had one of the largest experiences with radiation therapy and with the use of irridium, and I guess we are as disappointed as any to see the outcome of what we have been doing for so many years as not being as beneficial as we had hoped.

With the fact that there are so many positive margins, it would make sense that radiation would be of benefit, but I think the difference between this analysis and many others in