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CLINICAL INVESTIGATION

SURVIVAL OUTCOMES IN RESECTED EXTRAHEPATIC CHOLANGIOCARCINOMA: EFFECT OF ADJUVANT RADIOTHERAPY IN A SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS ANALYSIS

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Purpose: **The benefit of adjuvant radiotherapy (RT) after surgical resection for extrahepatic cholangiocarcinoma has not been clearly established. We analyzed survival outcomes of patients with resected extrahepatic cholangiocarcinoma and examined the effect of adjuvant RT.**

Methods and Materials: **Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) program between 1973 and 2003. The primary endpoint was the overall survival time. Cox regression analysis was used to perform univariate and multivariate analyses of the following clinical variables: age, year of diagnosis, histologic grade, localized (Stage T1-T2) vs. regional (Stage T3 or greater and/or node positive) stage, gender, race, and the use of adjuvant RT after surgical resection.**

Results: **The records for 2,332 patients were obtained. Patients with previous malignancy, distant disease, incomplete or conflicting records, atypical histologic features, and those treated with preoperative/intraoperative RT were excluded. Of the remaining 1,491 patients eligible for analysis, 473 (32%) had undergone adjuvant RT. After a median follow-up of 27 months (among surviving patients), the median overall survival time for the entire cohort was 20 months. Patients with localized and regional disease had a median survival time of 33 and 18 months, respectively ($p < .001$). The addition of adjuvant RT was not associated with an improvement in overall or cause-specific survival for patients with local or regional disease.**

Conclusion: **Patients with localized disease had significantly better overall survival than those with regional disease. Adjuvant RT was not associated with an improvement in long-term overall survival in patients with resected extrahepatic bile duct cancer. Key data, including margin status and the use of combined chemotherapy, was not available through the SEER database.** **© 2010 Elsevier Inc.**

Cholangiocarcinoma, radiotherapy, Surveillance, Epidemiology, and End Results program, SEER, extrahepatic, bile duct.

INTRODUCTION

Extrahepatic bile duct carcinoma (EHBC) is a rare malignancy with devastating outcomes. Tumors can arise from the ductal epithelium anywhere within the major hepatic ducts, including the junction of the right and left hepatic ducts, in the common hepatic duct, and in the common bile ducts (1). Approximately 3,000–4,500 new cases are diagnosed annually in the United States (2–4), with 5-year survival rates of 20–30% (5). The actual cure rates are even lower because of the high relapse rates (5). Although a specific risk factor cannot be identified in most patients, primary sclerosing cholangitis and choledochal cysts remain the main predisposing factors associated with the development of EHBC in the United States (6).

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The tumor location and performance of a complete resection have a significant effect on the prognosis. Complete surgical resection with histologically negative margins has been reported as the most important factor to achieve optimal therapy in patients with EHBC (7, 8). The benefit of radiotherapy (RT) after surgical resection for extrahepatic cholangiocarcinoma has not been well established. Previous studies assessing the use of external beam RT and/or intraluminal brachytherapy have shown inconsistent results (2–16). Because EHBC is a rare malignancy, no randomized studies have been conducted to assess the use of postoperative RT. We analyzed the survival outcomes of patients with resected extrahepatic cholangiocarcinoma and evaluated the effect of adjuvant RT and various prognostic factors in these patients.

METHODS AND MATERIALS

Data and patient population

Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute between 1973 and 2003 (17). The SEER population-based registries collect and publish cancer epidemiology and survival data representing approximately 26% of the U.S. population. The data from 17 registries were included in our analysis. The study population included men and women who had confirmed EHBC, as defined by the *International Classification of Diseases for Oncology,* depending on the anatomic location and histologic type (ICD-0-3). The histologic codes with the topography code of C24.0 (18) were included, with 8140, 8160, 8260, 8500, 8480, and 8481 as the most common. No informed consent or approval by the institutional review board was required.

A total of 2,332 patient records were obtained. Because of changes in the database during the period used, the patients were divided into two groups: those with localized disease (Stage T1-T2) and those with regional disease (Stage T3 or greater and/or node positive). The following clinicopathologic factors were evaluated between the two groups: age, gender, race, stage at diagnosis, histologic type, tumor grade, and the use of adjuvant RT. The year in which the cancer was diagnosed was categorized by decade (1973–1979, 1980–1989, 1990–1999, and 2000–2003). No information regarding the use of adjuvant chemotherapy or margin status was available.

The exclusion criteria included previous malignancy, distant metastases, incomplete or conflicting records, and rare histologic types (*e.g.,* sarcoma). Patients who had undergone preoperative or intraoperative RT were not included to avoid multiple confounding variables. Patients who did not undergo curative surgery were also excluded. To ensure an opportunity to begin RT after surgical resection was present, all patients, both alive and dead, who had a follow-up of <3 months were excluded. The length of follow-up, disease status at the last follow-up visit, and cause of death were recorded. For the purposes of cause-specific survival analysis, cause of death was considered related to EHBC for the following categories in the SEER database: colon excluding rectum, gallbladder, intrahepatic bile duct, liver, miscellaneous malignant cancer, other biliary, and pancreas.

Statistical analysis

Statistical analysis was performed using Statistical Analysis Systems statistics (SAS Institute, Cary, NC) and R version 2.8.1 (19). A p value of $< .05$ was considered statistically significant.

The survival data between groups were compared using the log–rank test. Kaplan-Meier survival curves were created to estimate the distribution of overall survival. The Cox proportional hazards model was used for univariate and multivariate analyses of the variables that could potentially predict overall survival. Residual analysis was performed to warrant the validity of the proportionality assumption of the model. The effects of RT demonstrated violation of the assumption of proportional hazards. A new model was created, evaluating the hazard within each partition of time. The resulting time-partitioned model accounted for nonproportionality.

A subgroup analysis was performed to evaluate the differences in survival between patients with localized vs. regional disease by decade of diagnosis. In addition, staging information was obtained from patients coded using the 1988 10-digit Extent of Disease Codes and Coding System. Tumor stage was determined by the *SEER Program Coding and Staging Manual*. Differences in survival by stage and decade of diagnosis were then evaluated in patients who had undergone postoperative RT vs. those who had not.

Table 1. Patient demographics

Variable	Surgery alone *(n)*	Surgery plus RT *(n)*
Gender		
Female	440 (72)	170 (28)
Male	578 (66)	303 (34)
SEER registry site		
Alaska Natives, 1992+	3 (100)	0
Atlanta (Metropolitan), 1975+	42 (62)	26 (38)
California, 2000+	49 (62)	30 (38)
Connecticut, 1973+	125 (67)	61 (33)
Detroit, 1973+	149 (64)	83 (36)
Hawaii, 1973+	49 (50.5)	48 (49.5)
Iowa, 1973+	64 (65)	34 (35)
Kentucky, 2000+	16 (73)	6 (27)
Los Angeles, 1992+	128 (72)	50 (28)
Louisiana, 2000+	22 (81)	5 (19)
New Jersey, 2000+	28 (68)	13 (32)
New Mexico, 1973+	38 (81)	9 (19)
Rural Georgia, 1992+	1 (100)	0
San Francisco-Oakland, 1973+	140 (79)	38 (21)
San Jose-Monterey, 1992+	15 (50)	15 (50)
Seattle (Puget Sound), 1974+	118 (68)	55 (32)
Utah, 1973+	31 (100)	0
Stage		
Localized (T1-T2)	325 (79)	86 (21)
Regional (T3 or greater and/or node positive)	693 (64)	387 (36)
Histologic grade		
1	218 (71)	91 (29)
2	367 (66)	190 (34)
3/anaplastic	199 (62)	124 (38)
Unknown	234 (77)	68 (23)
Decade of diagnosis		
1973–1979	165 (89)	21 (11)
1980–1989	255 (75)	83 (25)
1990–1999	331 (60)	218 (40)
2000–2003	267 (64)	151 (36)
Race		
White	837 (69)	375 (31)
Asian	110 (60)	72 (40)
Black	55 (74)	19 (26)
American Indian	5 (63)	3 (37)
Other	11 (73)	4 (27)

Abbreviations: RT = radiotherapy; SEER = Surveillance, Epidemiology, and End Results.

Data in parentheses are percentages.

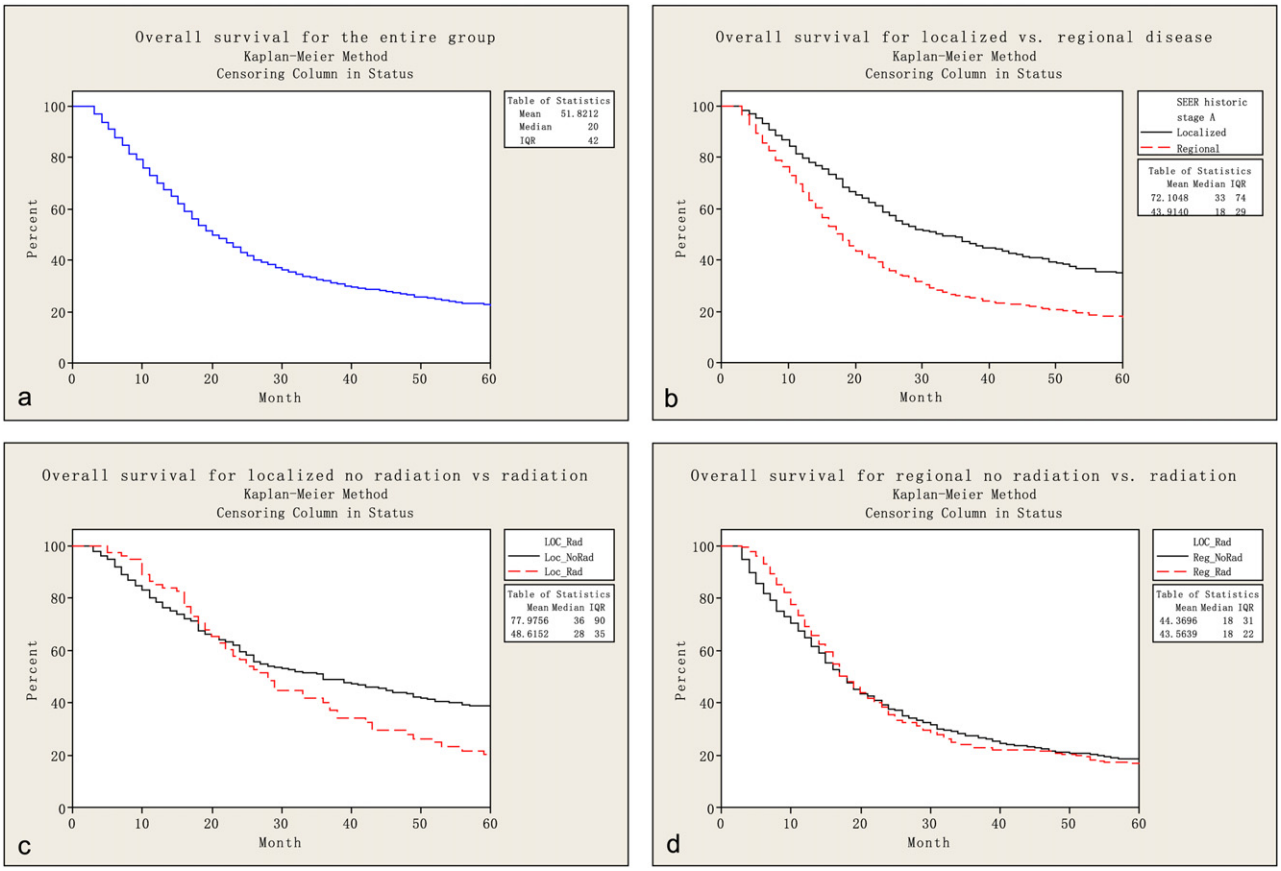

Fig. 1. Overall survival. (a) Overall survival for entire group. (b) Overall survival for patients with localized vs. regional disease. (c) Overall survival for patients with localized disease who had not undergone adjuvant radiotherapy vs. those who had undergone adjuvant radiotherapy. (d) Overall survival for patients with regional disease who had not undergone adjuvant radiotherapy vs. those who had undergone adjuvant radiotherapy.

RESULTS

Demographics

Of the 2,332 patient records obtained, 1,491 patients were eligible for our analysis. The patient demographic characteristics are summarized in Table 1. This cohort contained 881 men (59%) and 610 women (41%). The median age of the patients overall was 66 years (range, 22–97). Of the 1,491 patients who met our inclusion criteria, 411 (28%) had localized disease and 1,080 had regional disease (72%). Of the 411 patients with localized disease, 86 (21%) had undergone postoperative adjuvant RT. Of the 1,080 patients with regional disease, 387 (36%) had undergone adjuvant RT.

Survival

A total of 340 patients (23%) were alive at the last follow-up point. After a median follow-up time of 27 months among surviving patients, the median overall survival time for the entire cohort was 20 months. Patients with localized disease had a significantly greater overall median survival time than that of the regional disease group (33 vs. 18 months, respectively, $p < .001$; Fig. 1).

The patients with localized disease who were treated with and without postoperative adjuvant RT had a median overall survival time of 28 and 36 months, respectively ($p = .038$). No difference was found between the patients with regional disease who had received adjuvant RT and those who had not (18 vs. 18 months, $p = .80$). Cause of death is specified in Table 2.

Kaplan-Meier curves examining cause-specific survival are presented in Fig. 2. Of the group, 84% of patients died of causes related to EHBC, with a median survival time of 23 months. Patients with localized disease had a significantly greater cause-specific survival time than the regional group (42 vs. 19 months, $p < .001$). Of the patients with localized disease, those who had not undergone RT had a longer cause-specific survival time than those who had received RT; however, it did not reach statistical significance (46 vs. 33 months, $p = .057$). For the patients with regional disease, no difference in survival was seen between those treated with or without RT (19 months for both groups).

Prognostic factors

Univariate and multivariate analyses were performed, including age, year of diagnosis, race, gender, stage, and RT. The age at diagnosis correlated with a poorer prognosis on univariate analysis ($p < .001$). In addition, both moderately and poorly differentiated tumors had a negative effect on

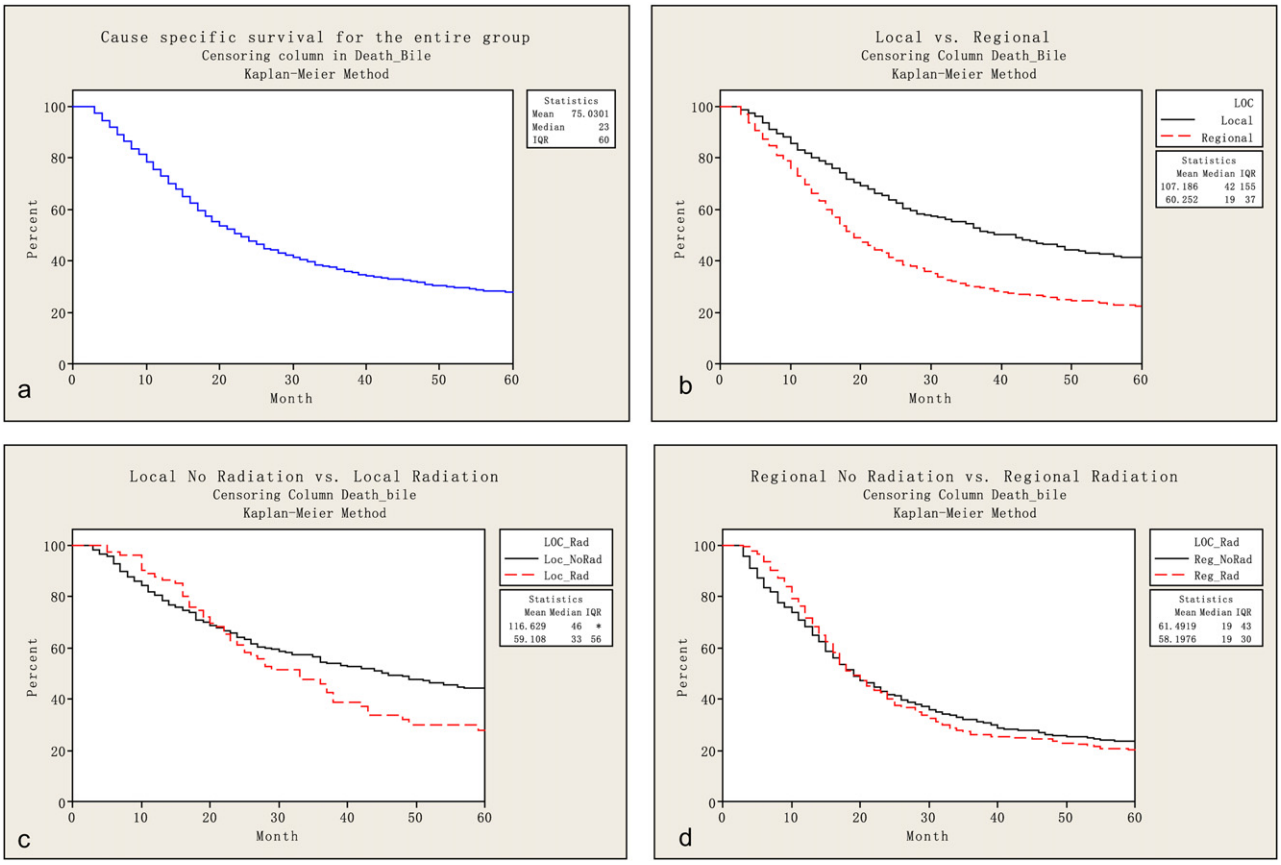

Fig. 2. Cause-specific survival. (a) Cause-specific survival for entire group. (b) Cause-specific survival for patients with localized vs. regional disease. (c) Cause-specific survival for patients with localized disease who had not undergone adjuvant radiotherapy vs. those who had undergone adjuvant radiotherapy. (d) Cause-specific survival for those with regional disease who had not undergone adjuvant radiotherapy compared with those who had undergone adjuvant radiotherapy.

survival ($p = .008$ and $p < .001$, respectively). Localized disease was associated with a better prognosis ($p < .001$). However, race and gender had no effect on survival. On multivariate analysis, age at diagnosis, grade, and disease extent remained statistically significant indicators of survival. The use of adjuvant RT did not reach significance on univariate analysis ($p = .074$). On multivariate analysis, an initial positive effect on survival was seen for patients who had received RT in the short term ($p < .001$). However, the use of adjuvant RT resulted in a negative effect on survival in the long term ($p < .001$). These analyses are listed in Table 3. Both univariate and multivariate analyses demonstrated that the year of diagnosis to be a predictor of overall survival. In addition, patients whose cancer was diagnosed and treated after 1990 had a greater reduction in mortality than those diagnosed before 1990. Gender and race were not contributory to the prognostic factors for EHBC.

A subgroup analysis by decade was performed comparing the survival outcomes between patients with localized and regional disease. Patients with localized disease had a significantly greater median overall survival in each decade (Table 4).

Of the 1,036 patient records entered into the SEER database using the 1988 10-digit SEER code and coding system, the complete disease extent and staging data were available for 942 patients. The years of diagnosis for this subgroup of patients was 1973–2001). These patients were divided by stage and year of diagnosis to perform and subgroup analysis comparing patients who had received RT with those who had not. Those not included in the subgroup analysis were 128 patients diagnosed in 1980–1989, 111 patients diagnosed in 1990–1999, and 216 patients diagnosed in 2000–2003. These data are listed in Table 5. Patients with Stage IA disease who had not undergone adjuvant RT had a greater median survival than those who had undergone RT. These differences reached statistical significance for the patients diagnosed between 1980 and 1989 ($p = .005$). Similar findings were evident among patients with Stage IB disease, with statistical significance obtained between 1973 and 1979 ($p = .007$).

DISCUSSION

Surgical resection remains the foundation of treatment and potential cure for patients with EHBC. However, most patients do not qualify for curative surgery. Although only 25–30% of localized cancers arising in the distal bile duct can be totally resected, an even lower percentage of proximal

Table 2. Patient outcomes and cause of death by last follow-up

Variable	Patients *(n)*
Alive	340
Dead	1,151
Cause of death	
Accidents and adverse effects	2 (<1)
Alzheimer's disease	1 (<1)
Anus, anal canal, and anorectum	1 (<1)
Atherosclerosis	1 (<1)
Breast	1 (<1)
Cardiovascular disease	47 (4)
Cerebrovascular disease	16 (1)
Chronic liver disease and cirrhosis	8 (1)
Chronic obstructive pulmonary disease	3 (<1)
Colon excluding rectum	10 (1)
Diabetes mellitus	2 (<1)
Esophagus	1 (<1)
Gallbladder	40 (3)
In situ, benign or unknown-behavior neoplasm	3 (<1)
Intrahepatic bile duct	297 (26)
Liver	28 (2)
Lung and bronchus	8 (1)
Miscellaneous malignant cancer	22 (2)
Myeloma	2 (<1)
Nephritis, nephrotic syndrome, and nephrosis	1 (<1)
Other biliary	390 (34)
Other cause of death	31 (3)
Other digestive organs	4 (<1)
Pancreas	183 (16)
Pneumonia and influenza	2 (<1)
Rectum and rectosigmoid junction	1 (<1)
Septicemia	8 (<1)
Small intestine	4 (<1)
State DC not available or available but no COD listed	28 (2)
Stomach	1 (<1)
Stomach and duodenal ulcers	1 (<1)
Suicide and self-inflicted injury	2 (<1)
Symptoms, signs and ill-defined conditions	2 (<1)

Abbreviations: COD = cause of death; DC = death certificate; other abbreviations as in Table 1.

Data in parentheses are percentages.

lesions can be completely removed because of the surrounding structures and the greater likelihood of direct invasion (7). Adjuvant RT has been studied as a therapeutic modality to prevent locoregional recurrence and improve long-term survival. Because the incidence of EHBC is extremely low, no definitive studies have been done demonstrating the utility of adjuvant RT in the treatment of patients with completely resected disease. In the present retrospective review of patients with localized or regional disease, no improvement in long-term survival was seen with the addition of adjuvant RT after surgical resection.

The role of RT for EHBC is unclear. Previous series have demonstrated variable results (Table 6). Several reports have suggested that RT might improve overall survival for patients with resected EHBC. In some of these studies, however, the patients who received RT were more likely to have had better prognostic factors than those who had not undergone RT (who had had metastatic disease, unresectable tumors, or poor Karnofsky performance status) (20–24). Not all reviews have supported the therapeutic benefit of adjuvant RT. Pitt *et al.* (16) reported a similar conclusion that RT had no effect on the median survival time for patients who had undergone resection compared with those who had not received adjuvant therapy (20 vs. 20 months). The use of a greater radiation dose and the addition of brachytherapy to external beam RT have been proposed as potential contributors to improved survival (14, 20–22, 25). Alden *et al.* (22) found that patients who had undergone combined external beam RT and intraluminal bile duct implantation with doses of 55–80 Gy achieved greater median disease-specific survival compared with those who had received <55 Gy (24 vs. 6 months, respectively). However, the data remain inconclusive, with concerns for the limitations of the surrounding normal tissue tolerance and the actual effectiveness for local control.

The tumor location along the extrahepatic bile duct has been shown to affect survival. Alden *et al.* (13) compared 81 patients with either proximal or distal lesions, who had undergone resection with or without adjuvant RT. The 5-year overall survival rate for the group was 26% (median overall survival time, 21 months). Patients with distal bile duct lesions had a greater 5-year survival rate than those with proximal lesions (53% vs. 13%, respectively, $p < .01$). No significant difference was found in survival between the groups with distal lesions who underwent resection with or without RT, although a trend was seen toward a decreased survival time in the group that had received RT ($p = .27$). The cohort that had undergone RT included more patients with poorer prognostic factors, such as advanced disease and residual disease after resection (13). These patients benefited from combined therapy, because their overall outcome was similar to that of patients who had not undergone adjuvant RT.

Some studies have suggested a benefit is present for using adjuvant RT for patients with microscopic residual disease. Free margins are difficult to obtain because of the longitudinal spread and increased likelihood of microscopic invasion into the surrounding structures. Previous studies have demonstrated an increased median survival time with tumor-negative margins in the resection of bile duct cancer. Oh *et al.* (9) analyzed the effect of postoperative RT in R0 and R1 patients with negative-node pathologic findings. The overall survival and progression-free survival rate at 2 years was 53% and 55% in R0 patients and 40.7% and 36.7% in R1 patients, respectively. No statistically significant differences were seen in overall survival ($p = .56$) and progression-free survival ($p = .98$) between the two groups, suggesting that adjuvant RT might play a role in locoregional control. A retrospective review from Ben-David *et al.* (26) evaluated the outcomes of 81 patients with localized EHBC who had received adjuvant RT. The patients had undergone curative resection (R0/R1), had macroscopic residual disease (R2), or had unresectable disease. The patients with R0 disease had a superior overall survival time of 24.1 compared with 13.1 months for those with R2 lesions. Progression-free survival was also greater at 21.2 months for R0 patients compared

Table 3. Univariate and multivariate analyses of factors potentially affecting overall survival

	Univariate		Multivariate	
Variable	HR (95% CI)	*p*	HR (95% CI)	*p*
Female gender	1.118 (0.994–1.258)	.063	1.053 (0.934–1.188)	.400
Decade of diagnosis				
1973–1979	1.323 (1.111–1.57)	< .001	1.282 (1.059–1.551)	.011
1980–1989	1.109 (0.958–1.28)	.165	1.224 (1.049–1.427)	.009
1990–1999	1.000			
2000–2003	1.000 (0.845–1.18)	.999	0.846(0.713–1.001)	.058
Age at diagnosis	1.021 (1.01–1.021)	< .001	1.012 (1.007–1.017)	<.001
Grade				
1	1.000			
2	1.247 (1.06–1.47)	.008	1.190 (1.008–1.406)	.04
3	1.691 (1.41–2.02)	< .001	1.439 (1.197–1.732)	< .001
Race				
White	1.000			
Black	1.008 (0.770–1.32)	.284	1.080 (0.822–1.419)	.580
Asian	0.922 (0.775–1.10)	.359	0.945 (0.793–1.127)	.530
American Indian	1.180 (0.529–2.64)	.686	0.869 (0.386–1.957)	.730
Stage				
Local (0–5)*	0.617 (0.54–0.705)	< .001†	1.183 (0.712–1.968)	< .001
Local (5–10)*			1.235 (0.864–1.765)	.250
Local (10–end)*			0.601 (0.515–0.70)	< .001
Adjuvant RT				
None (0–5)*	0.89 (0.785–1.01)	.074†	267.33 (151.15–472.83)	< .001
None (5–10)*			11.651 (8.571–15.838)	< .001
None (10–end)*			0.586 (0.509–0.675)	< .001

Abbreviations: HR = hazard ratio; CI = confidence interval; RT = radiotherapy.
Data presented as overall HRs and *p* values.
* Multivariate time-partition model representing time in months.
† Univariate analysis not divided over time.

with 7.9 months for R2 patients ($p = .002$). Todoroki *et al.* (27) demonstrated that in patients with microscopic disease, the 5-year survival rate was greater with the addition of adjuvant RT compared with that for patients who had undergone resection alone (33.9% vs. 13.5%, respectively). Because of an inherent bias, patients with positive resection margins might be more likely to receive adjuvant RT to optimize locoregional control. Margin status was unavailable in the present review; however, this could potentially explain the lower cause-specific survival for the patients with locoregional disease.

The present study is one of the larger retrospective reviews of EHBC; however, it was limited by the information available in the SEER database. Although >1,000 patients were included in the analysis, the reporting sites constituted only a small percentage of the U.S. Population (17). In addition, detailed staging information was only available for patients coded using the 1988 10-digit Extent of Disease Codes and Coding System. We performed a subgroup analysis comparing patients who had received RT with those who had not by stage and decade of diagnosis. Statistically significant differences were demonstrated in patients with Stage IA and IB disease, with greater median survival for those patients who had not undergone RT. These detrimental findings were for patients treated before 1990 and thus could have been related to less-advanced radiotherapeutic techniques at treatment. Improved surgical intervention and conformal RT planning might decrease the treatment-related morbidity and mortality. In addition, these survival differences could have resulted from a selection bias from variables that remain unknown. Despite this, we failed to identify a benefit of RT for survival, even for patients treated at a later date.

Additional limitations of the present study included that the patient information was inconsistently updated in the SEER database. The database was queried again in an attempt to update the survival months and vital status of the

Table 4. Subgroup analysis of survival outcomes by decade of treatment

		Overall survival (mo)			
Treatment decade	Patients *(n)*	Median	Localized disease	Regional disease	*p*
1973–1979	186	16	18	14	.009
1980–1989	338	19	29	16	< .001
1990–1999	549	23	44	18	< .001
2000–2003	418	22	36	19	< .001

Table 5. Survival outcomes between radiotherapy and no radiotherapy groups by stage and decade of diagnosis

		RT		No RT		
Stage	Decade of diagnosis	Patients *(n)*	Overall median survival (mo)	Patients *(n)*	Overall median survival (mo)	*p* (log–rank)
IA						
	1973–1979	7	33	24	68	.185
	1980–1989	21	36	30	119	.005
	1990–1999	19	33	86	46	.677
	2000–2003	5	NA	14	NA	NA
IB						
	1973–1979	3	17	11	44	.007
	1980–1989	20	18	21	24	.283
	1990–1999	26	22	25	62	.110
	2000–2003	8	20	7	40	.866
IIA						
	1973–1979	14	26	22	33	.687
	1980–1989	36	29	45	29	.942
	1990–1999	33	21	76	31	.313
	2000–2003	6	NA	17	19	.583
IIB						
	1973–1979	18	17	24	15	.804
	1980–1989	49	17	27	13	.615
	1990–1999	61	17	79	15	.463
	2000–2003	15	19	31	16	.187
III						
	1973–1979	1	10	7	56	.426
	1980–1989	8	16	4	33	.695
	1990–1999	17	19	15	17	.499
	2000–2003	5	NA	5	12	.146

Abbreviations: NA = data not available; other abbreviations as in Table 1.

Staging determined using SEER program *Coding and Staging Manual:* Stage IA, T1N0M0; Stage IB, T2N0M0; Stage IIA, T3N0M0; Stage IIB, T1-T3N1M0; Stage III, T4, any N, M0.

patients included in our original analysis. However, the patients had all been de-identified and had been assigned new patient identifiers, preventing us from revising the essential survival data. Data were also not available for the tumor location, extent of surgical resection, margin status after resection, postoperative complications, and disease recurrence, all of which play a role in survival. The use of chemotherapy was another variable not available through the SEER database. A similar SEER analysis was recently published examining the role of adjuvant RT for extrahepatic cholangiocarcinoma and its effect on overall survival (28). Although data were obtained from the same source, their conclusions differed from those of the present study. Shinohara *et al*. (28) noted an increased overall median survival time for patients who had undergone adjuvant RT compared with those who had undergone surgery alone (16 vs. 9 months, respectively, $p < .0001$). However, on further analyses of the propensity score, no significant difference was identified between the two groups, similar to our findings. In addition, their Kaplan-Meier projections also demonstrated a crossing of survival curves, with initial survival benefit for those receiving combined therapy. However, over time, those who had undergone surgery alone had greater overall survival rates. One major difference between these two reviews was our exclusion of patients who had follow-up of <3 months to ensure that patients had an opportunity to undergo RT. The effects of minor changes in the exclusion criteria further exemplifies the inherent difficulty in evaluating the validity of the SEER analyses, especially when considering its application in patient care. Perhaps the most important information that SEER lacks in evaluating the usefulness of RT is any information regarding the dose, fields, and treatment length of the RT, let alone the quality of the therapy. Furthermore, information regarding local and distant disease control, as additional endpoints, cannot be evaluated with SEER data because of a lack of inclusion of these parameters in the database.

The outcomes for patients with resected EHBC have significantly improved during the past 30 years. Although surgical resection remains the mainstay of therapy for EHBC, the prognosis continues to be poor, with locoregional failure in more than one-half of the patients with complete tumor resection (9, 12, 15). The results of the present retrospective review suggest that adjuvant RT has a limited benefit in patients with either localized or regional EHBC. However, of the 31.7% of patients who received postoperative RT, more patients were found to have regional disease (36% vs. 21%, respectively), suggesting that patients were highly selected, perhaps owing to the presence of high-risk features. This is suggested because the disease-specific survival rate was lower for the patients who had received RT. In addition, the present review has demonstrated a potential detriment to long-term survival for patients who received adjuvant RT. It is unclear why the survival might have been decreased in these patients.

Table 6. Comparison of outcomes with and without use of adjuvant radiotherapy

Investigator	Comparison	Patients *(n)*	Outcome
Alden *et al*. (13)			
Proximal lesions			6-mo OMS
	Resection only	22	
	Resection + RT	34	
Distal lesions*			17-mo OMS
	Resection only	15	
	Resection + RT	10	
Borgehero *et al*. (29)			
	Resection only (pN0, R0)	23	42% 5-y SR
	Resection + chemotherapy/RT (pN+ or R+)	42	36% 5-y SR
Hanna et al[8]			
	No RT	3	11-mo OMS†
	RT	14	12.3-mo OMS
Heron *et al*. (3)			
Proximal lesions	No RT (5 resected)	11	Trend toward improved survival for patients undergoing RT vs. those without
	RT (23 resected)	54	(p = .1)
Kamada *et al*. (35)			
	Resection only	20	8-mo OMS
	Resection + RT	71	24-mo OMS
Pitt *et al*. (16)			
	No RT	27	15-mo OMS‡
	RT	23	14-mo OMS
Schoenthaler *et al*. (23)			
	Resection only	62	6.5-mo OMS§
	Resection + conventional RT	45	11-mo OMS§
Todoroki *et al*. (27)			
	Resection only	19	13.5% 5-y SR
	Resection + RT	47	33.9% 5-y SR
Shinohara *et al*. (28)			
	Resection only	1,372	9-mo OMS
	Resection and RT	701	16-mo OMS

Abbreviations: OMS = overall median survival; RT = radiotherapy; SR = survival rate.

* No statistical significance between groups with distal lesions; trend toward lower survival in group that underwent RT (p = .27).

† Too small for clinical significance but suggested benefit.

‡ No statistical significance.

§ Patients treated with curative intent had same overall survival in each group (16 vs 16 months).

Although a negative effect on survival was demonstrated in patients with early-stage disease who underwent RT, the reasons are unclear and could have resulted from variables that remain unknown. The potential factors include long-term complications associated with RT or a selection bias for high-risk patients who ultimately died of aggressive metastatic disease.

However, the important variables affecting treatment and survival outcomes, such as margin status and lymphovascular space invasion, could not be accounted for in the present analysis. Treatment has varied by center, physician, and patient postresection status. Thus, an inherent bias could have been present in the selection of patients with regional disease who had received adjuvant RT. Clinically, they might have had a greater risk of relapse and mortality. It has been suggested in a recent analysis of 65 patients with resected cancer that RT might be able to improve the outcome of patients with positive margins or positive nodes by improving locoregional disease control (29). In that study, only patients with positive nodes or positive margins were treated with RT, and the locoregional control was improved and the survival was the same as for the group of patients without these adverse prognostic features.

Adjuvant RT could be a useful therapeutic modality to reduce locoregional recurrence and improve long-term outcomes, as has been demonstrated in other gastrointestinal malignancies (30–34). However, some of these studies have utilized concurrent chemoradiation to achieve these gains.'' Shinohara *et al*. (33) completed a SEER analysis of RT for intrahepatic cholangiocarcinoma. Their results suggested that both adjuvant and definitive RT prolong survival; however, the cure rates remained low. Similar to the present

review, they encountered difficulties in incorporating variables, such as chemotherapy, technique, and brachytherapy, all of which have potential effects on long-term survival. When combined with radiosensitizers, increased locoregional control might be achieved, especially in patients with microscopic residual disease. Investigators from the Duke University Medical Center reported on the use of concurrent chemoradiotherarpy for resected extrahepatic cholangiocarcinoma (34). Of the 45 patients included in their retrospective review, 33 received adjuvant RT and 12 were treated with neoadjuvant therapy. All but 1 patient received concurrent 5-fluorouracil. The 5-year overall survival, disease-free survival, metastasis-free survival, and locoregional control rate was 33%, 37%, 42%, and 78%, respectively. Patients who received neoadjuvant therapy showed a trend toward improved survival compared with those treated postoperatively (5-year survival rate, 53% vs. 23%; $p = .16$). With the advantages of improving tumor resectability and minimizing tumor seeding perioperatively, neoadjuvant therapy might have a role in enhancing locoregional control. New strategies need to be developed and investigated to improve overall patient quality of life and survival outcomes through prospective studies.

CONCLUSION

Analysis of the SEER database revealed that patients with localized EHBC had improved survival compared with patients with regional disease. The decade in which the patient was treated, disease grade, and stage were useful predictors of survival, but gender and race were not. Postoperative RT did not affect long-term survival in patients with resected EHBC. RT might have an appropriate application for local control; however, its role could not be determined from the current database. Additional studies evaluating its use combined with radiosensitizing agents and techniques are necessary to determine its effectiveness in the treatment of EHBC.

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