Original Article

Comparison of external beam radiation and brachytherapy to external beam radiation alone for unresectable extrahepatic cholangiocarcinoma

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Background: Extrahepatic cholangiocarcinoma (EHC) is a rare malignancy with a relatively poor prognosis. There are no randomized, prospective data to help define the optimal method of radiation delivery for unresectable EHC. The purpose of this study was to evaluate the benefit of adding brachytherapy to external beam radiation therapy (EBRT) for unresectable EHC.

Methods: A retrospective review of 1,326 patients with unresectable EHC using the Surveillance, Epidemiology, and End Results (SEER) database was completed. Kaplan-Meier methods were used to analyze the primary endpoint, overall survival. Univariate and multivariate analysis was performed to identify and control for potential confounding variables, including age at diagnosis, sex, stage, grade, histology, race, year of diagnosis, and reason for no surgery.

Results: Of the 1,326 patients with unresectable EHC, 1,188 (92.9%) received EBRT only, while 91 (7.1%) received both EBRT and brachytherapy. Patients receiving combined modality radiation therapy were more likely to be treated prior to the year 2000. Median overall survival for patients receiving EBRT and EBRT plus brachytherapy was 9 and 11 months, respectively (P=0.04). Cause specific survival was 12 months for those receiving EBRT only, and 15 months for those who received EBRT + brachytherapy (P=0.10). Survival analysis performed on patients with locoregional disease only revealed a trend towards prolonged overall survival with those receiving EBRT + brachytherapy (P=0.08). Multivariate analysis revealed grade and stage of disease were correlated with both overall survival and cause specific survival (P≤0.05).

Conclusions: Among patients with unresectable EHC, the addition of brachytherapy to EBRT is associated with a prolonged median overall survival. However, the use of brachytherapy boost decreased in the last decade of the study.

Keywords: Brachytherapy; cholangiocarcinoma; extrahepatic; radiation

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Introduction

Cholangiocarcinoma is a rare malignancy of the biliary tract, with only 0.6 to 1 of 100,000 persons in the United States being diagnosed per year (1-3). These tumors are subcategorized by location, either intrahepatic or extrahepatic, with the latter including both perihilar and distal bile duct tumors (2,4). Extrahepatic cholangiocarcinoma (EHC) portends a poor prognosis and surgery is generally thought to be the only curative modality (5,6). Unfortunately, surgery has to result in an

R0 resection to provide benefit to the patient and this is not attainable most of the time (7-9).

Treatment options for unresectable extrahepatic cholangiocarcinoma (UEC) are limited to chemotherapy, radiation, or a combination of both (10). When utilized, external beam radiation therapy (EBRT) can be delivered with or without a brachytherapy boost (11,12). Combining EBRT with brachytherapy allows for the delivery of an elective dose to larger areas, including nodal basins when desired, while delivering a more definitive dose to the tumor that doesn't tend to increase dose to organs at risk (13-18). The benefit of EBRT in combination with brachytherapy has been previously evaluated in multiple single-institution retrospective series with the majority either showing an overall survival or progression-free survival benefit (13-17,19).

There is also population-based evidence that the use of brachytherapy improves outcomes among unresectable cholangiocarcinoma patients (20). However, no large dataset analysis has investigated the benefit of adding a brachytherapy boost to EBRT. The purpose of this study was to evaluate if the addition of brachytherapy to EBRT provides a survival benefit among patients with UEC, using population-based data from the Surveillance, Epidemiology, and End Results (SEER) database.

Methods

The SEER database is an open access, population-based database that includes diagnostic, treatment, and survival data. It has been reported that SEER currently tracks 28% of the United States population. The data acquired for this study spanned from years 1974 to 2011 and all available registries were utilized for analysis. Internal review board approval was not required at our institution since the SEER database information is de-identified.

The International Classification of Diseases for Oncology (ICD-0-2 and ICD-0-3) codes were used to identify those with EHC according to anatomy and histology. The site code C24.0 for extrahepatic bile duct was included in our search with the following histology codes: 8010, 8020, 8040, 8070, 8140, 8144, 8160, 8161, 8162, 8260, 8310, 8480, 8490, and 8560. Only patients with unresectable disease who received radiation were included in the cohort. Patients who received brachytherapy only were excluded from our analysis. We included the following variables for the selected cohort: age at diagnosis, sex, race, and SEER registry location, year of diagnosis, grade, stage, type of radiation, and the reason for no-cancer-directed surgery. Survival months, vital status recode, and cause specific death classification were obtained for survival analysis.

Pearson chi-square analyses were used to compare treatment and tumor characteristics for categorical variables. Kaplan-Meier methods were then employed to analyze overall survival. Univariate and multivariate survival analyses were performed using Cox proportional hazards regression. To test whether overall survival becomes significantly different among groups, a log rank test was performed. Statistical analyses were performed using STATA 14.0. The level of significance was defined as $P<0.05$.

Results

A total of 1,326 patients were identified with UEC with available radiation data. Of these patients, 1,188 (89.6%) received EBRT only, 47 (3.5%) received brachytherapy only, and 91 (6.8%) received EBRT plus brachytherapy. Patients who received brachytherapy alone were excluded from the analysis. Fifty-nine percent of patients were diagnosed between the year 2000 and 2011. The cohort was predominantly male (56%), Caucasian (81%), and had locoregional disease (75%). The predominant reason for patients not undergoing surgery was due to surgery not being recommended (71%).

Patient demographic information was compared between those who received EBRT *vs.* those receiving combined modality treatment. Localized disease was more prevalent among those receiving both EBRT and brachytherapy (45% *vs.* 26%), while those receiving EBRT only were more likely to have distant disease (25% *vs.* 12%) (P=0.002). Patients receiving combined modality radiation therapy were also more likely to be treated prior to the year 2000 ($P\leq0.001$). The percentages of those treated with EBRT and brachytherapy for each decade are as follows: 1973–1979, 1.5%; 1980–1989, 8.3%; 1990–1999, 15.9%; 2000–2011, 4.6%. There was no significant difference in gender, race, grade, or reason for being unresectable (see *Table 1*).

Median overall survival for patients receiving EBRT only was 9 months (95% CI, 9–10 months) *vs.* 11 months (95% CI, 9–14 months) for those receiving combined modality radiotherapy (P=0.04). Median cause specific survival was 12 months (95% CI, 11–13 months) for those receiving EBRT only, and 15 months (95% CI, 10–19 months) for those receiving EBRT plus brachytherapy (P=0.10) (see *Figure 1*). Survival analysis was also performed after excluding patients with metastatic disease. Among this cohort

Table 1 Comparison of complete cohort patient demographics among different forms of radiation treatment

Variable	EBRT [%]	EBRT + brachytherapy [%]	P value
Total patients	1,188 [93]	91 [7]	
Sex			0.769
Female	528 [44]	39 [43]	
Male	660 [56]	52 [57]	
Race			0.431
White	961 [81]	72 [79]	
Black	64 [5]	3 [3]	
Other	162 [14]	16 [18]	
Year of diagnosis			<0.001
1973–1979	67 [6]	1 [1]	
1980–1989	200 [17]	18 [20]	
1990–1999	196 [16]	37 [41]	
2000–2011	725 [61]	35 [38]	
Grade			0.761
Grade I	99 [25]	6 [19]	
Grade II	153 [39]	14 [45]	
Grade III	134 [34]	11 [35]	
Surgery recommendation			0.988
Not recommended	848 [72]	65 [71]	
Recommended	338 [28]	26 [29]	
SEER stage			0.002
Localized	263 [26]	30 [45]	
Regional	487 [49]	29 [43]	
Distant	251 [25]	8 [12]	

P values computed from Pearson's χ^2 test. EBRT, external beam radiation therapy; SEER, Surveillance, Epidemiology, and End Results.

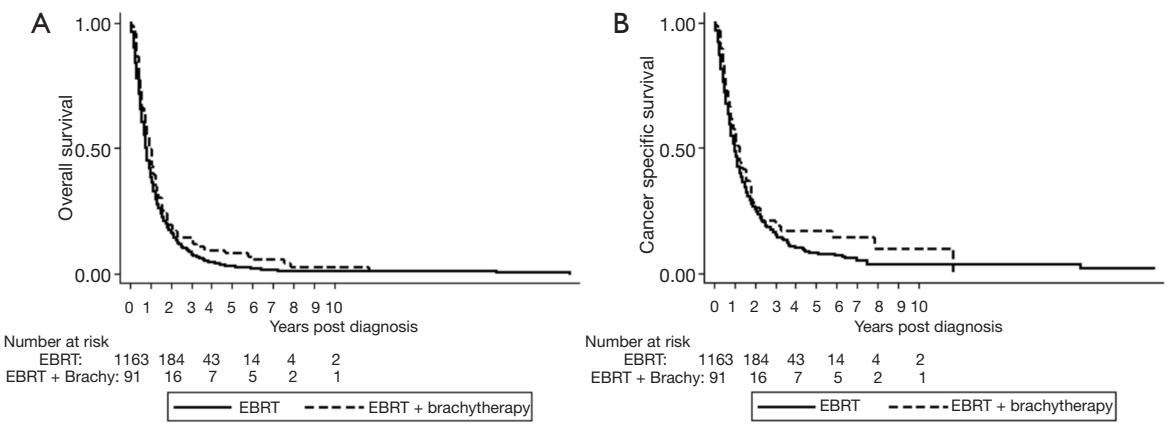

Figure 1 Overall and cancer specific survival by treatment type for unresectable extrahepatic cholangiocarcinoma. (A) Kaplan-Meier curve of overall survival. Survival curves for EBRT and EBRT plus Brachytherapy shown; (B) Kaplan-Meier curve for cause specific survival. Survival curves for EBRT and EBRT plus Brachytherapy shown. EBRT, external beam radiation therapy; Brachy, brachytherapy.

Table 2 Univariate and multivariate analysis for overall survival

Univariate covariate	Univariate		Multivariate*
	HR (95% CI)	P value	HR (95% CI)
Increasing age	1.05 (1.00–1.10)	0.051	1.01 (1.00–1.01)
Treatment			
EBRT	1	–	1
EBRT + brachy	0.78 (0.64–0.99)	0.049	0.94 (0.72-1.23)
Sex			
Male	1	–	–
Female	1.05 (1.00–1.10)	0.884	–
Race			
White	1	–	–
Black	0.88 (0.68–1.14)	0.338	–
Other	0.79 (0.59–1.06)	0.122	–
Year of diagnosis			
1973–1979	1	–	1
1980–1989	0.78 (0.59–1.03)	0.082	0.84 (0.62–1.14)
1990–1999	0.83 (0.63–1.09)	0.172	0.92 (0.68–1.25)
2000–2011	0.80 (0.62–1.04)	0.095	0.83 (0.63–1.09)
Grade†			
Grade I	1	–	–
Grade II	1.38 (1.07–1.78)	0.013	–
Grade III	1.45 (1.11–1.89)	0.006	–
Grade IV	1.44 (0.58–3.53)	0.431	–
Surgery recommendation			
Recommended	1	–	–
Not recommended	1.01 (0.89–1.15)	0.861	–
SEER stage			
Localized	1	–	1
Regional	1.04 (0.89–1.20)	0.639	1.06 (0.91–1.23)
Distant	1.70 (1.43–2.03)	<0.0001	1.77 (1.48–2.12)

*, Multivariate analysis included covariates significant (P<0.05) in univariate model and containing >30% of observations; †, missing >30% of data and not included in multivariate analysis. HR, hazard ratio; EBRT, external beam radiation therapy; SEER, Surveillance, Epidemiology, and End Results.

median overall survival was 10 months for patients receiving EBRT alone and 13 months for those receiving EBRT plus brachytherapy (P=0.08). Cause specific survival was 14 and 15 months for EBRT and EBRT plus brachytherapy, respectively (P=0.12).

On univariate analysis, a significant improvement in overall survival was noted in those who received combined modality radiation therapy [hazard ratio (HR) =0.78; 95% CI, 0.80–0.99] (*Table 2*). Increased grade (HR =1.18; 95% CI, 1.04–1.34) and greater extent of disease (HR =1.29; 95% CI, 1.18–1.42) were associated with a decrease in overall survival. On multivariate analysis, there was no association of combined modality radiation therapy with overall survival (HR =0.94; 95% CI, 0.72–1.23). However, grade (HR =1.15; 95% CI, 1.01–1.32) and extent of disease (HR =1.20; 95% CI, 1.02–1.41) continued to be negatively correlated with overall survival.

A trend towards improved cause specific survival was

Table 3 Univariate and multivariate analysis for cause-specific survival

Univariate covariate	Univariate		Multivariate*
	HR (95% CI)	P value	HR (95% CI)
Increasing age	1.05 (1.00–1.010)	0.051	–
Treatment			
EBRT	1	–	1
EBRT + Brachy	0.80 (0.64–0.99)	0.049	0.95 (0.70–1.29)
Sex			
Male	1	–	–
Female	1.01 (0.90–1.13)	0.884	–
Race			
White	1	–	–
Black	0.88 (0.68–1.14)	0.338	–
Other	0.79 (0.59–1.06)	0.122	–
Year of diagnosis			
1973–1979	1	–	1
1980–1989	0.78 (0.59–1.03)	0.082	0.82 (0.59–1.13)
1990–1999	0.83 (0.63–1.09)	0.172	0.89 (0.64–1.24)
2000–2011	0.80 (0.62–1.04)	0.095	0.72 (0.53–0.97)
Grade†			
Grade I	1	–	–
Grade II	1.38 (1.07–1.78)	0.013	–
Grade III	1.45 (1.11–1.89)	0.006	–
Grade IV	1.44 (0.58–3.53)	0.431	–
Surgery recommendation			
Recommended	1	–	–
Not recommended	1.01 (0.89–1.15)	0.861	–
SEER stage			
Localized	1	–	1
Regional	1.04 (0.89–1.20)	0.639	1.15 (0.96–1.37)
Distant	1.70 (1.43–2.03)	<0.0001	1.90 (1.55–2.33)

*, Multivariate analysis included covariates significant (P<0.05) in univariate model and containing >30% of observations; †, missing >30% of data and not included in multivariate analysis. EBRT, external beam radiation therapy; Brachy, brachytherapy

noted for those receiving EBRT plus brachytherapy (HR =0.90; 95% CI, 0.79–1.02) (*Table 3*). A later decade of diagnosis was associated with a significant improvement in cause specific survival (HR =0.92; 95% CI, 0.86–0.99), while increasing grade (HR =1.22; 95% CI, 1.06–1.40) and extent of disease (HR =1.36; 95% CI, 1.22–1.51) were also associated with a decrease in cause specific survival. On multivariate analysis, there was no association between the addition of brachytherapy and cause specific survival (HR =1.09; 95% CI, 0.86–1.40). Grade (HR =1.19; 95% CI, 1.02–1.39) and extent of disease (HR =1.28; 95% CI, 1.07–1.54) were associated with worsening of cause specific survival as well. Recent decades of diagnoses were associated with an improved cause specific survival (HR 0.85; 95% CI, 0.75–0.96).

After excluding metastatic patients, univariate analysis revealed a trend towards improved overall survival among those receiving EBRT plus brachytherapy (HR =0.82; 95% CI, 0.65–1.03). This trend was also seen on cause specific survival (HR =0.81; 95% CI, 0.61–1.06). Multivariate

analysis on this cohort again revealed no correlation between combined modality radiation and overall survival (HR =0.97; 95% CI, 0.84–1.12) or cause specific survival (HR =0.97; 95% CI, 0.82–1.14).

Discussion

This is the first large, population-based study evaluating the survival benefit of brachytherapy when added to EBRT for UEC patients. We selected for patients that were not surgical candidates and specifically evaluated the benefit of combined modality radiotherapy by comparing those treated with EBRT alone and those receiving EBRT plus brachytherapy. Due to the size of our cohort, we were able to elucidate demographic and clinical factors predictive of overall survival. This is the first study of its kind which shows a potential overall survival benefit when brachytherapy is added to EBRT in unresectable UEC. Our study reveals a two month overall survival benefit of adding brachytherapy to EBRT (P=0.04), which was also seen on univariate analysis (HR =0.89; 95% CI, 0.80–0.99). In spite of its apparent efficacy, brachytherapy boost saw declining use from the 1990's to the 2000's.

Brachytherapy has the advantage of delivering higher doses of radiation therapy with less dose to the surrounding normal tissues, thus minimizing toxicity in patients with UEC (14,21). Early studies revealed survival was proportional to the dose of radiation delivered. Patients receiving greater than 55 Gray (Gy) have an improved 2-year survival when compared to those receiving less than 55 Gy (48% *vs.* 0%) (22). More recently, ablative doses of EBRT of up to 100 Gy in 25 fractions prescribed as a boost to the internal portion of intrahepatic cholangiocarcinomas were shown to outperform more conventional lower doses in overall survival (23). Better outcomes with higher doses have led many to the practice of using brachytherapy as a boost to EBRT. Several retrospective series have shown a progression-free and overall survival benefit with the addition of brachytherapy to EBRT (13-17). One of the proposed mechanisms in these small studies was felt to be secondary to increasing longevity of stent patency (17,24). Stent patency can also enhance patients' tolerability to chemotherapy by decreasing bilirubin levels (25).

For malignancies with a low-incidence such as EHC, the SEER database is a useful way to aggregate larger numbers of patients to analyze outcomes (26). Shinohara *et al.* utilized the SEER database to evaluate the benefit of radiation therapy of all patients with EHC. In patients with unresectable disease, radiotherapy improved overall survival with a HR of 0.61 (95% CI, 0.54–0.70) (27). However, no analysis was performed on the type of radiotherapy delivered. In a separate analysis, Shinohara *et al.* utilized the SEER database to evaluate the impact of brachytherapy (without regard to the use of EBRT) among patients with both intra- and extrahepatic cholangiocarcinoma (20). The cohort also included patients who received surgery as a part of their definitive treatment. When compared to patients who did not receive any type of radiation, the use of brachytherapy (with or without EBRT) was associated with a significant overall survival benefit of 11 *vs.* 4 months (P<0.05). Race, stage of disease, and an earlier year of diagnosis were associated with a poorer prognosis. A comparison of patients receiving EBRT plus or minus brachytherapy was not completed.

In contrast to the studies performed by Shinohara *et al.* we selected for patients with EHC that were not surgical candidates. Our results also differ, as stage and grade were found to be a significant prognostic indicator in this cohort, while race was not. The potential benefit of including brachytherapy appears to be among those patients surviving greater than 2 years following diagnosis. This could be explained by an existing subpopulation within the cohort with more aggressive tumor biology more likely to die of distant rather than local disease. Those with local tumors would be the most likely to benefit from brachytherapy. Our subset analysis excluding patients with metastatic disease showed a trend toward improved survival with combined modality radiation, though this was not found to be statistically significant. Given that patients with metastatic disease had decreased survival rates, regardless of the type of radiation delivered, may be due to decreased statistical power, or may hint at the importance of local control in EHC.

Our study has some unavoidable limitations. The SEER database itself is known to be associated with several pitfalls including coding reliability and underreporting of radiation therapy (28). There is no information about dose, fractionation, field size, prescription point/volume, or other RT parameters. The lack of important variables such as performance status and use of chemotherapy could confound the correlations we found. In our particular cohort, there were significant differences between the two treatment groups. Patients receiving combined modality treatment were more likely to have local disease and to be treated before 2000. The benefit of combined modality RT was shown on univariate and log-rank analysis; however, the correlation did not hold on multivariate analysis. This

could be due to confounding of variables that are unequal between the two arms. For example, patients treated with brachytherapy were more likely to be diagnosed before 2000, when suboptimal or antiquated chemotherapy regimens would have been used. The benefit of newer agents such as gemcitabine, or concurrent chemotherapy with 5-fluorouracil was not established until the early 2000s (29,30). Brachytherapy could also have been implemented to compensate for the lack of chemotherapy use due to either contraindication, intolerance, or both.

It is important to note that these results do not negate other potential benefits of combined modality radiotherapy. The SEER database lacks information concerning local recurrence or patient reported outcomes. Such data could inform the discussion of brachytherapy in this setting in terms of providing palliation of symptoms or prolonging the disease-free interval. Our results also suggest that the addition of brachytherapy to EBRT in patients with UEC for these reasons would not be associated with a survival decrement.

Conclusions

UEC is rare malignancy associated with a poor prognosis. Among UEC patients treated with radiotherapy, grade and extent of disease are negatively associated with overall and cause specific survival. When compared to those receiving EBRT alone, those receiving EBRT plus brachytherapy have a prolonged median survival. In spite of this apparent benefit, brachytherapy boost utilization has dropped significantly over the last decade of this study.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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