Multimodality therapy for locoregional extrahepatic cholangiocarcinoma: a population-based parametric analysis.

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2) tables: 2
3) illustrations: 4

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Abstract

Introduction: While surgical resection is the mainstay of treatment for extrahepatic cholangiocarcinoma (EHCC), most patients present with advanced disease. Owing in part to numerical rarity, the optimum role of radiotherapy (RT) for EHCC, as well as its relative benefit is an area of debate. The specific aim of this series is to estimate survival for EHCC patients receiving surgery and adjuvant RT using a robust population based dataset.

Methods: Data was extracted from the Surveillance, Epidemiology, and End Results (SEER) limited-use dataset for selected EHCC cases. Lognormal multivariate survival analysis was implemented to estimate survival for patients for treatment cohorts based on extent of surgical intervention and RT.

Results: Parametric estimated median survival for patients receiving total/radical resection+RT was 26 months, 25 months for total/radical resection alone, 25 months for subtotal/debulking resection+RT, 21 months for subtotal/debulking resection, 12 months for RT alone, and 9 months for those not receiving surgery or RT. Parametric multivariate analysis revealed age, AJCC Stage, grade, and surgical/radiation regimen as statistically significant covariates with survival. Surgery-alone and adjuvant radiotherapy cohorts showed evidence of improved survival compared to no treatment; comparatively, radiation alone was associated with survival decrement on multivariate analysis. Early improvement in survival in adjuvant cohorts was not observed at later time-points.

Conclusions: Survival estimates using SEER data suggest an early survival advantage for adjuvant radiotherapy for locoregional EHCC. While future prospective series are needed to confirm these observations, SEER data represents the largest domestic population-based EHCC cohort, and may provide useful baseline survival estimates for future studies.
Introduction:

Primary cancers of the bile ducts, known as cholangiocarcinomas, are rare tumors, with an annual incidence of 0.6-1/100,000 persons in the United States\(^1\). Despite their rarity, cholangiocarcinomas are highly lethal\(^3\).

Therapeutic interventions for cholangiocarcinomas are predicated on the distinction between intrahepatic and extrahepatic cholangiocarcinomas\(^1,4\), as well as the resectability of disease. At present, surgical resection is the preferred therapy for extrahepatic disease\(^5\). Unfortunately, the vast majority of patients present with locally advanced or metastatic disease which is not amenable to definitive resection, with reported 5-year overall survival rates of 0-39\(^%\)\(^6\). While definitive and adjuvant radiotherapy techniques have been investigated, typically via retrospective data from single institutions, outcomes remain suboptimal\(^7\)-\(^15\). At present, the utility of incorporating radiotherapy, as well its impact on disease outcome, is an area of debate\(^13,14\), owing in part to the numerical rarity of these tumors\(^16\).

The purpose of this study was to use multivariate regression analysis to evaluate survival differences between extrahepatic cholangiocarcinoma patients treated with multimodality therapy, specifically investigating the impact of radiotherapy and extent of surgical intervention.

Specific aims of this study are:

1. Determination of observed mortality differentials, if any, for patients receiving combined surgical/radiotherapy treatment compared with surgery only, radiotherapy only, or non-surgery/non-radiotherapy cohorts.

2. Generation of potential population-based survival benchmarks and hypotheses for institutional and cooperative group trials.

Methods:

Patient data from cases diagnosed from 1973-2005 was obtained from the April 2008 (based on the November 2007 submission) version of the Surveillance, Epidemiology, and End Results (SEER) limited-use dataset\(^17\).

Included cases of extrahepatic cholangiocarcinoma were identified by topography codes representing
extrahepatic bile ducts (C24.0) and histology codes representative of cholangiocarcinoma (histology codes 8010, 8020, 8041, 8070, 8140, 8144, 8160, 8162, 8260, 8310, 8490, and 8560). Perihilar cholangiocarcinomas, or Klatskin’s tumors, were specifically identified by topography codes C24.0 and specific histology code 8162/3; since these tumors cannot be reliably differentiated from EHCC, in accordance with previously described identification analysis of cases in SEER datasets, they therefore were included in this analysis. Case data with malignant primary indicator status denoting second (or greater) primary tumor(s) and those cases not specifically denoting local or regional disease (e.g. SEER Historic Stage A indicating distant/unknown extent of disease) were excluded from analysis. Cases were included if a positive microscopic confirmation, exfoliative cytology, or positive laboratory test/marker study was specified. SEER variable data were derived from direct accession via SEER*Stat, and extracted as tab-delimited data into commercial statistical analysis software (StatView and JMP v6.0, SAS Institute, Cary, NC). The following variables were extracted from SEER data: Age, Radiation, Surgery of Primary Site, Site Specific Surgery, Lymph Node Surgery, Histologic Grade, Sex, Extent of disease, and Cause of Death. Specific nominal variables were created using SEER data and software-scripted logic statements to create composite variables for analysis. As AJCC staging was unavailable directly from SEER data for all patients, for those patients whom extent of local/regional involvement and nodal status could be ascertained, AJCC stage (6th edition) was assigned by the authors using custom scripting of logic statements to pool available case data. Cases without sufficient information for AJCC grouping via custom scripting (e.g. TX, NX, MX, or “unknown” extent of disease values) were excluded. Cases were coded by therapeutic modalities received as a logic statement using the Radiation and Surgery of Primary Site/Site Specific Surgery variables derived from SEER*Stat, matching the therapeutic data to the appropriate SEER documentation. Cases with denotation of either external beam radiotherapy, or no radiotherapy in the Radiation variable of SEER*Stat were included; other radiation modalities (e.g. brachytherapy) were excluded. Site Specific Surgery variables were utilized to exclude nontherapeutic intent procedures (i.e. biopsy only, or exploratory surgical procedures). Those cases with Site Specific Surgery codes indicating potential therapeutic intent resection were included. Cases with Site Specific Surgery variables
denoting “radical” or “total” resection were grouped; all other cases indicating “debulking” or “subtotal” resection were pooled.

Patients receiving radiotherapy without indication of surgical intervention were coded as EBRT alone. All cases with SEER-extracted notation of therapeutic surgical resection without indication of radiation therapy were categorically coded as either “subtotal resection alone”, or “total/radical resection alone”. Those with notation indicating potentially therapeutic surgical intervention and radiotherapy were denoted as combined modality therapy recipients, “subtotal resection+RT”, or “total/radical resection+RT”, depending on extent of surgical resection recorded. Any case not showing evidence of either potentially therapeutic surgical resection or radiotherapy was classified as non-treatment (No TX). In order to account for perioperative mortality as a potential confounding factor, statistical analyses were performed only on patients who had survived >2 months from diagnosis.

Evaluation of the main variable of interest, therapeutic regimen, was evaluated using univariate parametric lognormal survival analysis\(^{18}\), after visual inspection revealed crossing of survival curves with graphic representation of product-limit survival curves\(^{19, 20}\). Since the proportional hazard assumption could not be met for the variable of interest\(^{21}\), as determined by Schoenfeld residual calculation\(^{22}\), for multifactorial/multivariate analysis, a parametric lognormal analysis was performed, obviating the need to hazard proportionality throughout follow-up. A parametric lognormal\(^{18}\) full-factorial model, which included the following variables (derived from literature review to impact survival with EHCC), was utilized: age (as a continuous measure), year of diagnosis (as a continuous measure), therapy cohort (No treatment, EBRT alone, subtotal resection, subtotal resection+RT, total resection, total resection+RT), grade (Well-differentiated/Grade I, moderately-differentiated/Grade II, poorly-differentiated/Grade III, Undifferentiated/Grade IV, Unknown/Not specified), and derived AJCC Sixth Edition Stage (IA, IB, IIA, IIB, III). Survival estimation was performed utilizing lognormal parametric survival regression with a maximum likelihood approach to calculate \(\beta\), the factor effect of the aforementioned variables, as well as the 95% confidence interval of \(\beta\), assuming an approximation of a normal distribution. For categorical variables \(\beta\) values >0 indicate a positive association with regard to survival; \(\beta<0\) suggest an association with survival decrement. For continuous variables (age, year of diagnosis), positive
\[ \beta \text{ values indicate increasing probability of survival with increasing numeric value of the variable in question.} \]

Statistical significance for each variable was evaluated using a chi-square approximation set at a \( \alpha = 0.05 \), with \( n-1 \) degrees of freedom, where \( n \) is the number of subvariables within a categorical variable of interest, and was uncorrected for multiple comparisons.

Results:

A total of 1,569 cases of primary loco-regional EHCC met inclusion criteria. Median age at diagnosis was 68 years (mean 66.9, SD 12.4, range 25-97). Demographic parameters are described in Table 1 for the study population, stratified by treatment cohort. Overall product limit and lognormal-fit of survival are shown in Figure 1 for the study population.

Kaplan-Meier plots by treatment cohort are shown in Figure 1, with comparison to lognormal-fit event curves in Figure 2; median survival was 17 months (CI 16-18) for all patients with a survival of > 2 months. On univariate analysis, patients receiving surgery and radiotherapy exhibited superior median estimated survival times to those receiving either radiotherapy or surgical intervention alone, and all had outcomes superior to patients for whom no therapy was described (Table 2). Results from multivariate lognormal parametric survival analysis revealed a log-likelihood \( > \chi^2 \) probability of <0.001, and are presented graphically in Figure 4. Age (as a continuous variable), grade, therapy cohort, and AJCC grouping were observed to have a statistically significant association with alteration in survival in multivariate analysis (all \( p < 0.001 \)); year of diagnosis was not \( (p=0.88) \).

Discussion

With an estimated annual incidence of 3,000 cases annually in the United States, EHCC remains a rare but aggressive neoplasm. While complete surgical resection remains the foundation of curative intent therapy for EHCC, owing to its anatomical location and natural history, the majority of patients present with locally advanced disease at diagnosis. The rarity of EHCC has precluded mounting of large-scale randomized controlled trials. Thus, at present, the role of adjuvant therapy for EHCC remains controversial, despite promising institutional data. Consequently, while imperfect, the utilization of large-scale population-based
datasets, such as SEER, represent a useful mechanism for mortality risk estimation. Such data may be especially useful for tumors such as cholangiocarcinoma, where single institutions have difficulty accruing sufficient numbers to afford appropriately statistically powered analyses.

The data presented herein suggest that the addition of radiotherapy to therapeutic intent surgical interventions was associated with improved median survival compared to either surgery alone, radiotherapy alone or nonsurgery/nonradiotherapy cohorts in a multifactorial model. However, it should be noted that, with sufficient follow-up (i.e. >5 years), in univariate survival analysis, the mortality curves for the surgical and combined modality cohorts converge, and, as shown in Figures 2 and 3, adjuvant radiotherapy may be associated with long-term (>5 years) survival decrement. Long-term outcomes were uniformly dismal with 5-year survival rates of 18% for surgery alone, 16% for surgery+RT, and under 3% for those receiving radiotherapy alone or no recorded therapy. The majority of detected survival benefit from the addition of radiotherapy appears to be had within the initial 1-2 years following therapy (Figures 2 and 3). Why this effect dissipates over time is unclear. This observation may be due to delayed local recurrence in those patients receiving surgical resection and radiotherapy; alternately, it may be attributable to treatment-related factors unaccounted for in SEER (e.g. chemotherapeutic regimens not recorded in SEER, performance status differentials, variant radiotherapy techniques and/or fractionation/dose schedules, post-therapy complication rates, delay in distant metastatic progression due to improved local control26). Alternatively, prognostic variables not recorded in SEER might lead to negative selection bias for definitive or adjuvant radiotherapy (e.g. positive margins after resection, advanced pathologic features). The surgical margin status issue is of special significance, and unfortunately, is not a recorded variable within the SEER dataset. It is possible that the adjuvant radiotherapy cohort includes many patients who received radiotherapy secondary to suboptimal resection. If true, radiotherapy might confer some deferral of disease progression, but would be inadequate for eradicating bulk disease. If many suboptimally resected cholangiocarcinomas are de facto unresectable tumors7, it becomes apparent, as Crane et al. have noted previously, that conventional radiation-only regimens are insufficient to ensure local control10, and may only be able to defer disease progression temporarily. However, such explanations are purely conjecture in the absence of prospective clinical trial data.
Since SEER represents the largest domestic cholangiocarcinoma dataset, the observed phenomena whereby early survival is improved by the addition of radiotherapy, while late survival is either unaltered or decreased, may explain the relatively contradictory findings in smaller institutional series. Some posit minimal utility for adjuvant therapy, while others suggest an appreciable survival benefit. Consequently, our findings may demonstrate both opinions to be correct, with early survival improvement noted despite minimal benefit in the long-term (see Figures 2 and 3). Some authors have observed series where suboptimal resections (R1) may derive minimal gain from the addition of surgery to radiotherapy. While not directly answered in this series, owing to the unavailability of margin status and other relevant pathologic (lymphovascular or perineural invasion) and clinical (performance status, comorbid conditions) confounders in SEER, the significantly poorer outcomes observed for the radiotherapy only cohort should at least give pause to implementation of radiation monotherapy for patients with potentially difficult resections, and should spur aggressive surgery whenever indicated clinically.

While SEER represents an exceedingly robust dataset, several limitations should be assiduously noted. SEER data does not afford analysis of chemotherapy regimen utilization, and thus it is impossible to impute what role, if any, the addition of chemotherapy to any treatment cohort may have on survival patterns. Furthermore, relevant specific information regarding surgical and radiotherapy treatment techniques (e.g. margin status, dose/fractionation, time between surgery and radiotherapy) are not captured within the SEER dataset. The SEER Historic Staging system, while affording ready comparison between distinct eras, is inherently imprecise in order to collapse patients based on extent of disease. Additionally, no EHCC patients diagnosed 1973-1998 received formal AJCC staging within SEER, making the logic-statement/scripting stage conversion by the authors necessary, based on available extent of disease data. While some information regarding the anatomic location may be gleaned from the SEER topography codes, insufficient information is available for rigorous definition of tumor location or resectability, major prognostic factors in many series. For example, Welzel et al. demonstrated that discrimination of Klatskin’s tumors from other extrahepatic cholangiocarcinomas is unreliable using SEER; consequently, the inclusion of Klatskin’s tumors within this series should be noted, and might skew results. SEER, like most registry data, has multiple “catch-all”
identifiers (e.g. “Surgery NOS”, “Unknown Grade”) which may obfuscate careful definition of categorical
cohorts. SEER data is limited geographically, as not all U.S. cancer registries contribute to SEER, and
temporally limited, as not all registries have contributed data for the same span of time. Though we utilized year
of diagnosis as a surrogate for evolving radiotherapy, surgery, or chemotherapy practice, SEER variables does
not directly account for technological improvement or changes in either surgical or radiation technique over
time. Finally, SEER data collection is dependent upon the quality of decentralized local registrars for
completeness and accuracy of data entry, with limited direct quality control.
Nonetheless, SEER provides the largest domestic population-based estimation of EHCC, with case numbers
several-fold greater than available in single-institutional series. The value of such numerical power should not
be underestimated. In addition, population-based datasets such as SEER may more accurately reflect the true
expected survival of EHCC patients in the community medical milieu, rather than only at specific academic
centers. These may explain why, in comparison to several retrospective series reported in the literature, survival
results from the present analysis show comparatively worse survival for adjuvant radiotherapy patients than the
markedly smaller, albeit more detailed, retrospective series available in extant literature.
Likewise, differentials in the clinical outcomes associated with tertiary centers (e.g. improved late survival at
high volume centers, or increased utilization of adjuvant radiotherapy in institutions with on-site radiotherapy
facilities) may be obscured in pooled registry data.
This dataset represents, to our knowledge, the first to characterize the effect of multimodality therapy as a using
parametric survival analysis in cholangiocarcinoma. The nonproportionality of the hazard functions observed in
this series with regard to therapeutic cohort necessitate a historically underutilized, but increasingly
implemented statistical comparison. Ahmed et al. have recently described several distinct methodologies for
accounting for nonproportionality in survival series. We have chosen lognormal survival fitting, which has a
long history within cancer survival analysis, as it is robust, applicable in cases of non-proportionality,
statistically succinct, and broadly interpretable as a mechanism for defining survival event estimates. While
more elegant corrections for nonproportionality are available, none are widely implemented. Additionally,
parametric analyses have the added benefit of the capacity to generate, given specific multivariate input
parameters, an estimation of the survival at any given time point in follow-up. We hope to eventually transform this dataset into a risk-profiling tool, as has previously been performed using SEER data regarding gallbladder carcinomas\textsuperscript{48}. 

Our data support recent work by Shinohara et al.\textsuperscript{49}, who showed a beneficial effect of radiotherapy for intrahepatic cholangiocarcinomas. As in that series, long-term survival was poor despite the addition of radiotherapy. There are other diseases, such as lung cancer, where early survival improvement alone may serve as a justification for radiotherapy, even though 5-year mortality is largely unaffected.

This early survival benefit, coupled with available data detailing patterns of failure for cholangiocarcinoma\textsuperscript{15, 50-56}, lend credence to the position that adding radiation post-operatively when possible for local/regional disease is a reasonable first-line therapeutic approach for EHCC, in the absence of more definitive data from randomized controlled trials.

Conclusion

Baseline data from SEER indicate an improved early survival profile for patients receiving multimodality therapy; however, long-term survival advantage was not demonstrated.
Table and figure legends:

Table 1: Demographic features of included cases, stratified by treatment cohort (number above, percent of total cases, below).

Table 2: Lognormal parametric survival analysis results by therapeutic cohort.

Figure 1: Product limit survival (red), with superimposition of lognormal fitted survival (blue), for included patients.

Figure 2: Product limit survival for all patients with EHCC surviving > 2 months, stratified by therapy cohort.

Figure 3: Lognormal fit of survival all patients with EHCC surviving > 2 months, stratified by therapy cohort.

Figure 4: Graphical representation of the parameter estimate of effect (\(\beta\)), with 95% confidence interval.
References


52. de Castro SM, Kuhlmann KP, van Heek NT, Busch OR, Offerhaus GJ, van Gulik TM, et al. Recurrent disease after microscopically radical (R0) resection of periampullary


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Table 1: Demographic features of included cases, stratified by treatment cohort (number above, percent of total cases, below).

Table 2: Lognormal parametric survival regression results by therapeutic cohort.
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